Tufts Clinical and Translational Science Institute

Translational Research Day 2017:
Sensors, Devices, and Biomarkers in Medicine

November 14, 2017

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Tufts Clinical and Translational Science Institute

Welcome and Introduction

Harry Selker, MD, MSPH

Dean and Principal Investigator
Tufts CTSI

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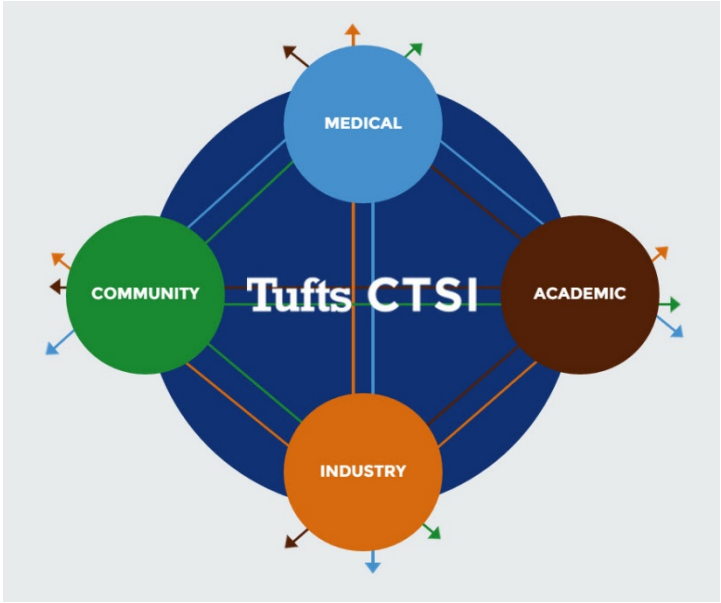
Tufts Clinical and Translational Science Institute

Tufts CTSI's Mission & Purpose

Established in 2008 to translate research into better health



- Stimulate and expedite innovative clinical and translational research, with the goal of improving the public's health
- *Entire spectrum* of clinical and translational research is critical to meeting the promise and the public's needs of biomedical science

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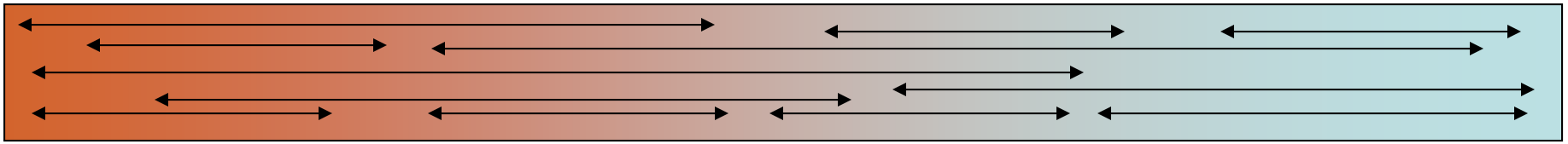
Spectrum of Translational Research



Bench to Bedside… **...to Clinical Practice…** **…to Widespread Care Delivery…** **…to Health Policy**

T1 ⟷ ***T2*** ⟷ ***T3*** ⟷ ***T4***

Bench and animal research

Clinical testing and trials

Testing in practice settings

Healthcare system delivery

Public health and health policy

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Tufts Clinical and Translational Science Institute (CTSI)

Research Service Organizations

- Study Design & Analysis
- Clinical Study & Regulatory Support
- Informatics

Conveners & Connectors

- Team Science
- Collaboration
- Multidisciplinary
- Stakeholder & Community-Engaged

Change Agents

- Innovation & Transformation
- Science of Science
- Process Improvement
- Addressing Roadblocks

Educator and Trainers

- Graduate Certificate, Masters, and PhD Programs
- Professional Development
- Fellowship and Career Development Programs

Tufts CTSI Partners & Collaborators

Tufts Schools & Centers

Cummings School of Veterinary Medicine
Fletcher School of Law & Diplomacy
Friedman School of Nutrition Science & Policy
Institute for Clinical Research & Health Policy Studies at Tufts Medical Center
Jean Mayer USDA Human Nutrition Research Center on Aging
Sackler School of Graduate Biomedical Sciences
Schools of Arts & Sciences
School of Dental Medicine
School of Engineering
School of Medicine
Tisch College of Civic Life
Tufts Center for the Study of Drug Development

Academic Partners

Brandeis University
Massachusetts Institute of Technology
Northeastern University
RAND Corporation

Tufts-Affiliated Hospitals

Baystate Medical Center
Lahey Hospital & Medical Center
Maine Medical Center
New England Baptist Hospital
Newton-Wellesley Hospital
St. Elizabeth's Medical Center
Tufts Medical Center

Industry/Non-Profit Partners

Baim Institute for Clinical Research
Blue Cross Blue Shield of MA
Eli Lilly and Company
The Jackson Laboratory
Pfizer, Inc.
Tufts Health Plan

Community-Based Partners

Action for Boston Community Development (ABCD)
Asian Community Development Corporation
Asian Task Force Against Domestic Violence
Asian Women for Health
Boston Chinatown Neighborhood Center
Center for Information and Study on Clinical Research Participation (CISCRP)
Greater Boston Chinese Golden Age Center
Health Resources in Action
Museum of Science, Boston
New England Quality Care Alliance (NEQCA)

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How Does Tufts CTSI Help Researchers?

- Consultations
- Connections to collaborators & research projects
- Research design & analysis
- Regulatory support
- Clinical studies & trials support
- Informatics tools
- Pilot Studies Awards
- Training & education opportunities
  - CTS Graduate Program
  - TL1 Fellowship Program
  - KL2 Scholarship Program
  - Professional Education

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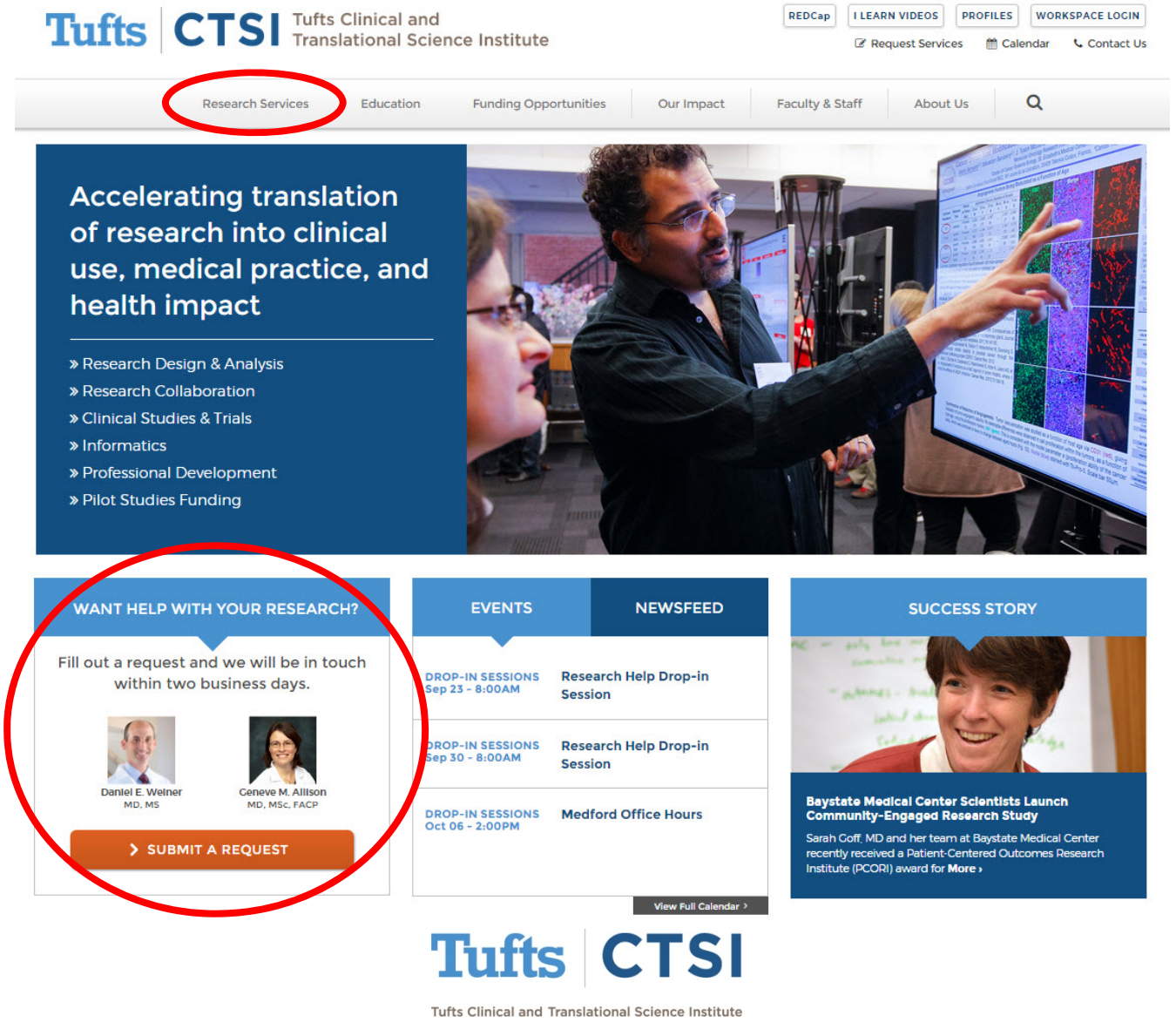
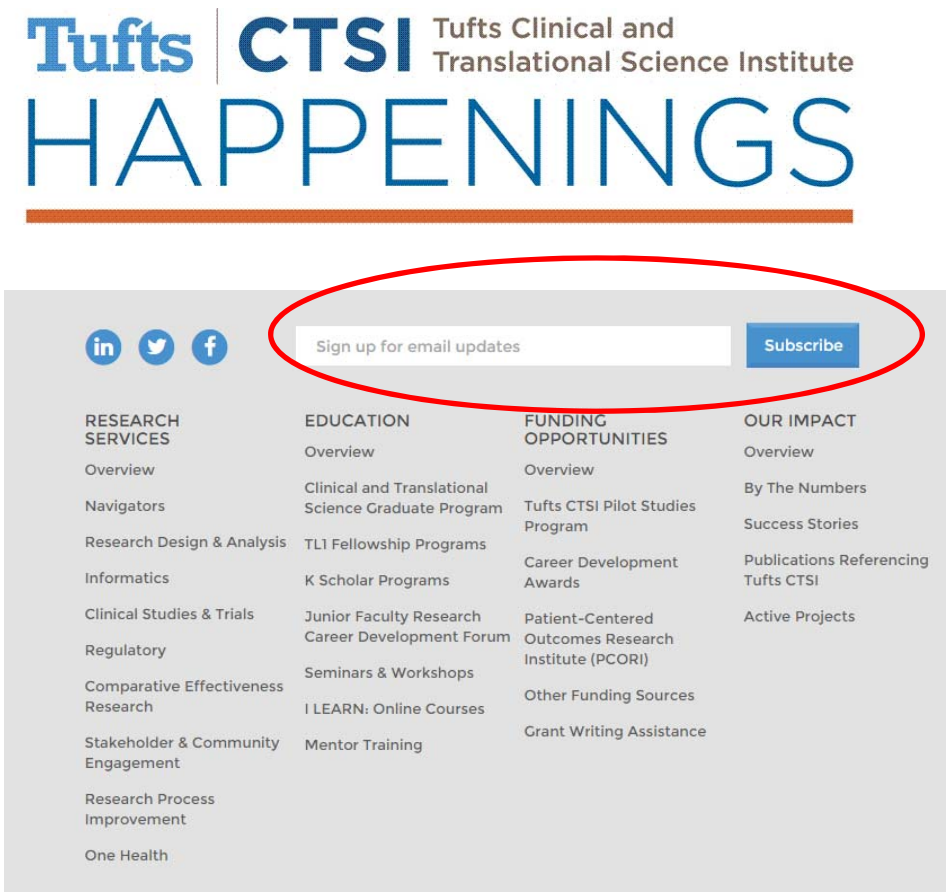
For more information: www.tuftsctsi.org



Get Connected: CTSI Happenings



- Weekly e-newsletter with news, professional development and funding opportunities, resources, and success stories.
- Issued every Monday at 8AM
- Sign up on our website or at *http://eepurl.com/C4d9X*

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Conference Objectives

Graham Jones, PhD

Associate Director and Director of Research Collaborations
Tufts CTSI

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Conference Objectives

- Recognize the different classifications of biomarkers and their potential in detecting early-stage disease and for personalizing interventions.
- Illustrate diverse approaches to advancing the capabilities of sensors and medical devices and their practical applications in improving health.
- Describe potential translational roadblocks in developing, testing, and using sensor- and device-based health prevention, detection, management, and intervention strategies.
- Identify Tufts CTSI resources and services that support team-based translational science.

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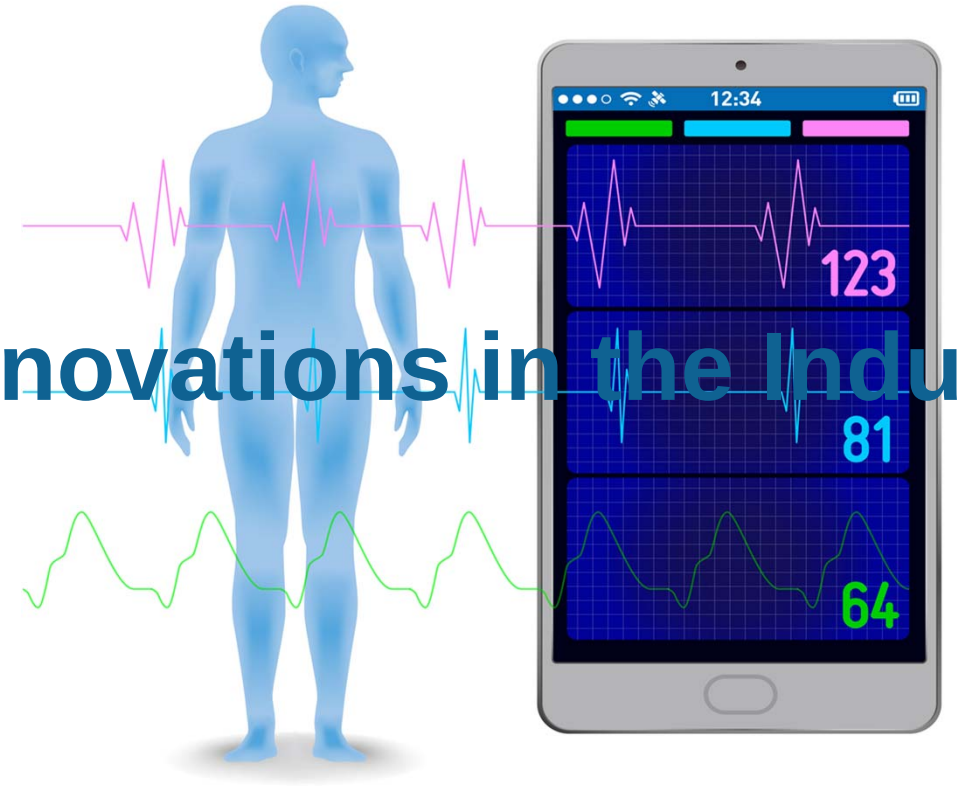

Innovations in the Industry

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Digital Monitoring Biomarkers Come of Age

Justin Wright, PhD

Vice President, Drug Delivery Innovation
Drug Delivery and Device R&D
Eli Lilly and Company

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Improving the Assessment of Functional Change in CNS Clinical Trials

Joshua Cosman, PhD

Project Lead, Pfizer Innovation Research Lab
Early Clinical Development
Pfizer, Inc.

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Improving the measurement of functional change in CNS clinical trials

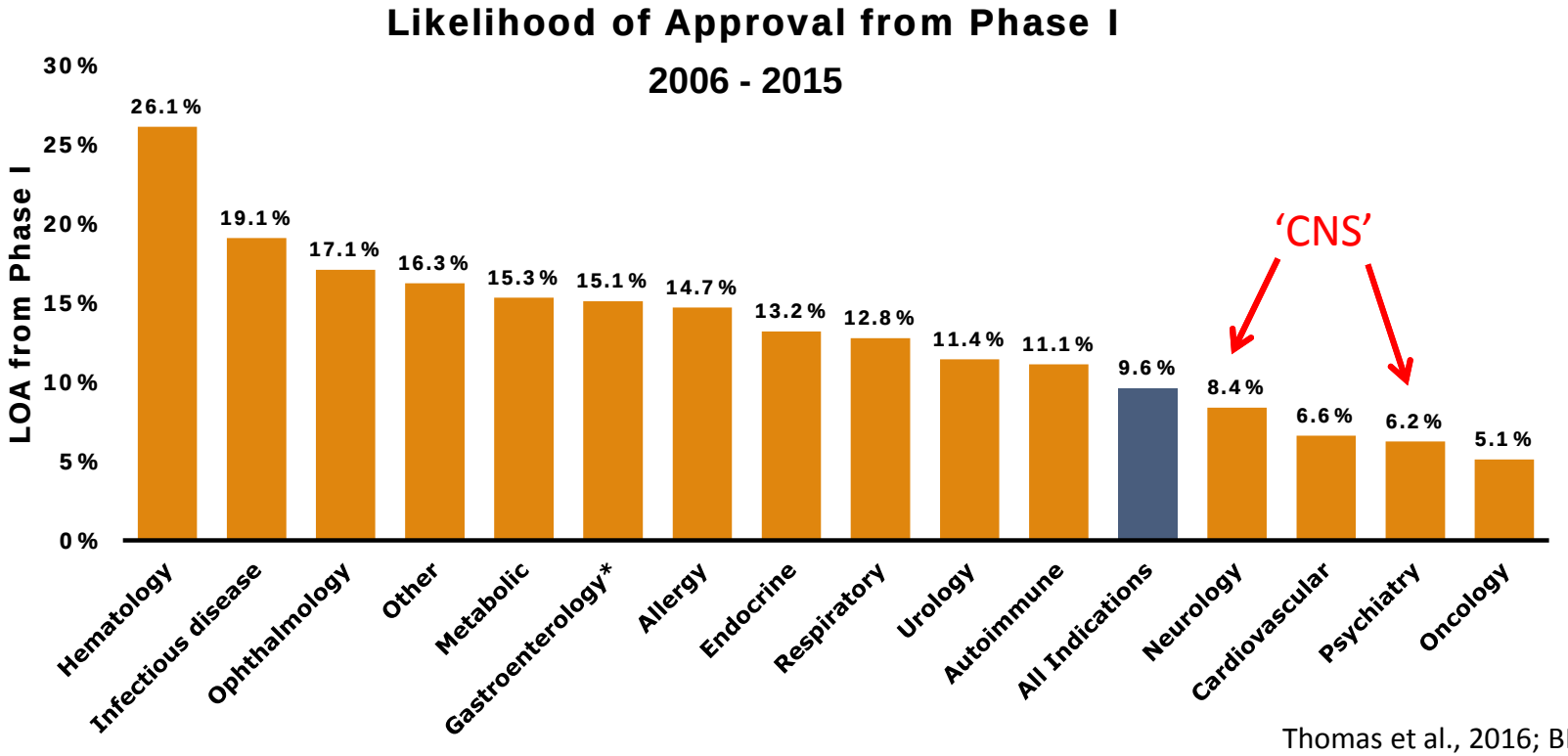
Josh Cosman, PhD.

Pfizer Innovation Research Lab / Digital Medicine

Early Clinical Development, Pfizer, Inc.

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

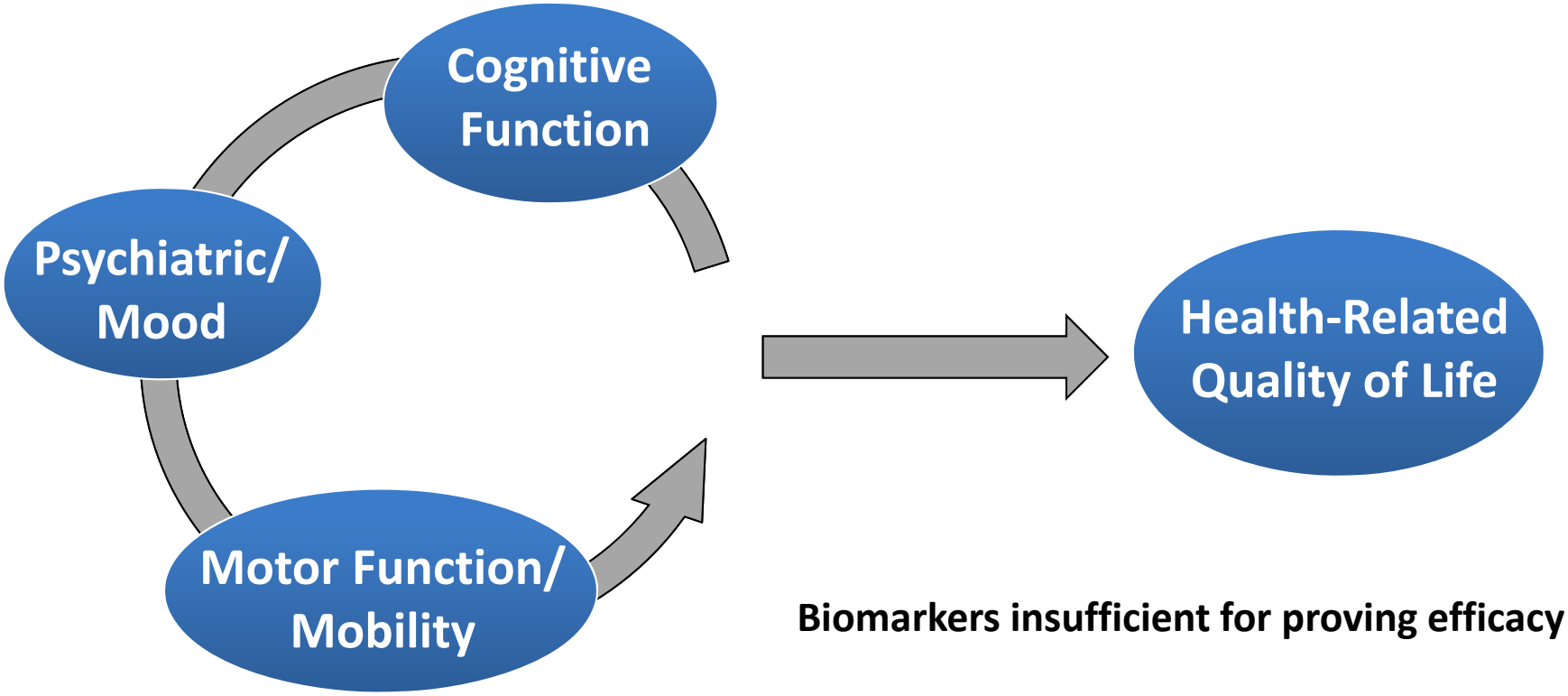


Thomas et al., 2016; BIO

One factor: Inability to robustly, reliably measure functional change

Functional Change

Disease-related changes in CNS function that impact subjects' daily lives



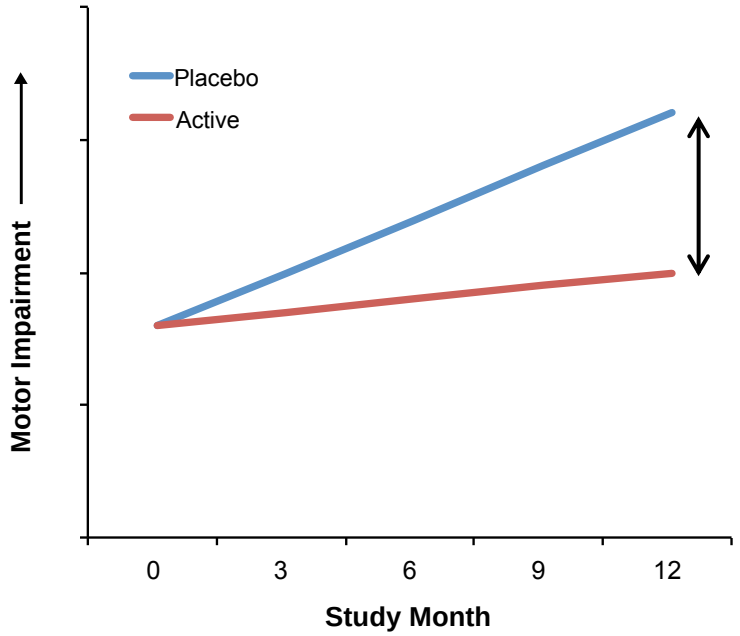
Biomarkers insufficient for proving efficacy

A Case Study: Measuring Functional Change in Parkinson's Disease

Disease modification in Parkinson's Disease (PD)

Hypothesis: Disease modifying treatments for Parkinson's Disease (PD) slow the rate of disease progression

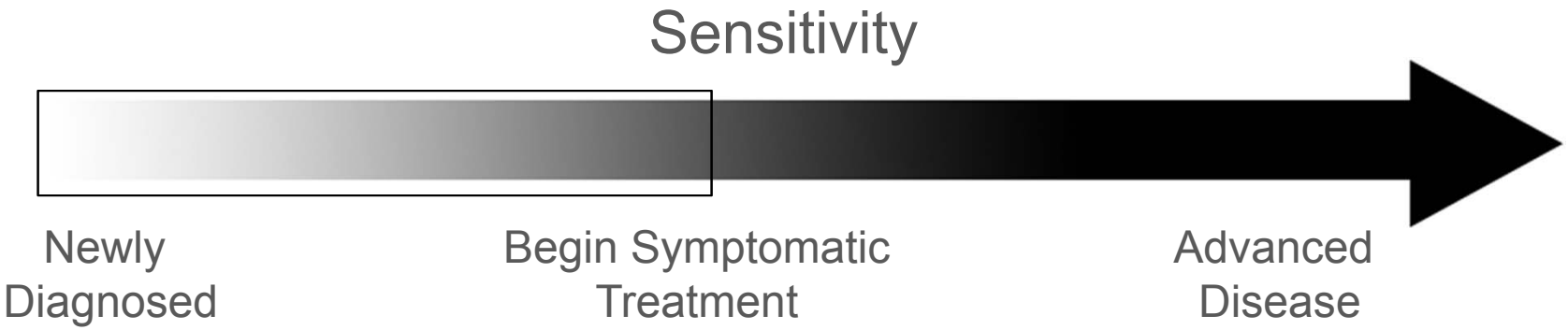
To establish that a treatment alters the progression of Parkinson's disease, must observe Δ in functional endpoint (Unified Parkinson's Disease Rating Scale; UPDRS)



'Disease Modification' Effect

Detecting functional change in PD

Detecting functional change in PD

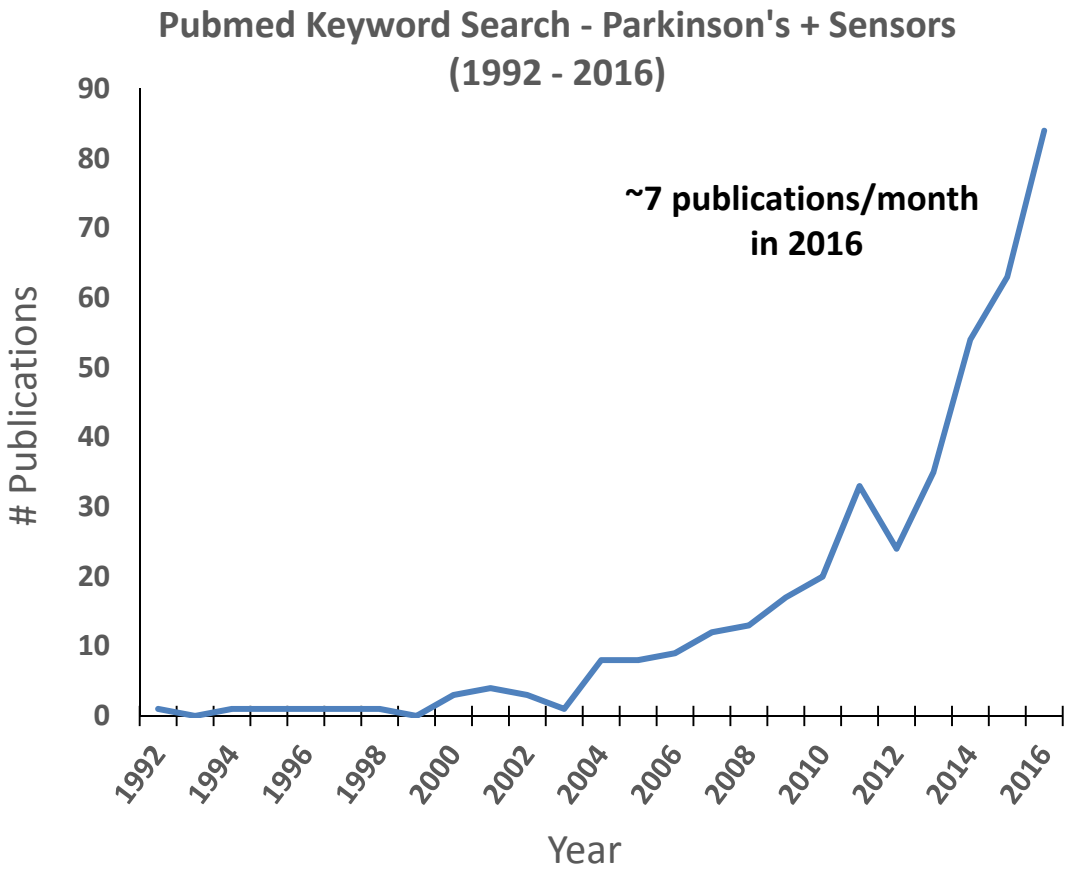


Factors impeding detection in the ‘gray zone’

- Poor tools – UPDRS relatively insensitive, subjective, prone to rater placebo effects in clinical trials
- Episodic measurement – inability to distinguish symptom fluctuation from progressive change

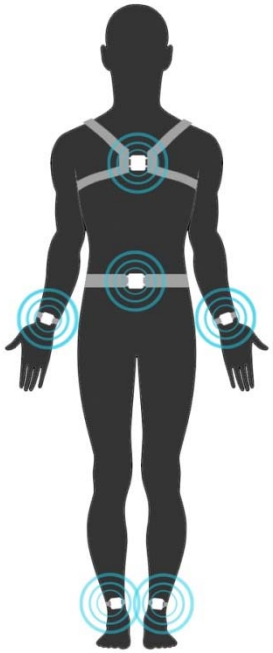
Improving the ability to measure functional change in PD

Objective, sensor-based measures of motor impairment

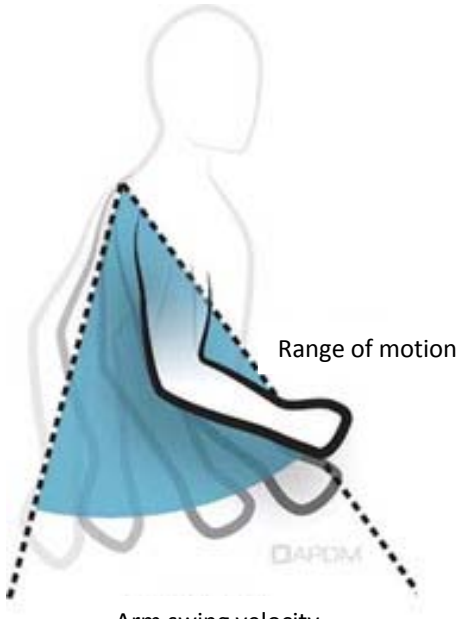


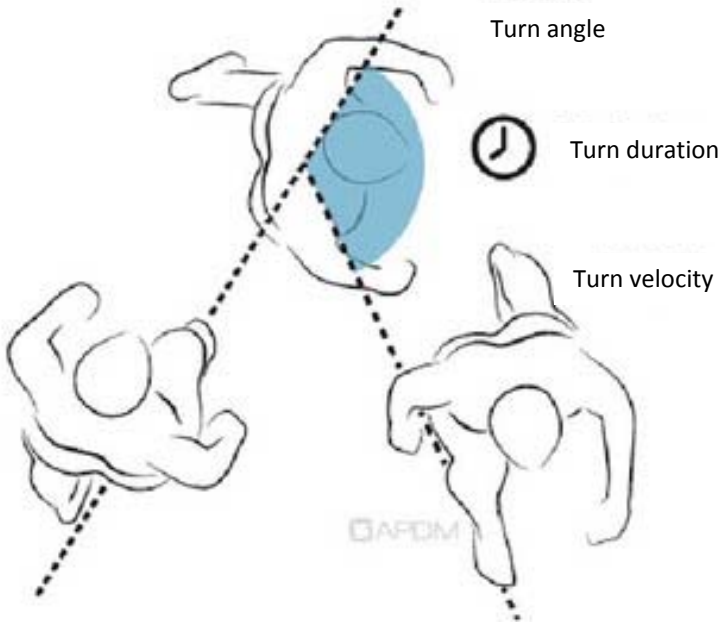
Tri-axial accelerometer, gyroscope, magnetometer for objective kinematic analysis

Objective, sensor-based measures of motor impairment



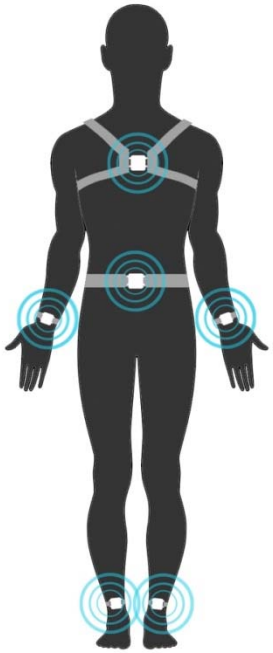
Objective measurement of gait, balance, posture





Mancini & Horak, 2015

Objective, sensor-based measures of motor impairment



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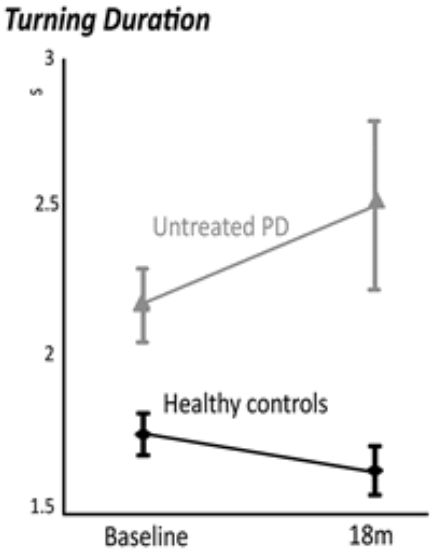
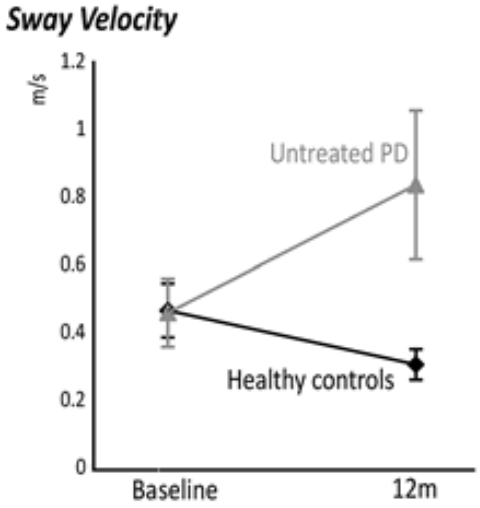


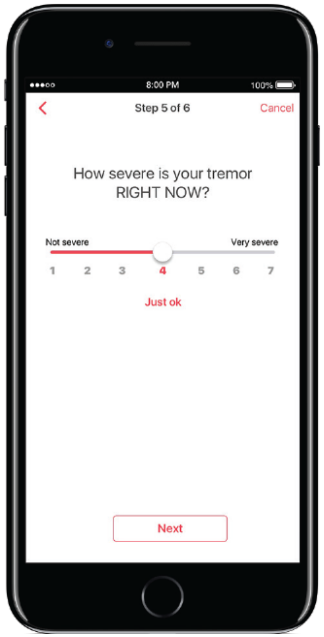


Mancini & Horak, 2015

However, difficult to scale so limited uptake in large trials or home-based monitoring

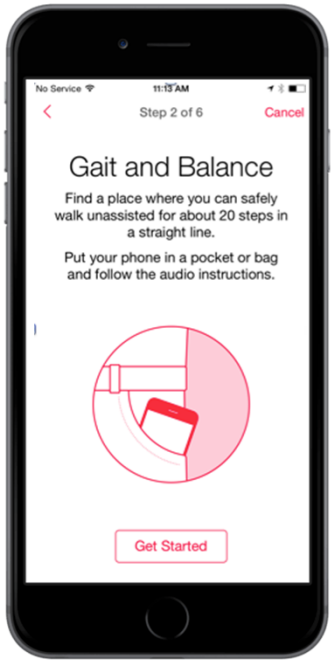
High-granularity symptom measurement via consumer devices

Symptom PRO



Cognitive/Psychomotor Tasks

Instrumented Motor Tasks



Active completion of mobile assessments at regular intervals

Passive collection of mobility and kinematic data throughout the day

Enable better separation of symptom fluctuation and progression

Measurement across the development cycle

Increasing trial size and complexity

Phase I | Phase II | Phase III | Phase IV

+

Bridge research and consumer devices to drive continuity across early and late-phase trials / boost ability to scale

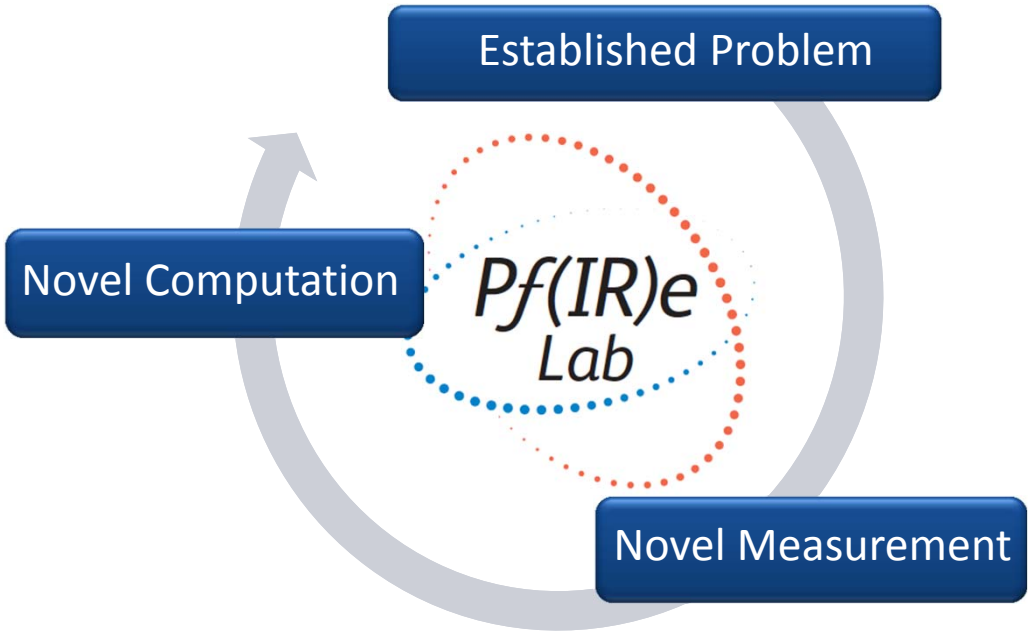
Why aren't we there yet?

Pharma lacks infrastructure for iterative 'experiment-driven' development

Lack of alignment between basic science and clinical development

How is Pfizer addressing these issues?

Pfizer Innovation Research (PfIRe) Lab



- ***Clinic-focused correlate of preclinical biology lab***
- ***Multidisciplinary - expertise in neurology, systems neuroscience, psychiatry, biomedical engineering, data science, informatics***

Pfizer Innovation Research (PfIRe) Lab - Mission

Provide space and infrastructure to run human subjects studies on-site that enable:

- Rapid evaluation/de-risking of novel tools and methodologies
- Deeper operational understanding of these tools
- Standardization of analytic approaches and data storage/handling
- Accelerated translation of technologies from academic labs to the clinical trial setting

Summary

Effectively transitioning from current clinical standards to novel functional assessment requires:

1. Focus on scalability
2. Ability to rapidly evaluate/iterate
3. Alignment with emerging technologies/approaches being employed in academia

Joshua.cosman@Pfizer.com

Innovations in the Industry

Q&A

Justin Wright, PhD

Joshua Cosman, PhD

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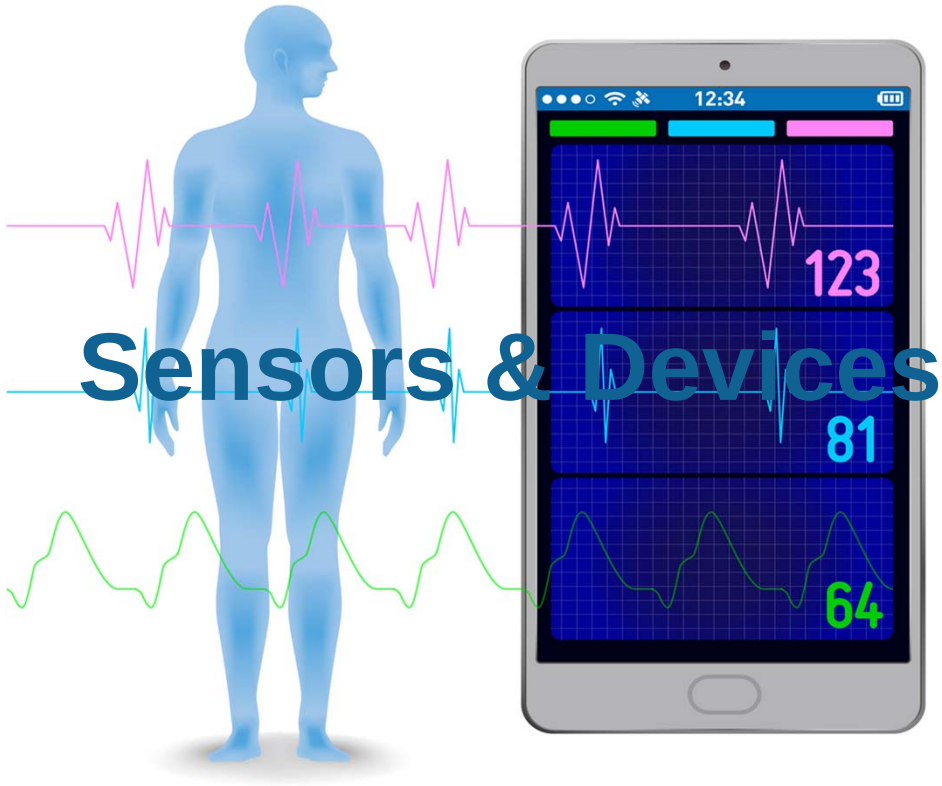

Sensors & Devices

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Smart Mechanical Support Devices for Cardiac Care

Navin Kapur, MD, FACC, FSCAI, FAHA

Associate Professor, Department of Medicine
Interventional Cardiology & Advanced Heart Failure Programs
Executive Director, The Cardiovascular Center for Research & Innovation

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Tufts Clinical and Translational Science Institute

Mechanical Circulatory Support Devices for Cardiac Care: New Paradigms and Innovations

Navin K. Kapur, MD, FACC, FSCAI, FAHA

Associate Professor, Department of Medicine

Interventional Cardiology & Advanced Heart Failure Programs

Executive Director, The Cardiovascular Center for Research & Innovation

Tufts Medical Center
The CardioVascular Center

The Acute MCS Working Group

SIRL

MCRI

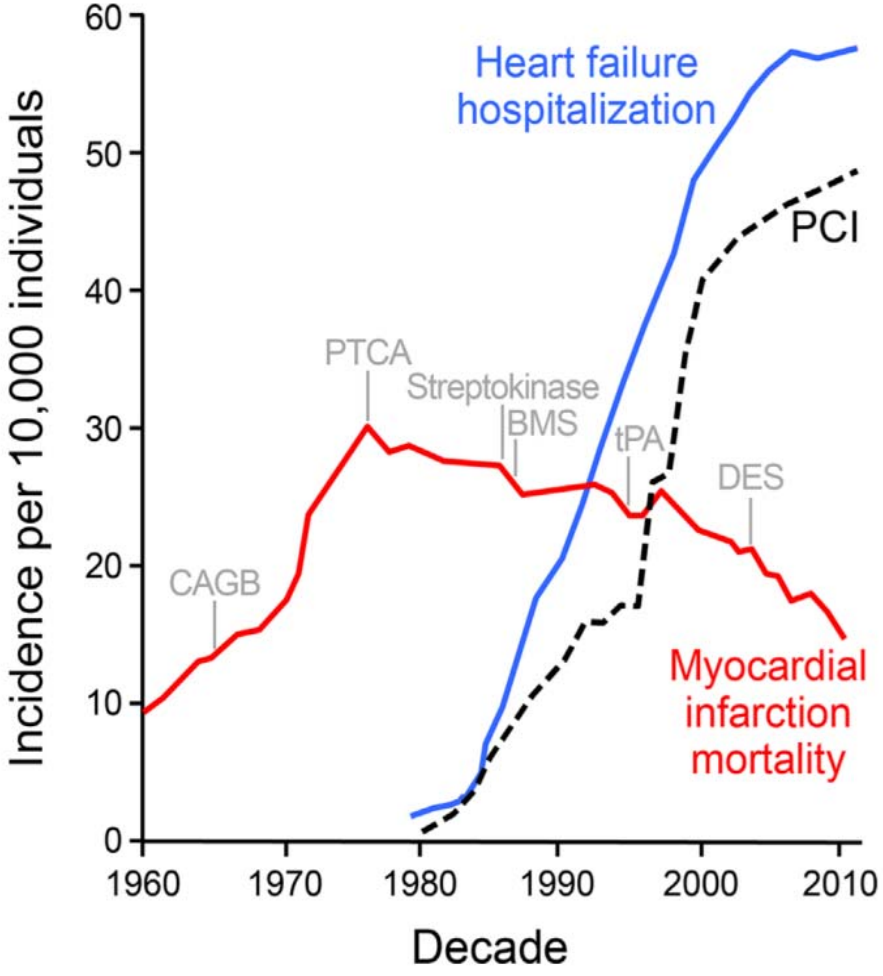
Relevant Disclosures

Research Funding: Abiomed, Maquet, Cardiac Assist, Abbott, Boston Scientific

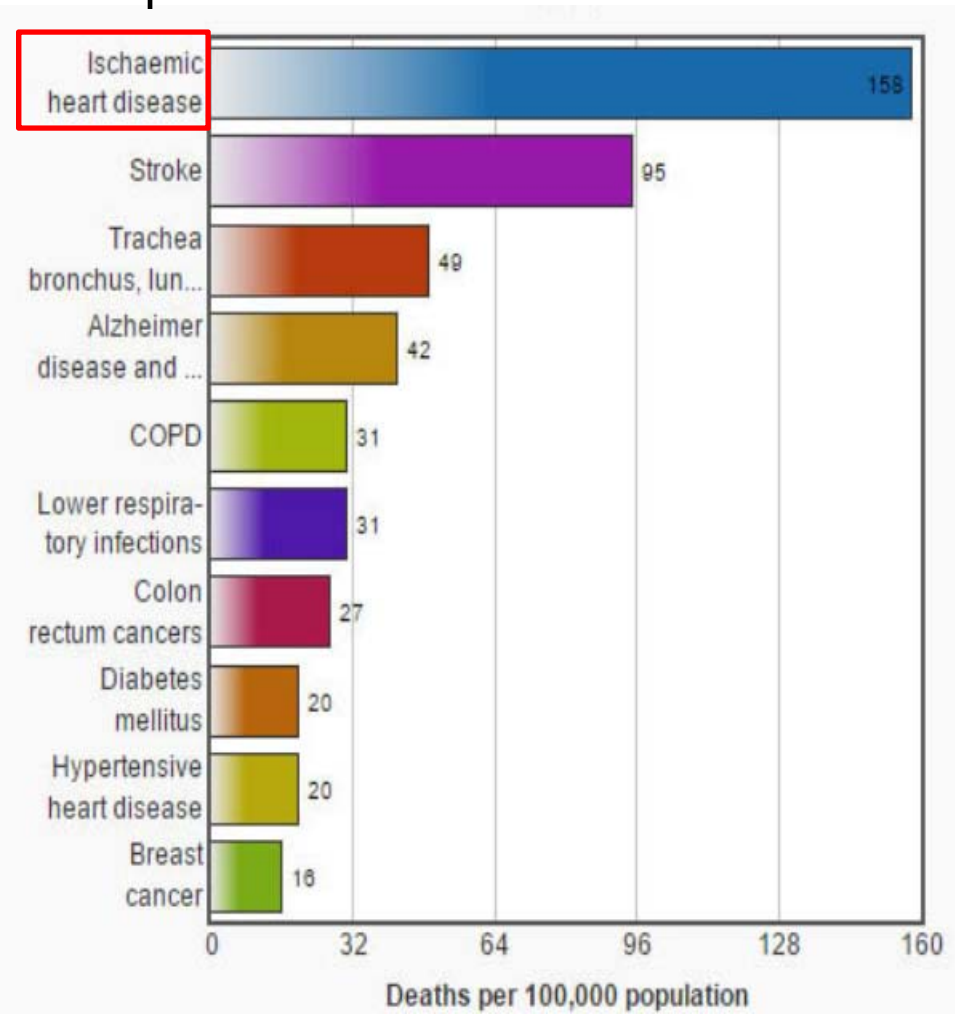
Speaker/Consulting Honoraria: Abiomed, Maquet, Cardiac Assist, Abbott

The Heart Failure Pandemic

From AMI to Ischemic Heart Failure



Top 10 Causes of Death Worldwide

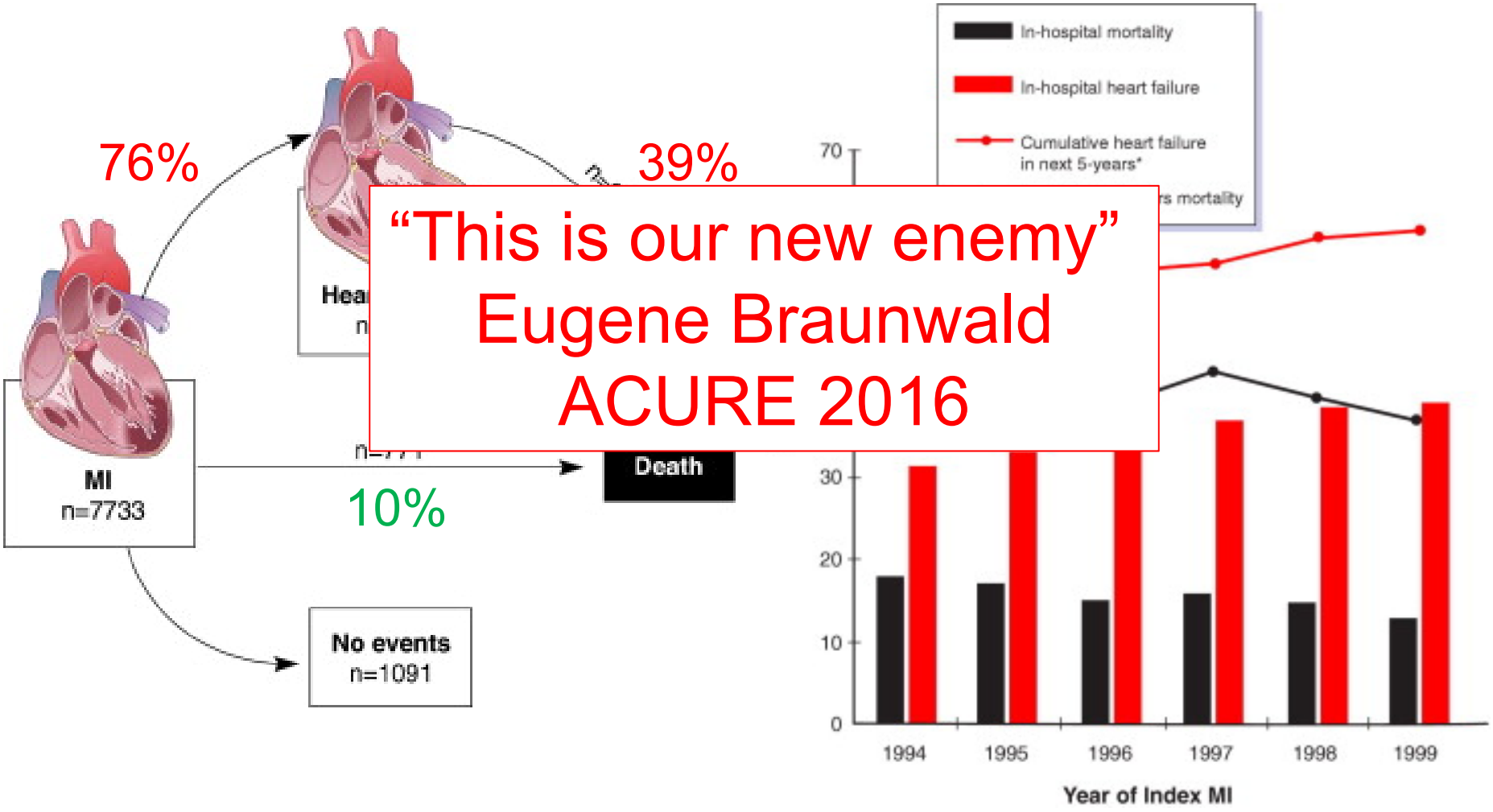


Terzic et al Trends in CV Med 2016

World Health Organization 2012

Heart Attacks Lead to Heart Failure

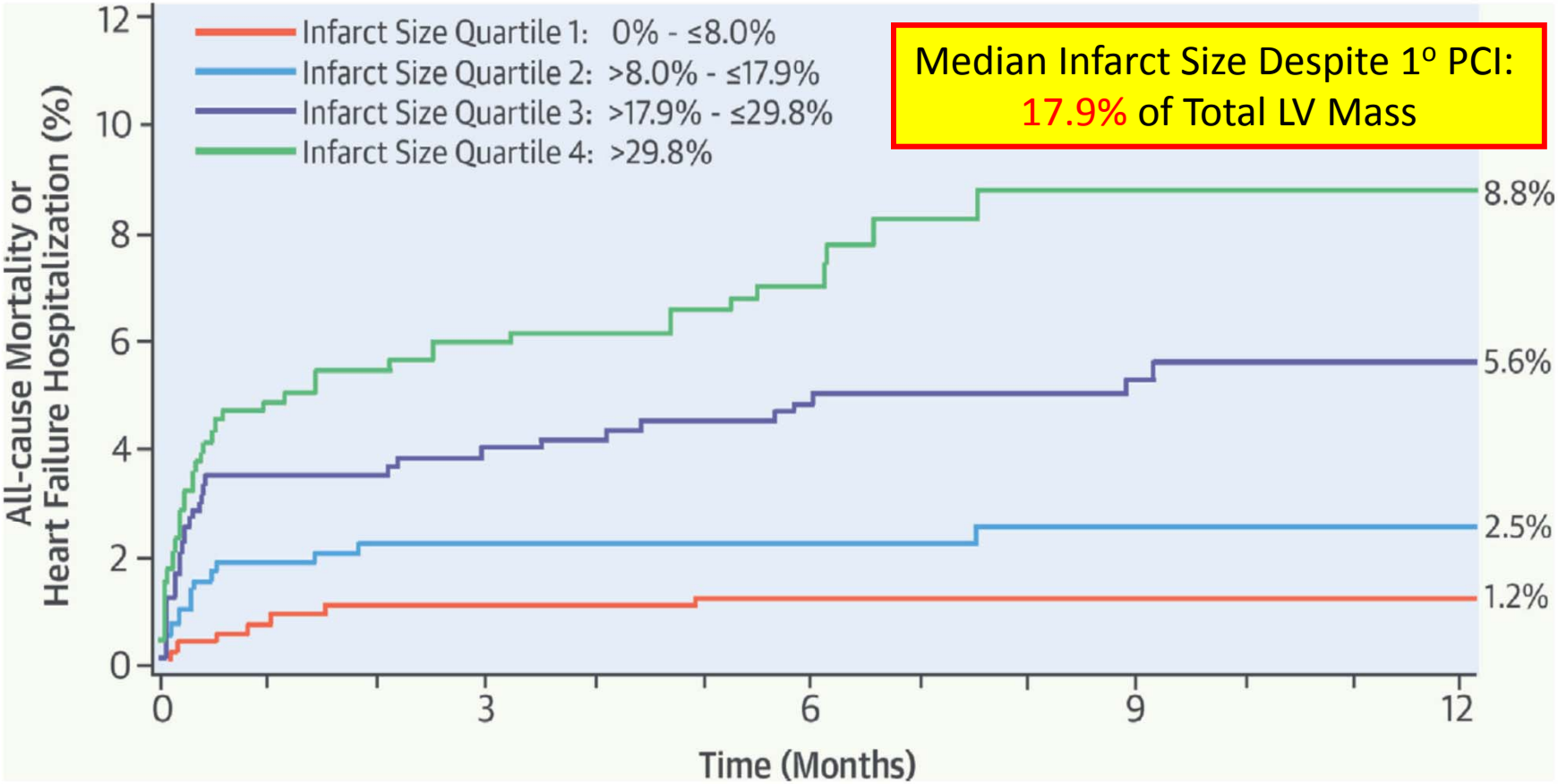
75% of AMI Patients Treated with Primary Reperfusion Develop Heart Failure Within 5 years



"This is our new enemy"
Eugene Braunwald
ACURE 2016

Ezekowitz JA et al JACC 2009

Myocardial Infarct Size: An Important Target of Therapy

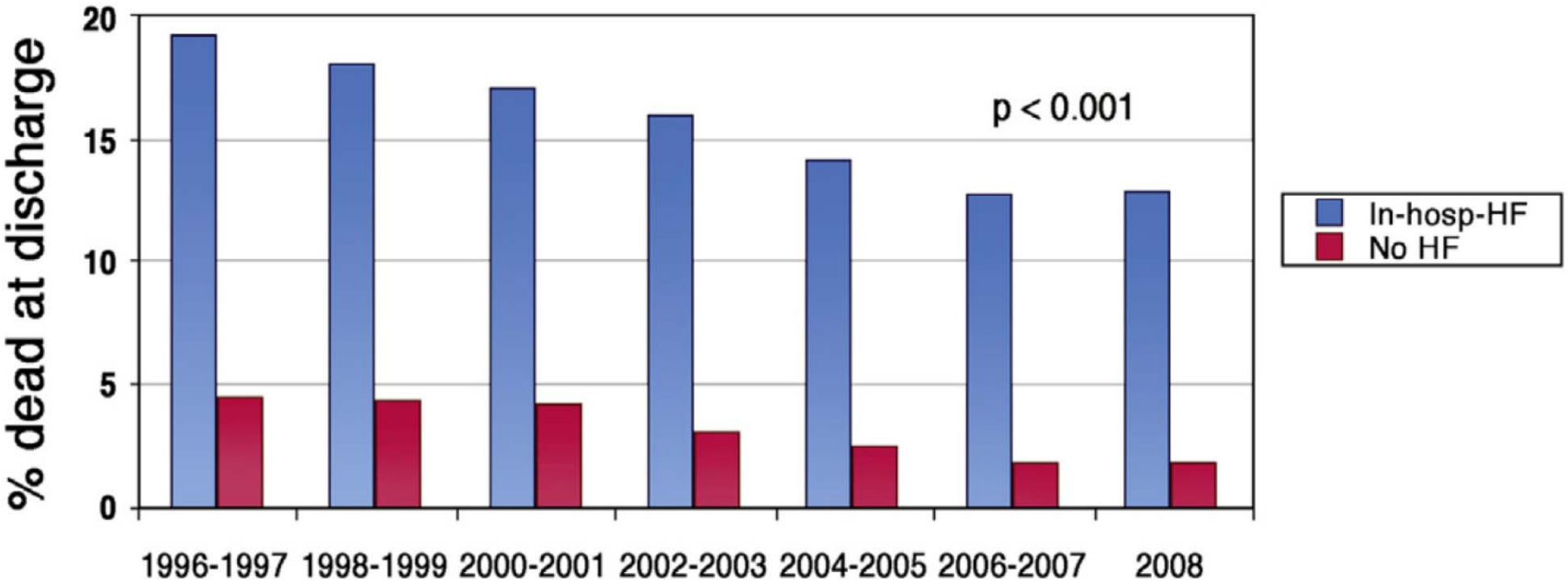


A recent analysis of >2600 patients treated with Primary Reperfusion identified that for every 5% increase in myocardial infarct size 1-year all-cause mortality increases by 19% and HF hospitalization by 20%.

Stone, Udelson et al. JACC 2016

Limiting Acute Heart Failure After Acute MI: An Important Target of Therapy

FIGURE 1 **In-Hospital Mortality Rate Trends in Patients With and Without Clinical HF During Hospitalization for an Index AMI**

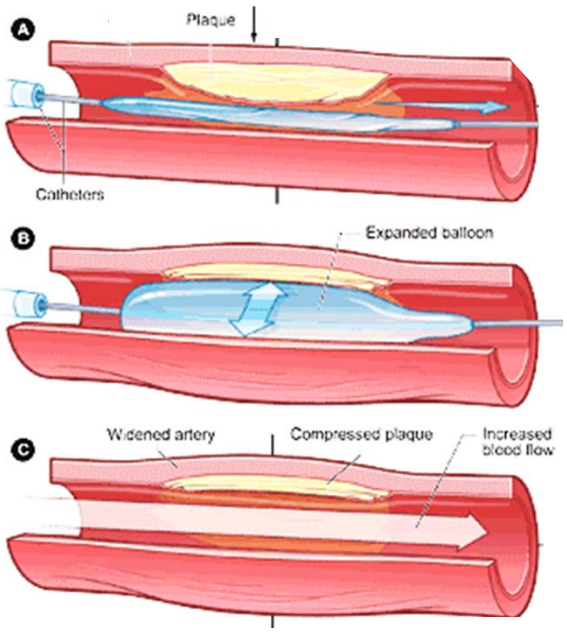


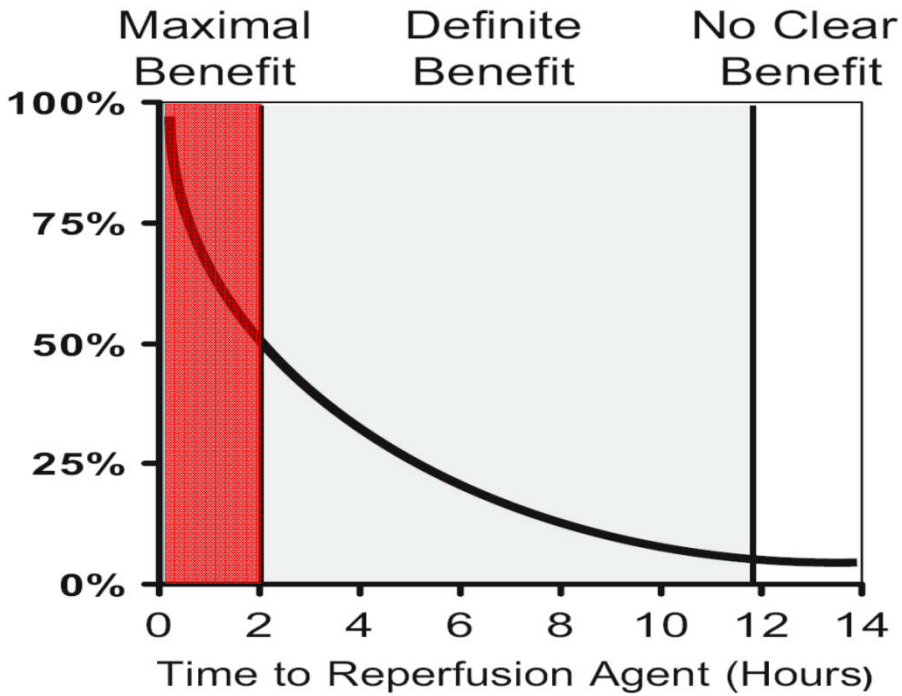
Patients who develop in-hospital heart failure after acute myocardial infarction (STEMI or NSTEMI) experience higher rates of in-hospital mortality compared to patients with AMI and without heart failure.

Desta et al. JACC HF 2015

Current Paradigm Focuses on Primary Reperfusion to Limit Myocardial Infarct Size

Door to Balloon Angioplasty (DTB)



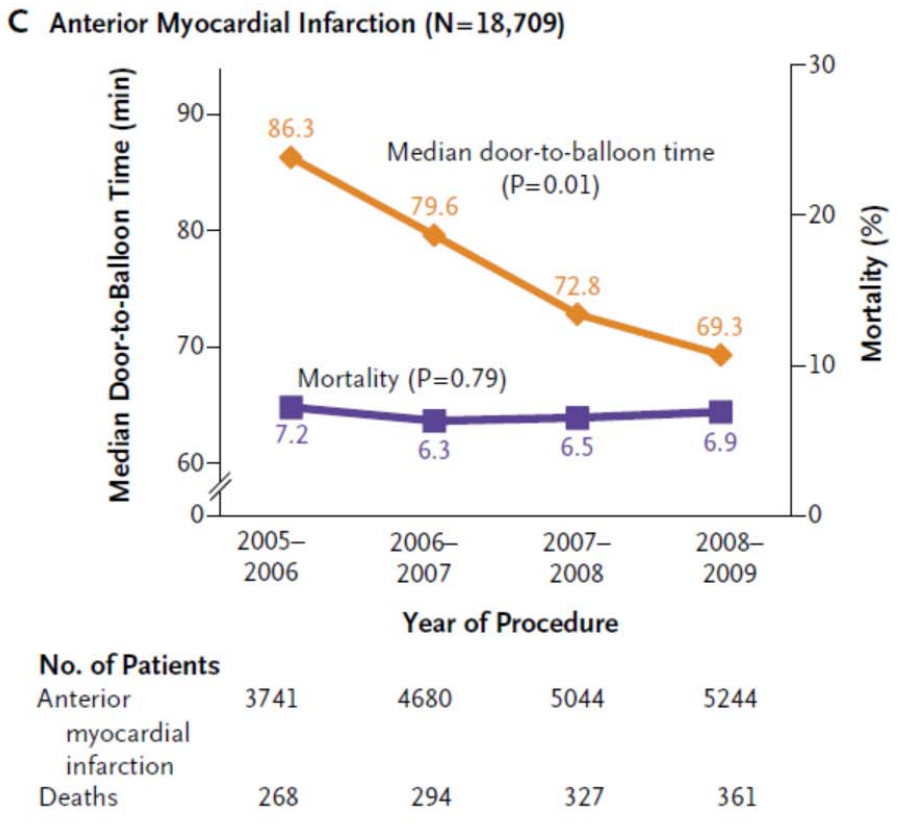


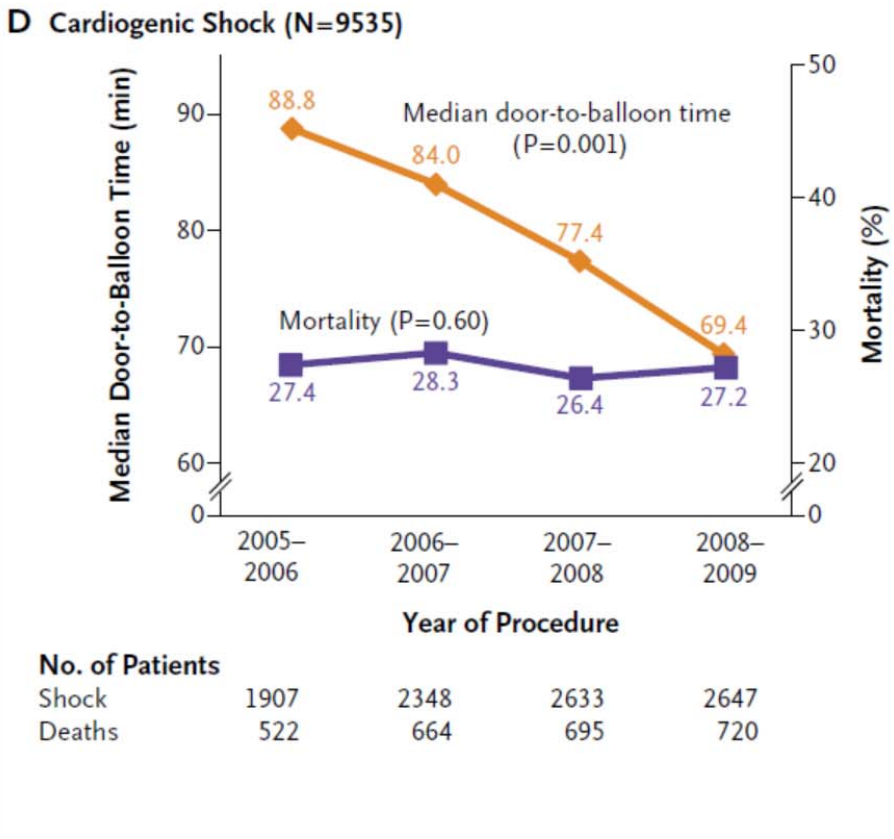
O_2 Supply ?

Myocardial Perfusion

US National Heart Attack Alert Program (NHAAP)

Current Paradigm Focuses on Primary Reperfusion to Limit Myocardial Infarct Size

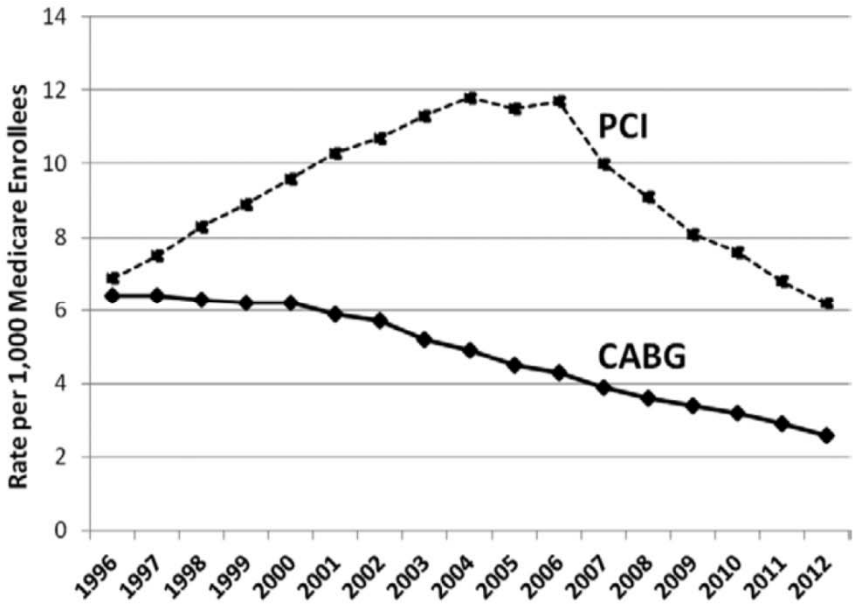


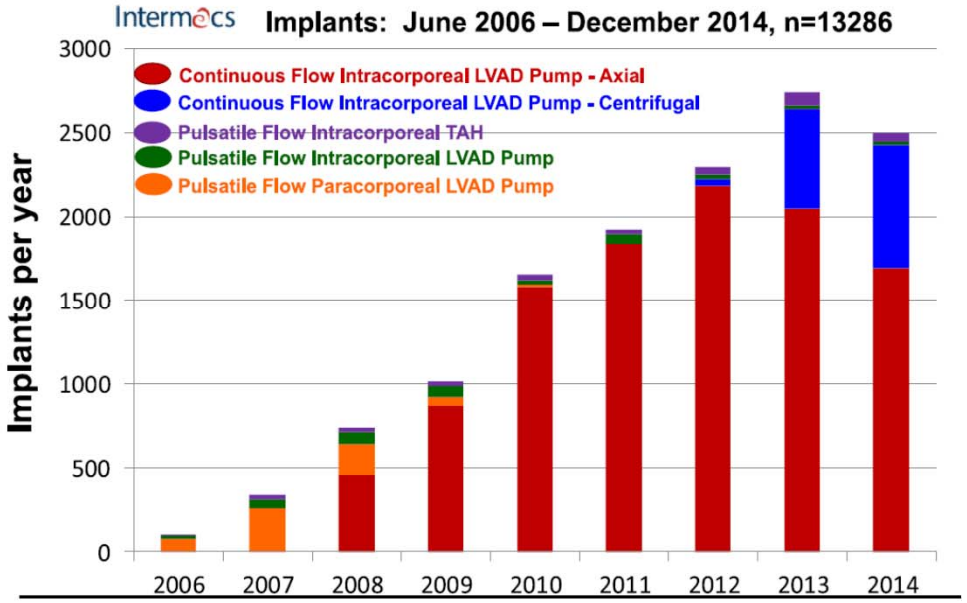


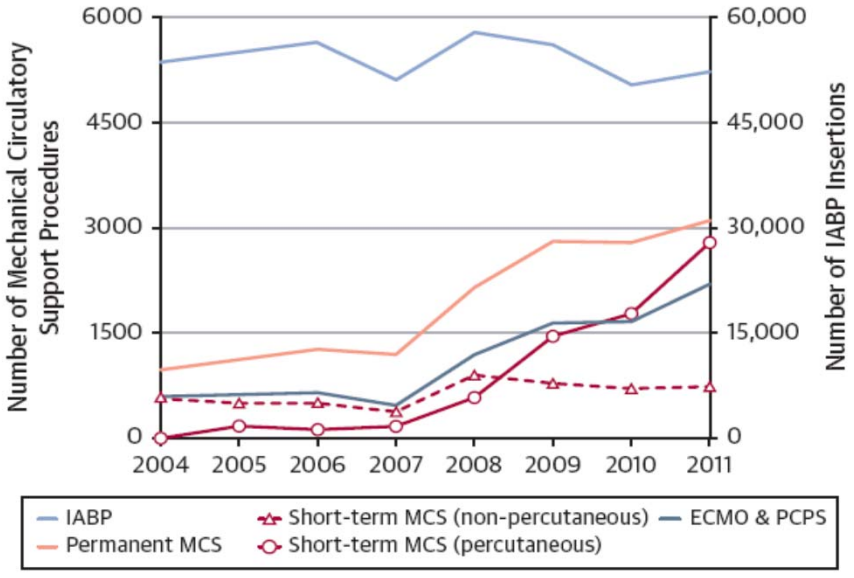
No incremental impact of DTB << 90 min on mortality.

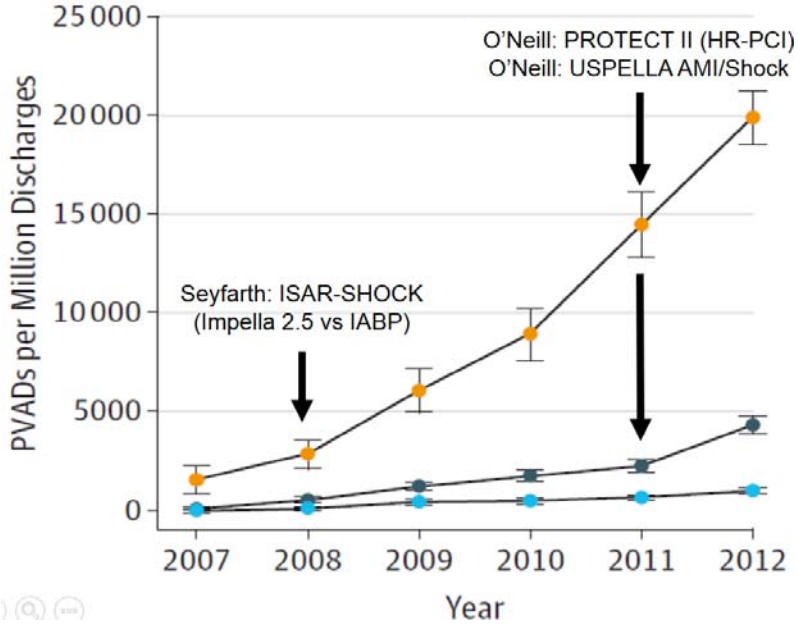
N Engl J Med 2013;369:901-9

2007: A Turning Point in Cardiovascular Medicine



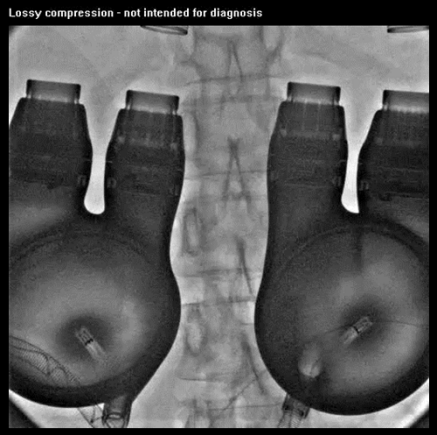




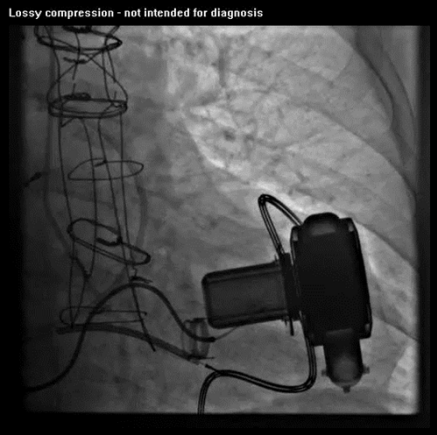


The Field of MCS: Robust with Innovation

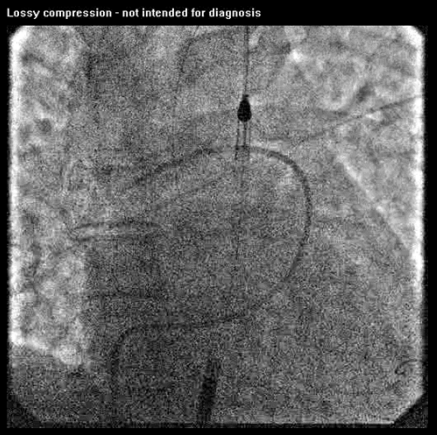
2007 → 2017



IVADs

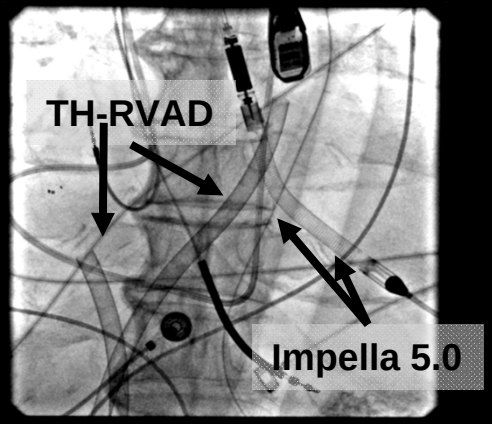


HVAD

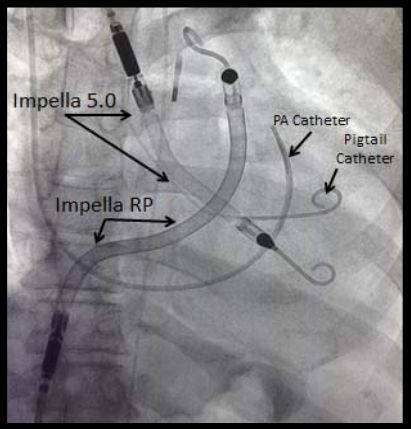


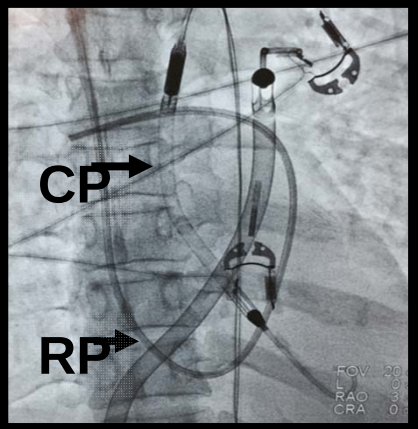
Impella CP

5.0 as a Bridge to Recovery



TH + 5.0





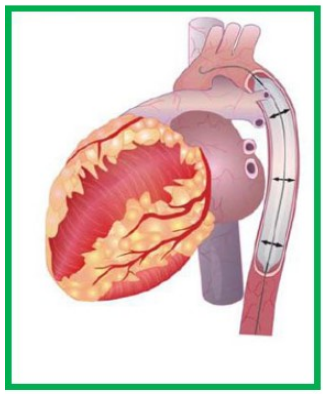
BiPellas

The Spectrum of Acute MCS Devices in 2017

Left Ventricle

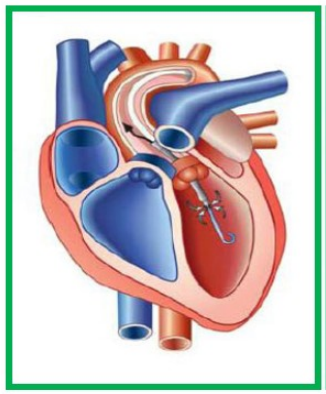
Continuous Flow Pumps

Pulsatile



IABP

Axial-Flow



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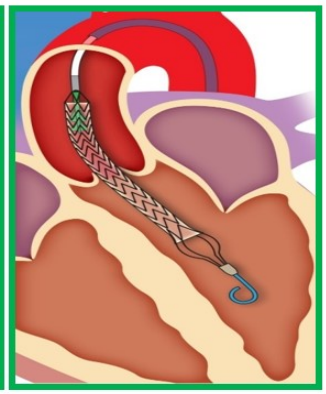
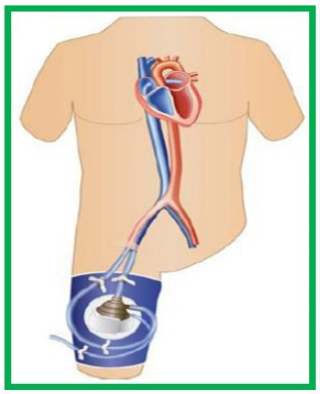
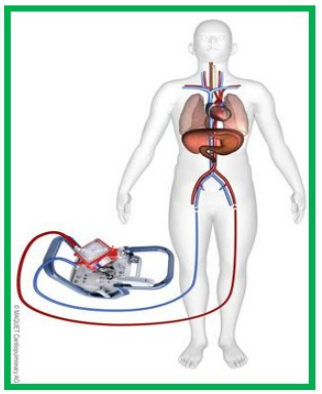


PHP *

Centrifugal Flow



TandemHeart

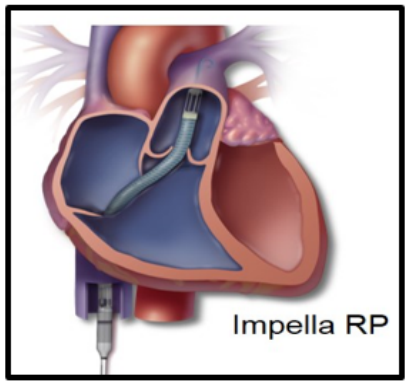


VA-ECMO

Intracorporeal | **Extracorporeal**

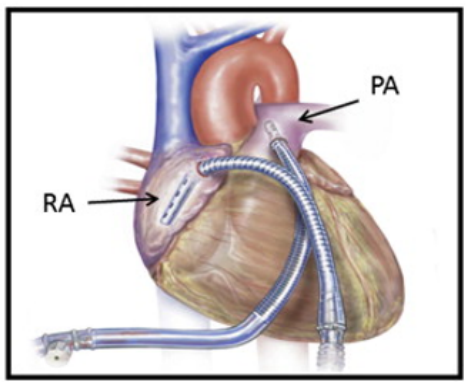
Right Ventricle

Axial Flow | Centrifugal Flow

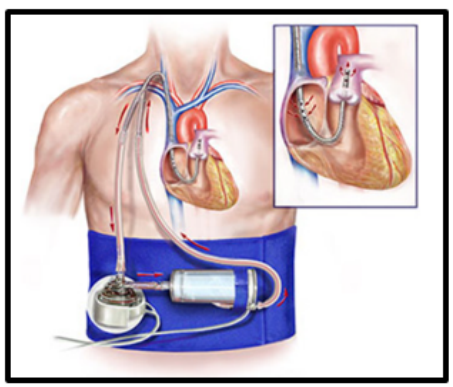


Impella RP

VA-ECMO

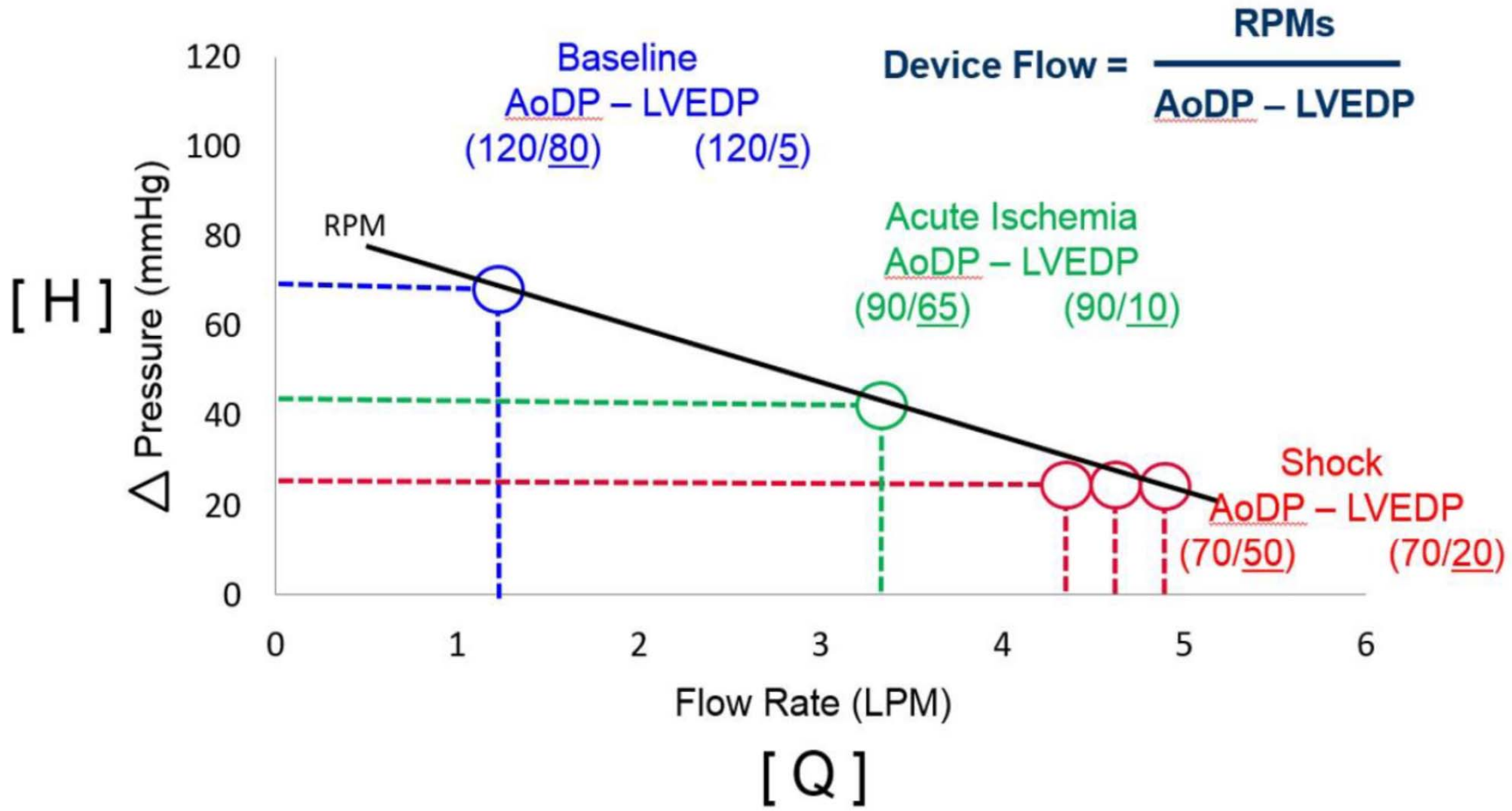


Tandem pRVAD



Protek Oxy-RVAD

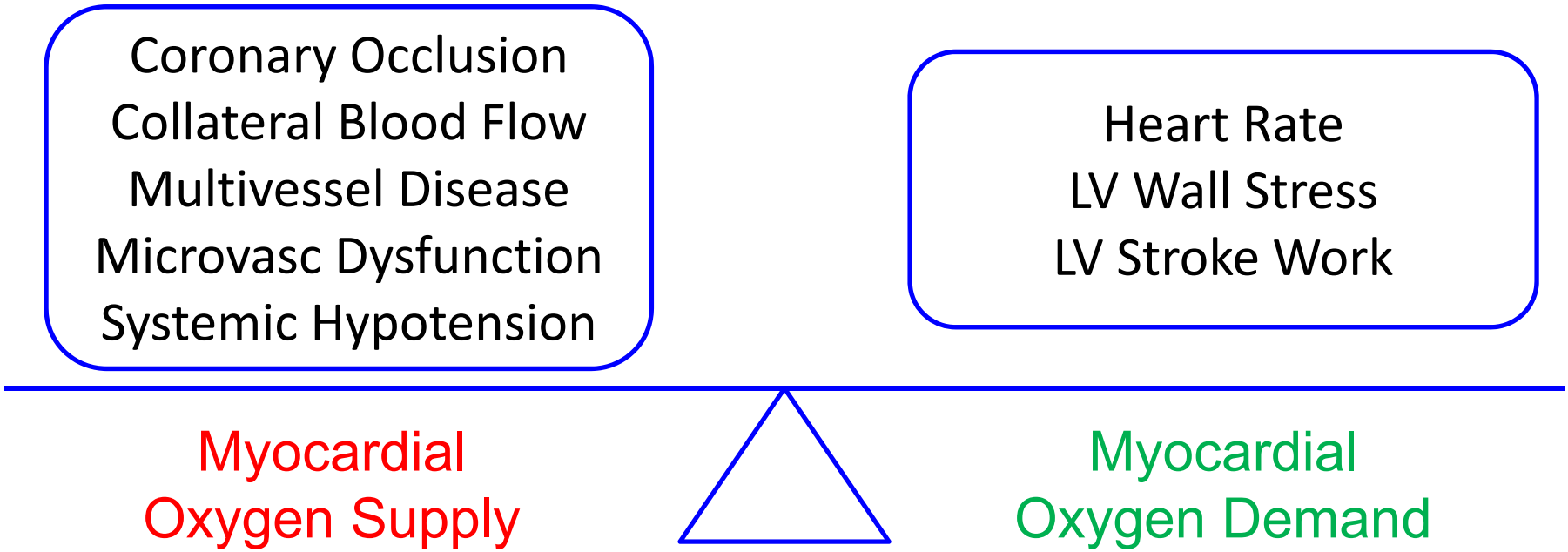
Hemodynamic Principles of Rotary Flow Pumps
Higher Flow with Lower Transvalvular Pressure Gradient



The more dysfunctional the ventricle,
the *more functional* a CF-AMCS device becomes.

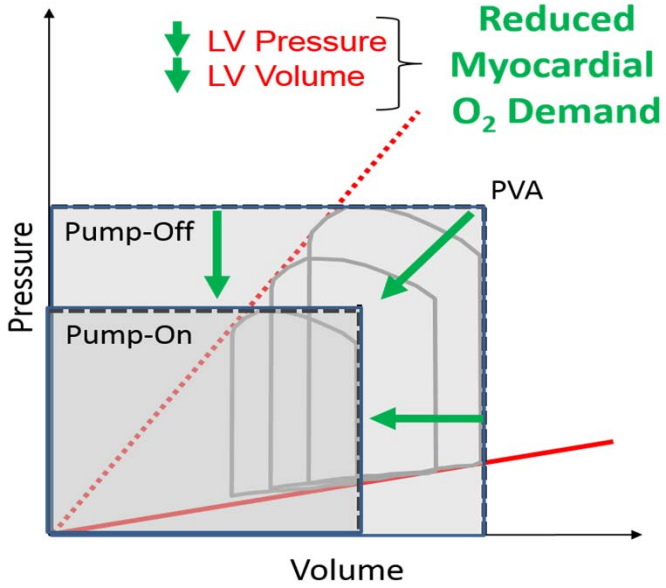
Kapur NK. CathSAP V. 2016

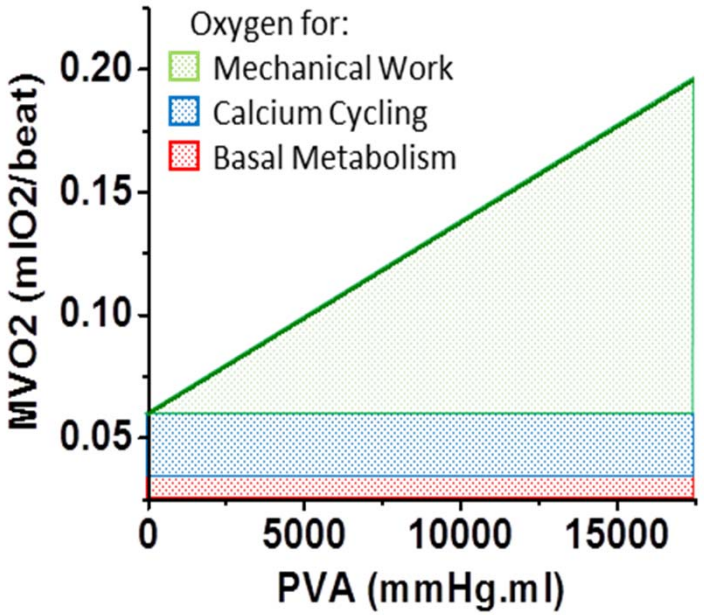
Novel Cardioprotective Paradigms To Limit Myocardial Infarct Size

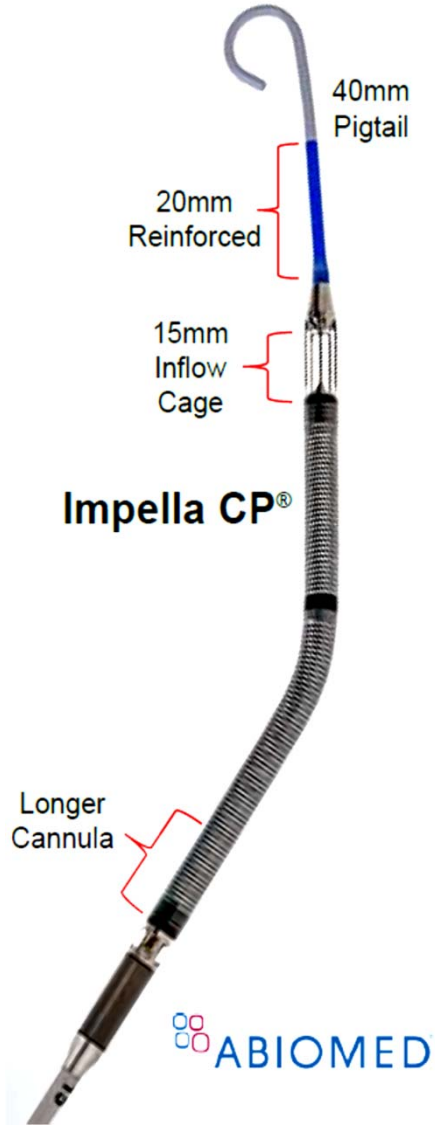


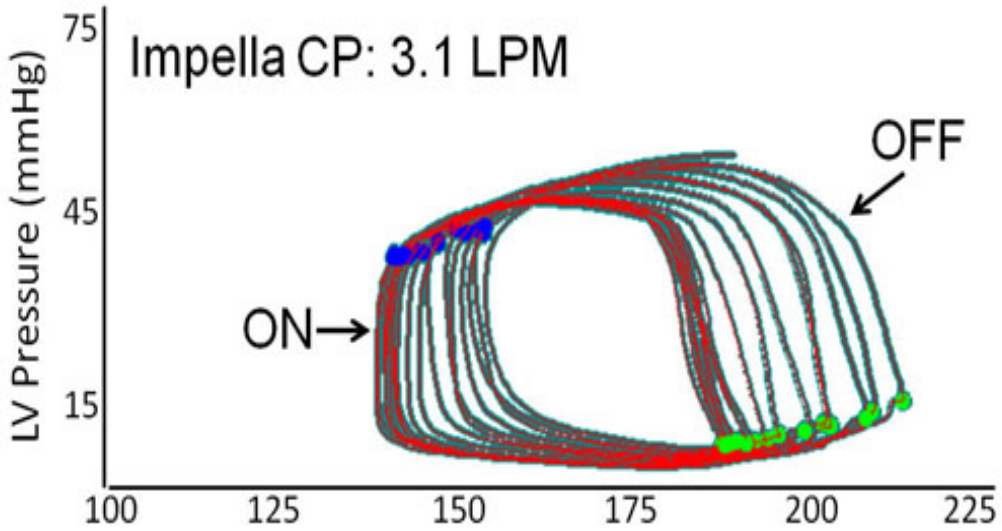
Can We Limit Myocardial Ischemia by First Limiting Oxygen Demand, then Restoring Oxygen Supply?

Reducing Myocardial Oxygen Demand with a Micro-Axial Flow Catheter



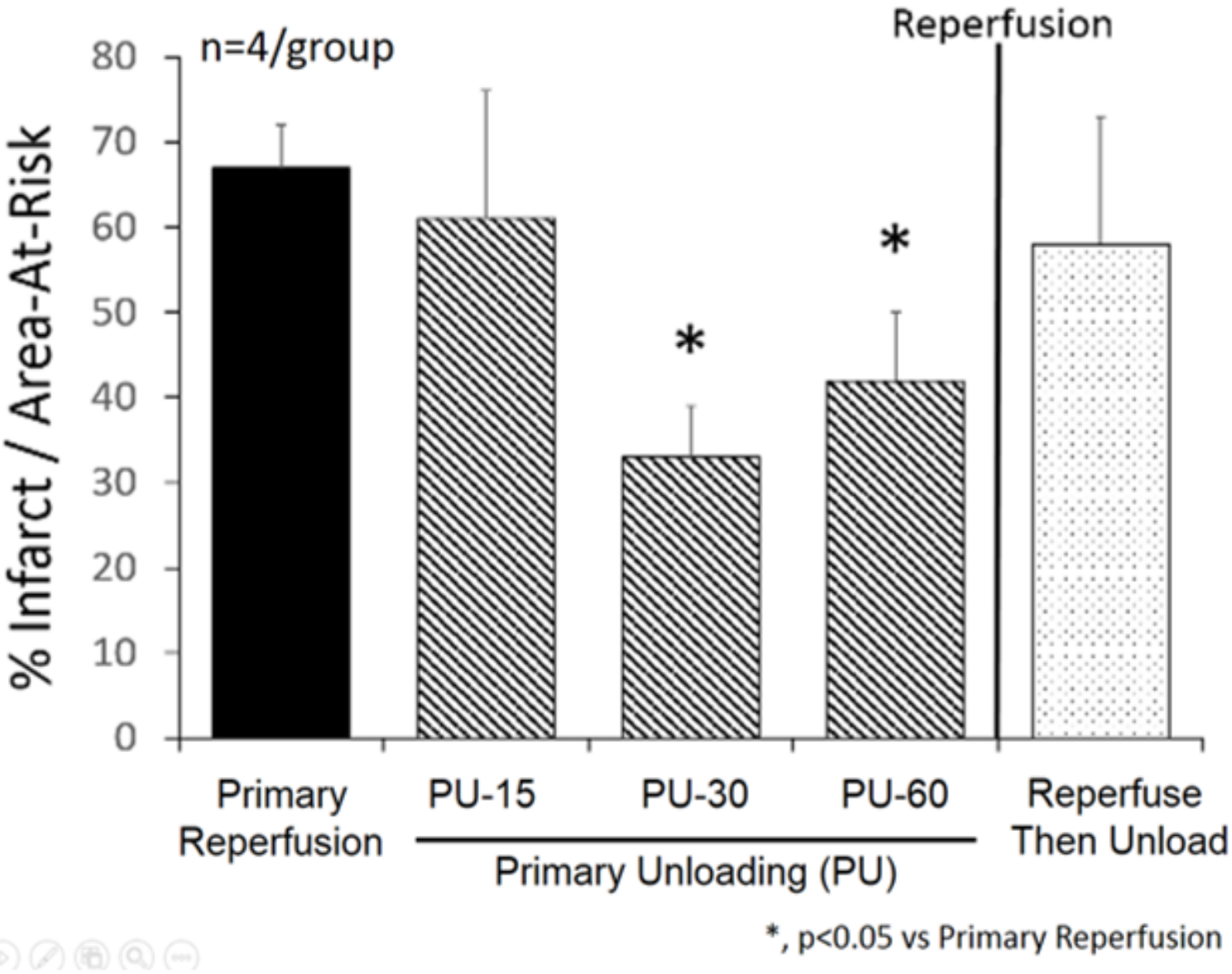






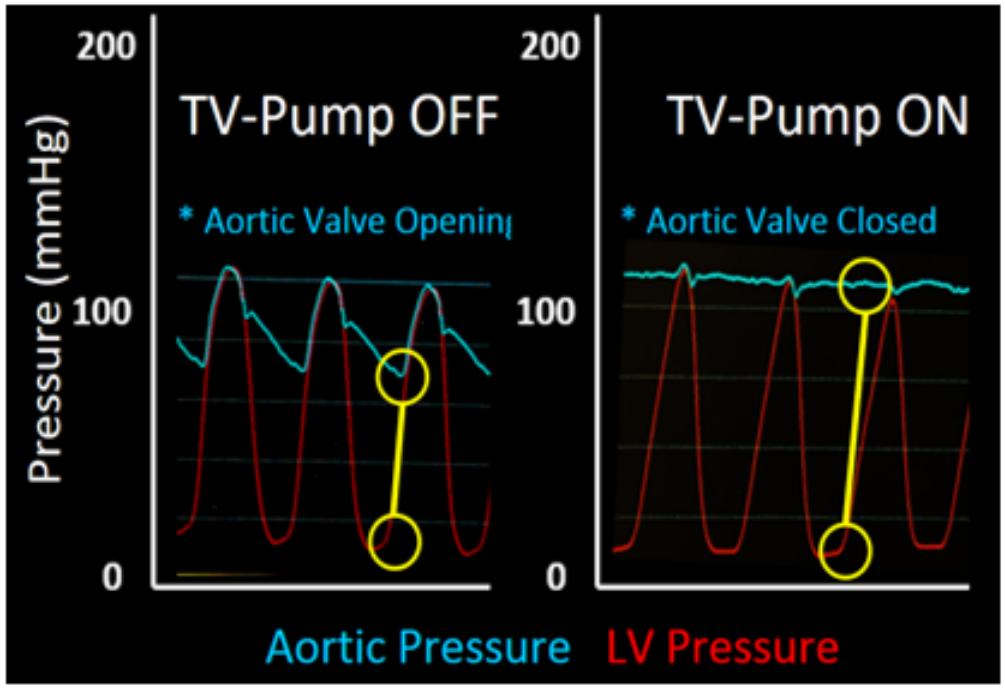
Kapur NK et al. ASAIO 2013

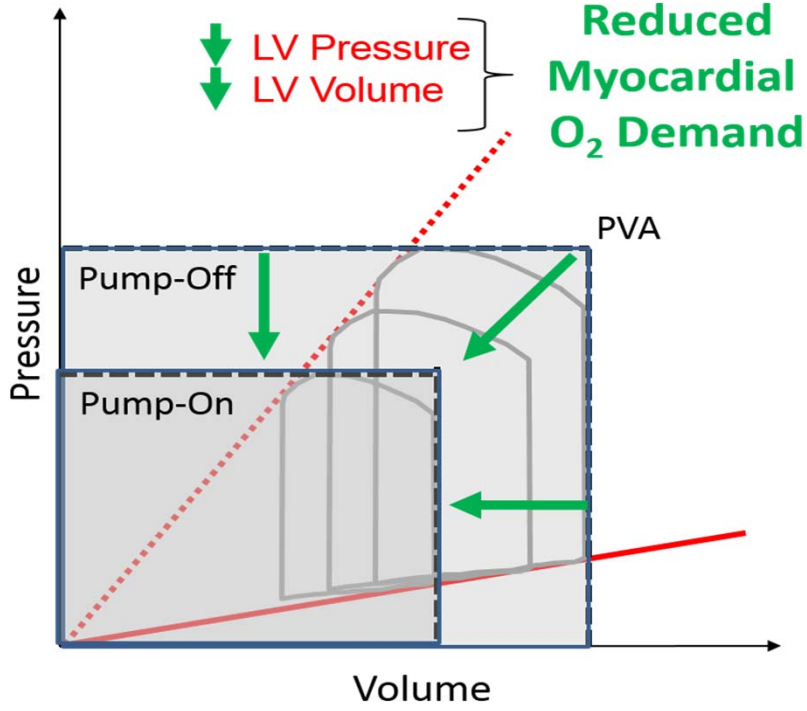
The Kinetics of Primary Unloading



Kapur NK et al. AHA 2016

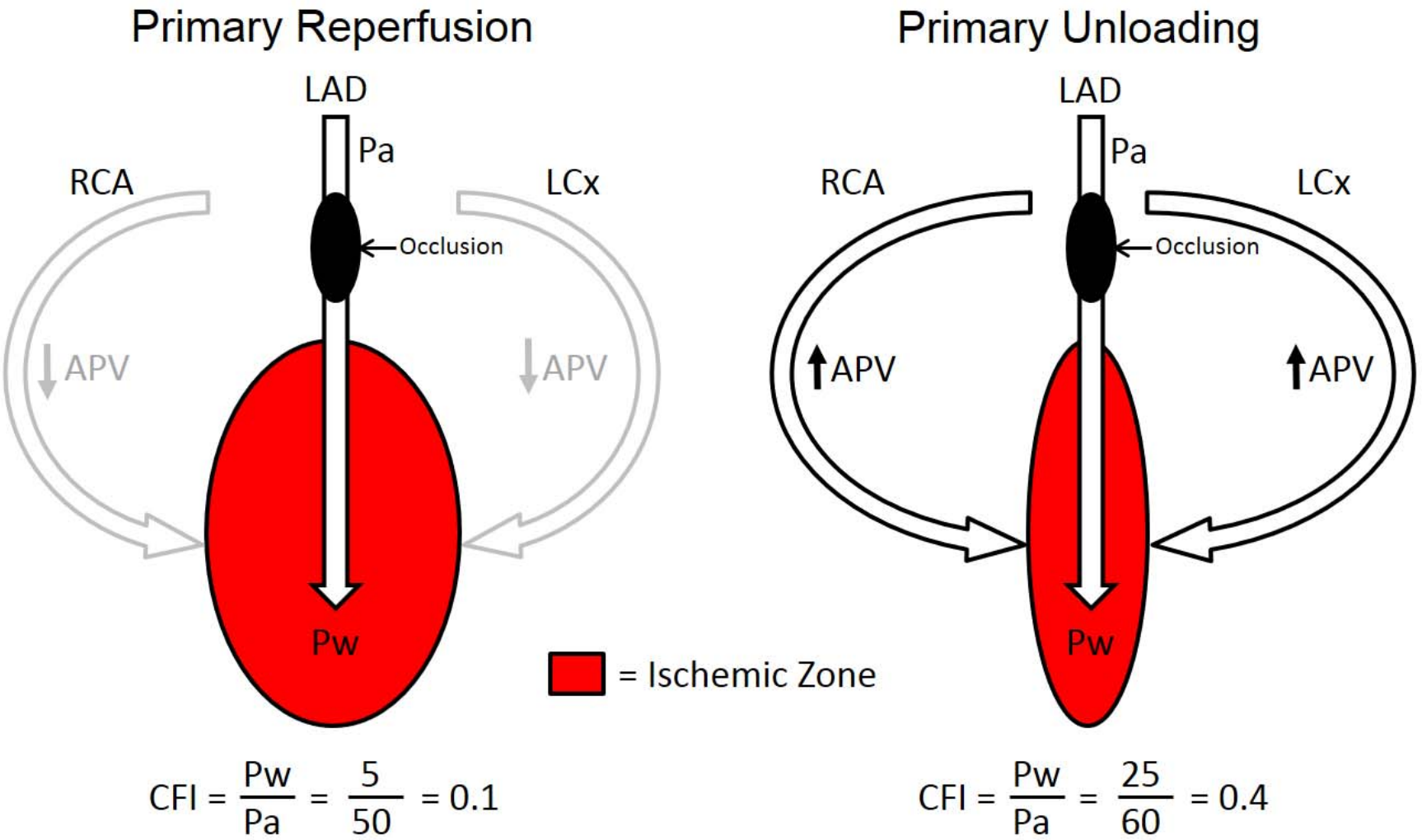
Primary Unloading: Mechanism 1
Reduced LV Work and Myocardial Oxygen Demand





Kapur NK et al. AHA 2016

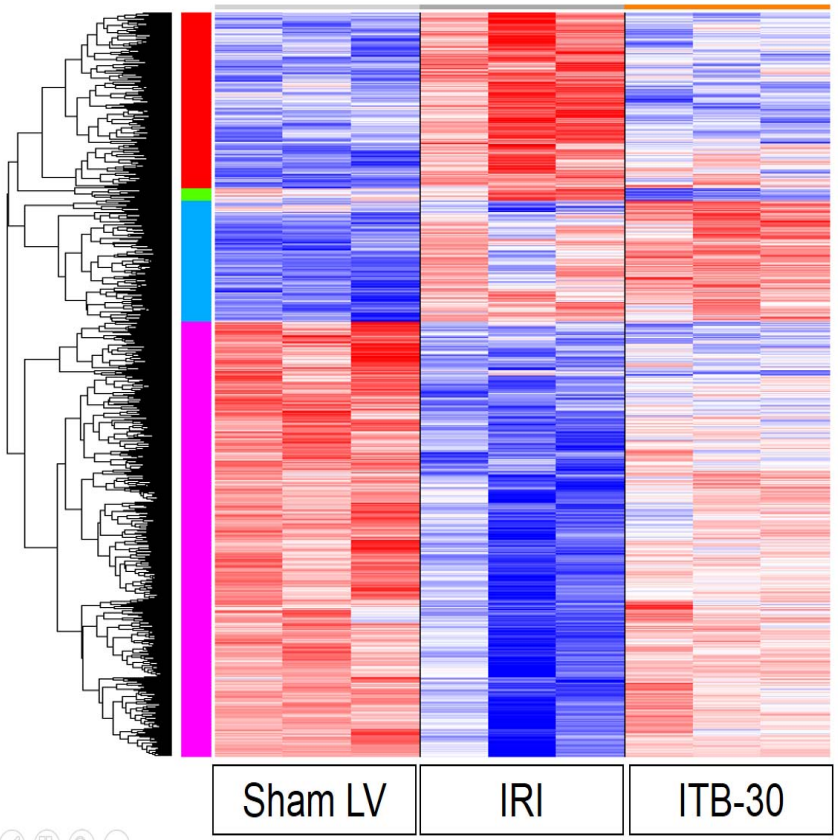
Primary Unloading: Mechanism 2
Functional Reperfusion of the Area at Risk

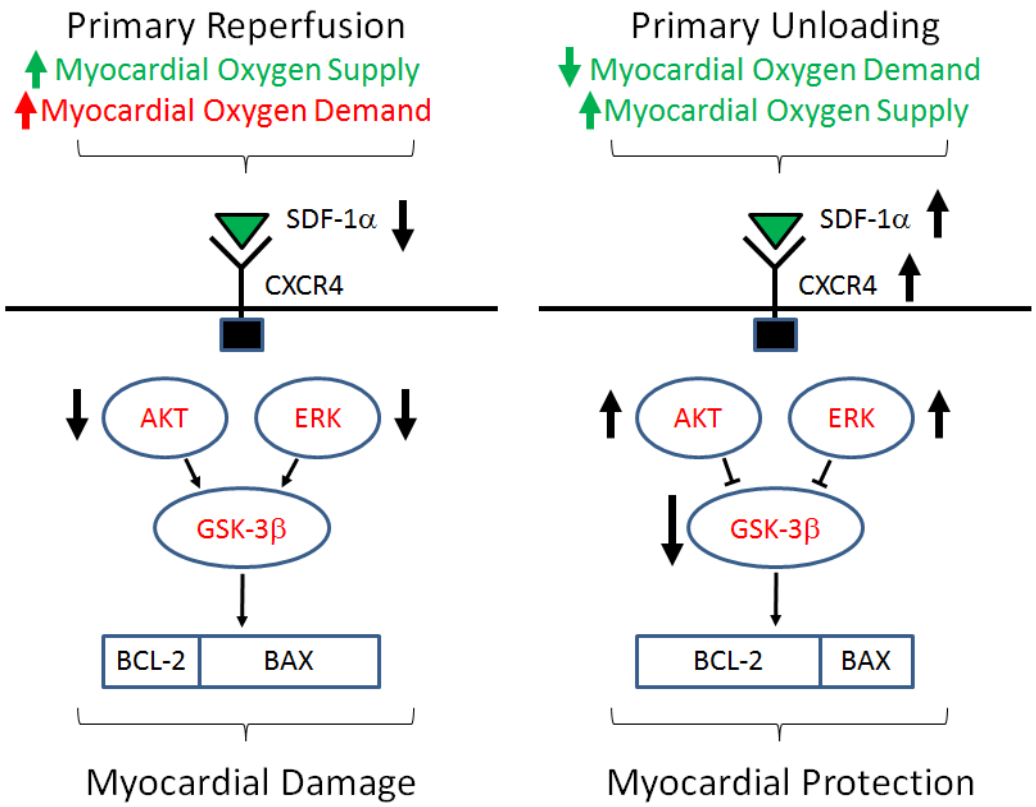


Kapur NK et al. AHA 2016

Primary Unloading: Mechanism 3

Mechanical Induction of a Global Shift in Myocardial Biology Favoring Cardioprotective Signaling

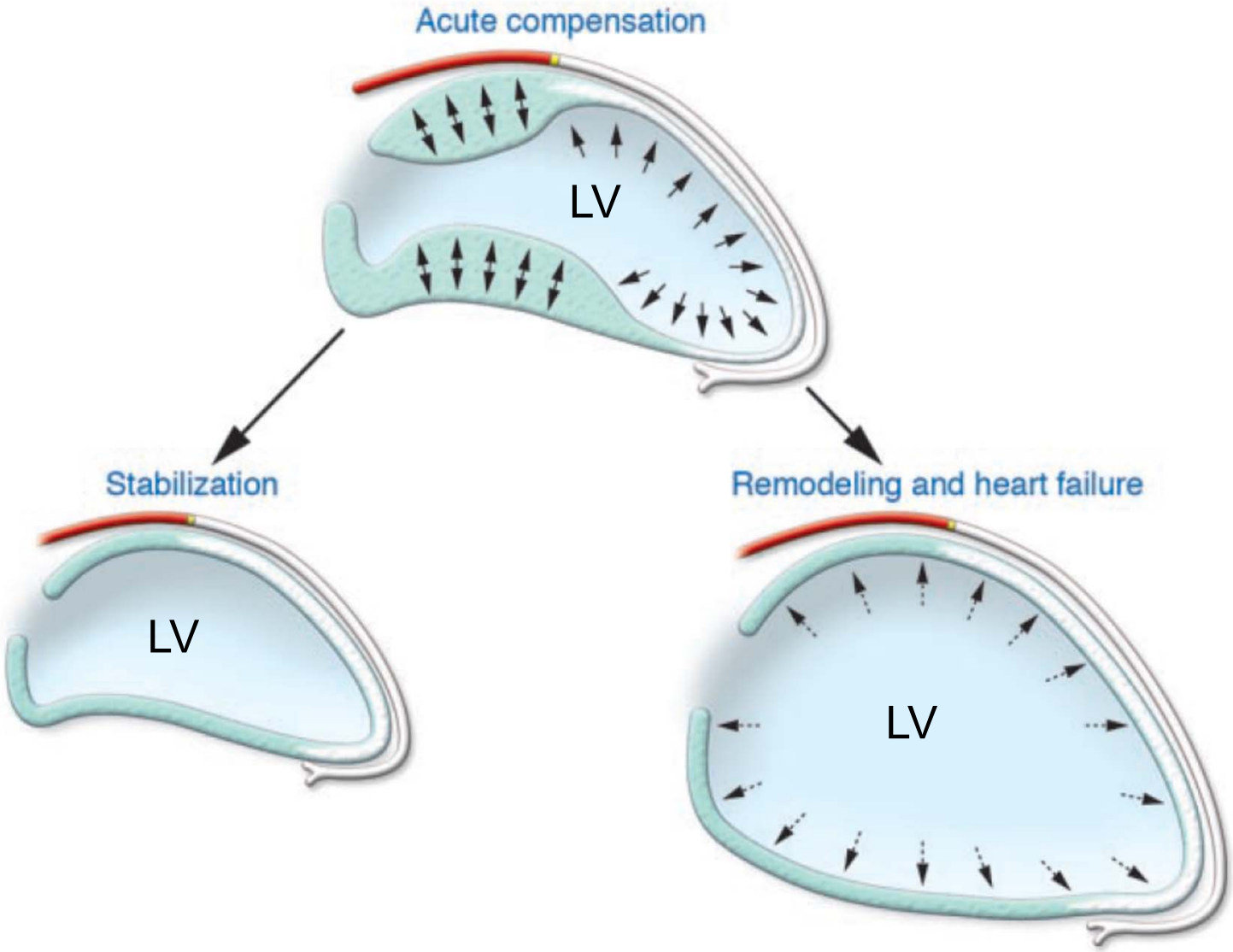




Kapur NK et al. AHA 2016

Kapur NK et al. JACC HF 2015

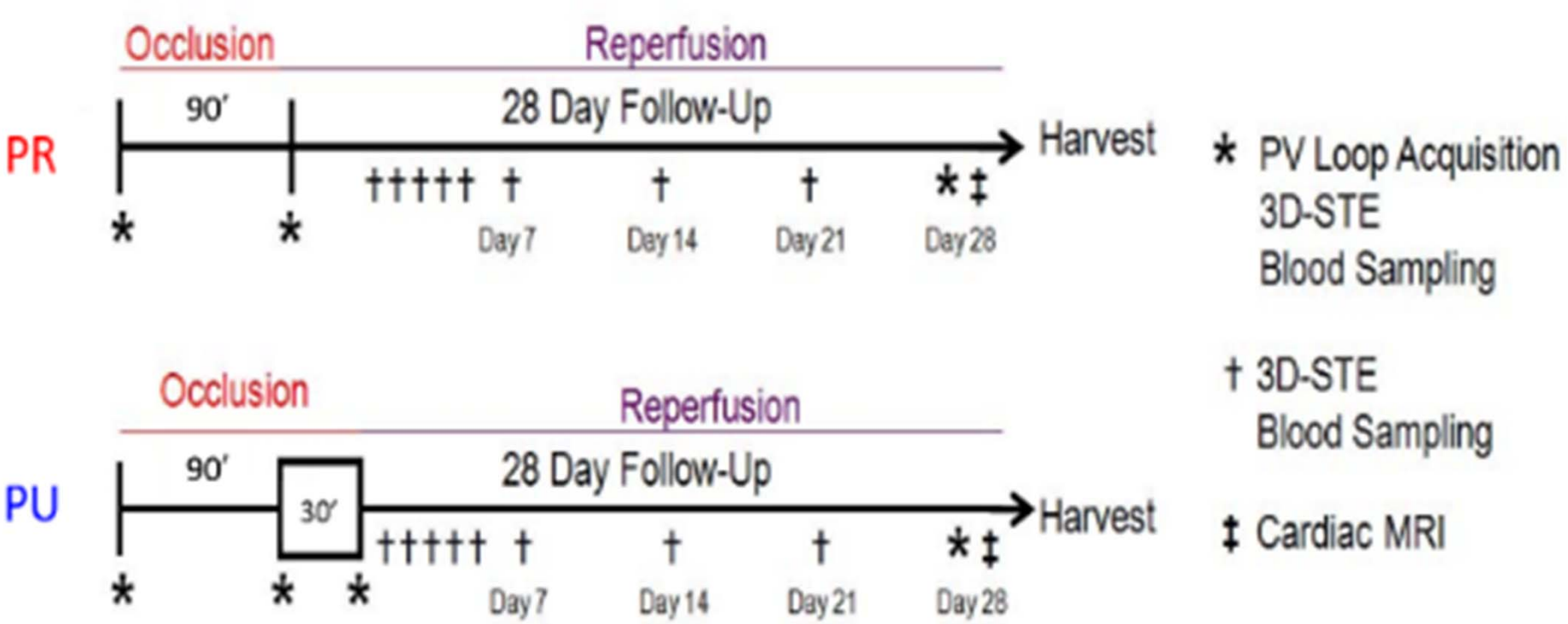
The Holy Grail: Does Primary Unloading Reduce Ischemic Heart Failure?



Whelan and Kitsis J(

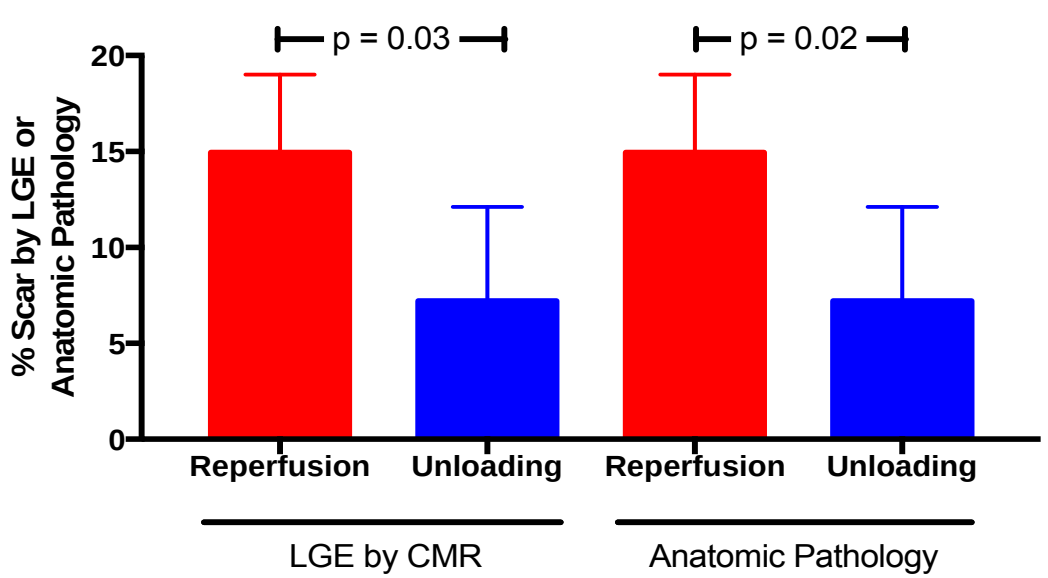
The Door to Unload Preclinical Trial

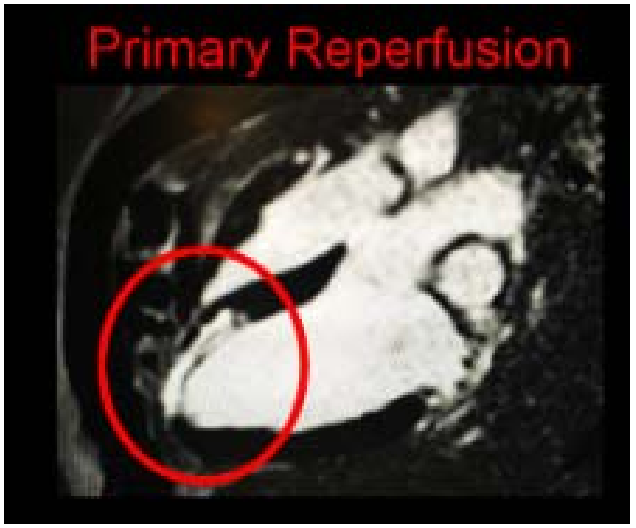
Hypothesis: Compared to Primary Reperfusion, Primary Unloading reduces LV scar 30 days after acute MI

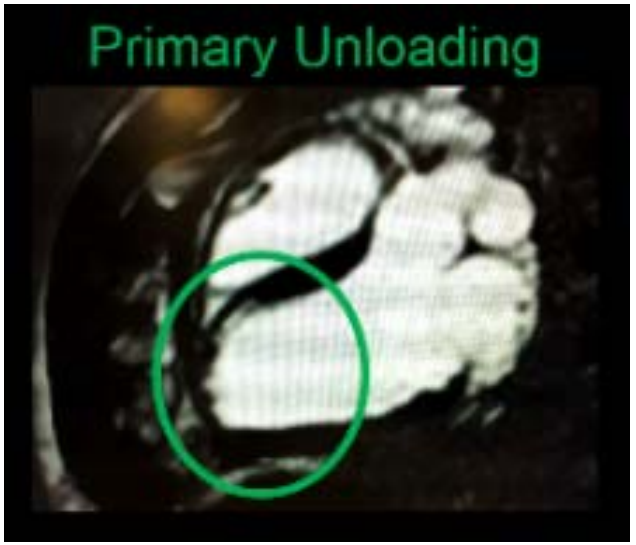


Kapur NK et al. TCT 2017

Primary Unloading Reduces LV Scar and Preserves Cardiac Output 30 days after Acute MI



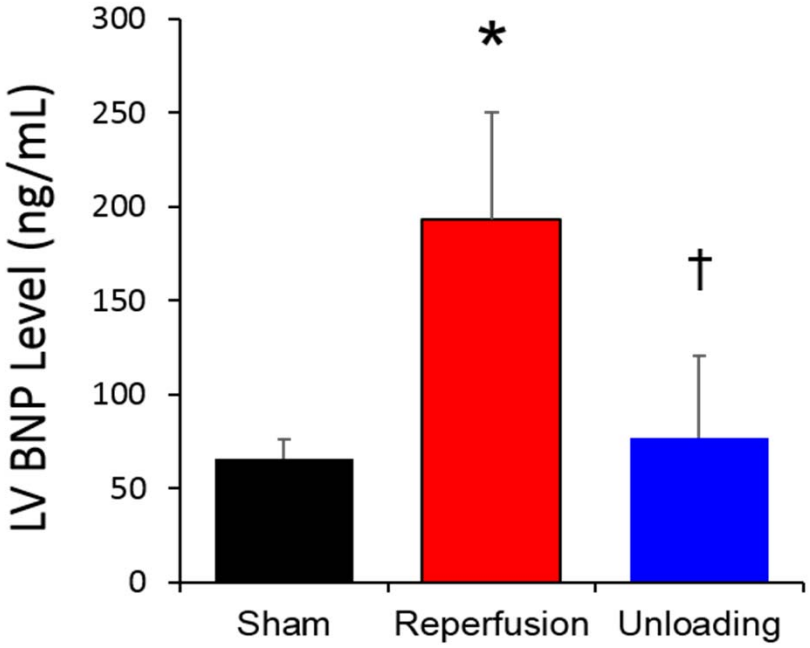


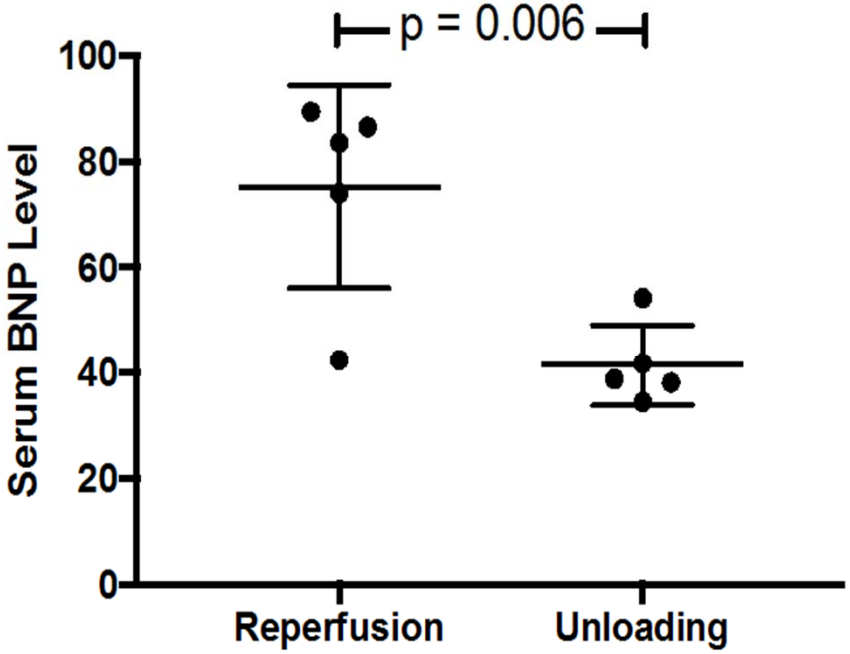


	Primary Reperfusion	Primary Unloading	p-value
Heart Rate	63±8	73±11	NS
Stroke Volume	39±5	54±7	0.008
Cardiac Output	2.5±0.2	3.9±0.6	0.002
LV Stroke Work	2168±273	3075±339	0.003
LV-EDV (CMR)	152±29	142±14	NS
LV-ESV (CMR)	86±26	74±6	NS

Kapur NK et al. TCT 2017

Primary Unloading Reduces Tissue Expression and Circulating Levels of Brain Natriuretic Peptide 30 days after Acute MI





Kapur NK et al. TCT 2017

It's a New Day for Acute MI Therapy

Door to Unloading Safety & Feasibility Study† approved

ABIOMED™

ABIOMED RECEIVES FDA IDE APPROVAL FOR INITIATION OF DOOR TO UNLOADING (DTU) PROSPECTIVE FEASIBILITY STUDY

Study Evaluates the Safety and Feasibility of Unloading of the Left Ventricle with Impella CP® in STEMI Patients, without Cardiogenic Shock

DANVERS, MA – October 26, 2016 – Abiomed, Inc. (NASDAQ: ABMD), a leading provider of breakthrough heart support and recovery technologies, announced today the U.S. Food and Drug Administration (FDA) approval of a prospective feasibility study to evaluate the use of the Impella CP heart pump for unloading of the left ventricle prior to primary percutaneous coronary intervention (PCI) in patients presenting with ST segment elevation myocardial infarction (STEMI), without cardiogenic shock. This trial will focus on feasibility and safety, and lay the groundwork for a future trial, designed to measure the impact that unloading may have on infarct size related to reperfusion injury – an acceleration of myocardial damage at the time of revascularization - in STEMI patients.

Study Steering Committee:

Navin K. Kapur, MD

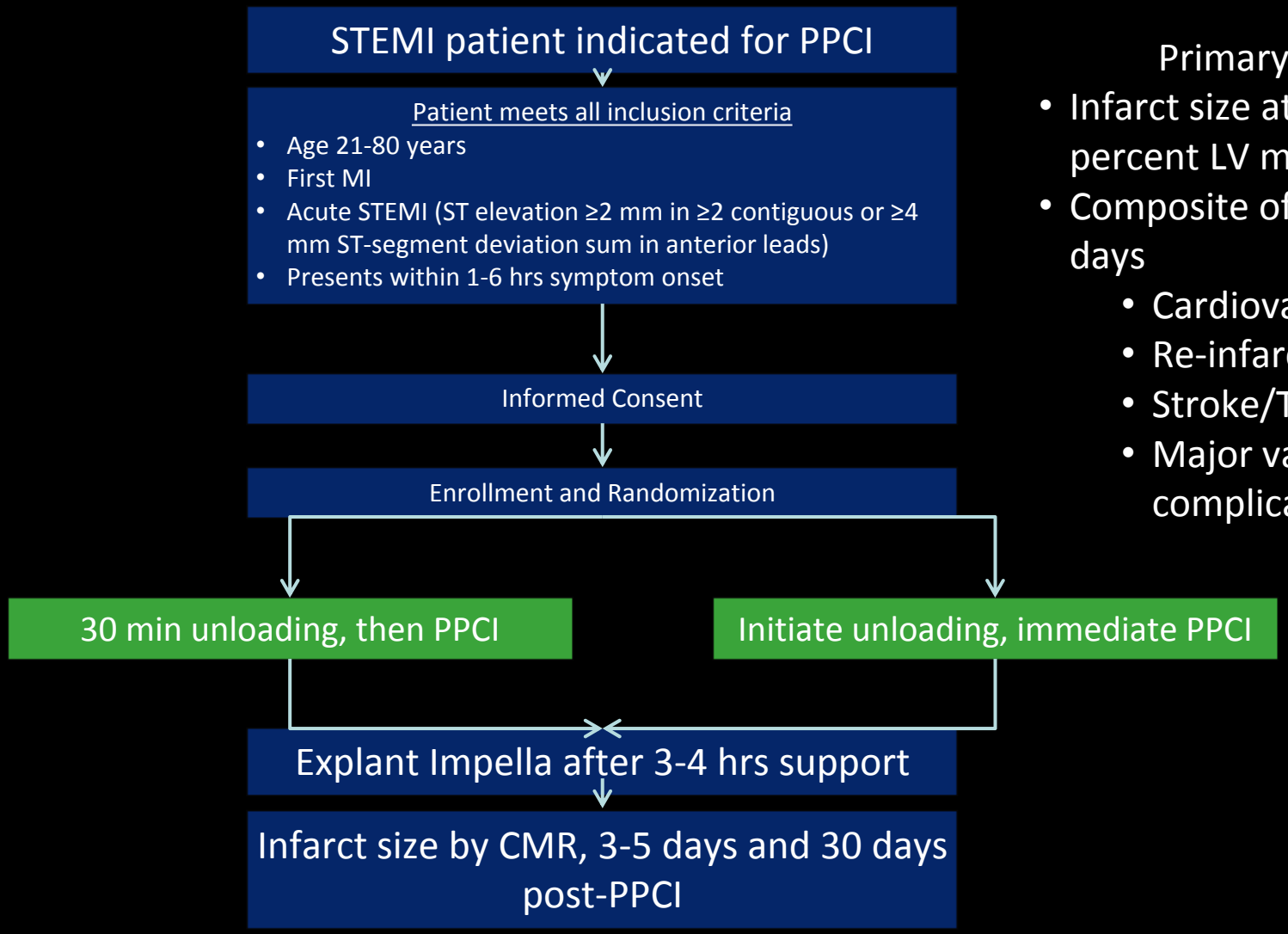
William W. O'Neill, MD

Jeffrey W. Moses, MD

Can we reduce the burden of ischemic heart failure after a heart attack?
What are the cardioprotective mechanisms underlying LV Unloading?

† *FDA granted approval of IDE application*

DTU Safety & Feasibility Study



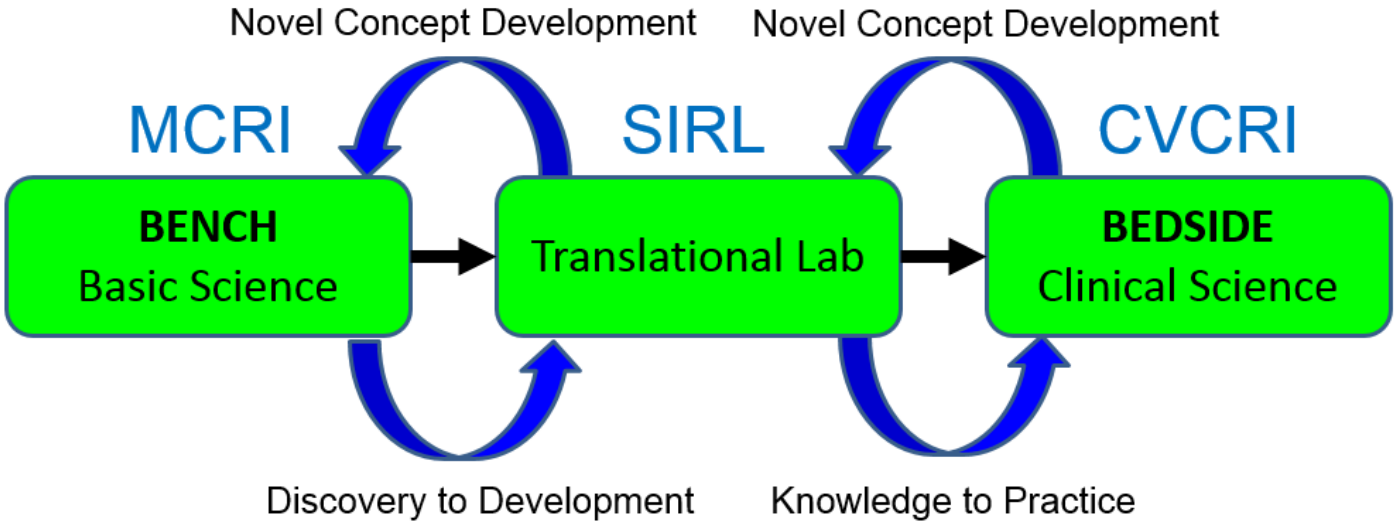
Primary Endpoints

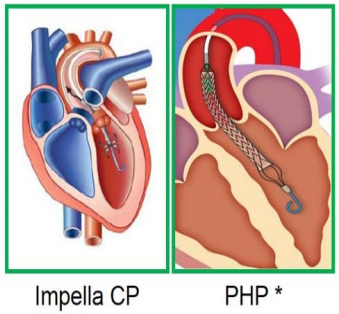
- Infarct size at 30 days as percent LV mass, by CMR
- Composite of MACCE at 30 days
  - Cardiovascular mortality
  - Re-infarction
  - Stroke/TIA
  - Major vascular complication

† *FDA granted approval of IDE application*

The Tufts Cardiovascular Center for Research and Innovation

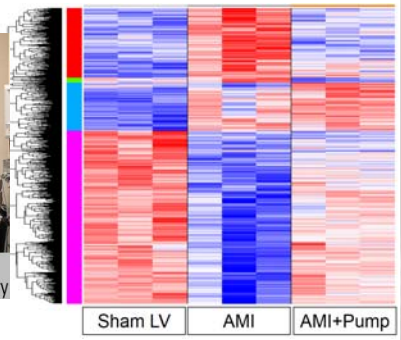
The CVCRI Innovation Engine



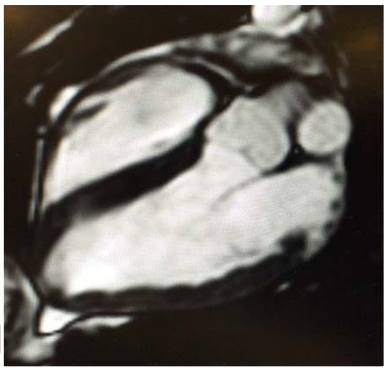


Clinical Excellence

Preclinical Testing



Fundamental Discoveries



Preclinical Trials

Novel Clinical Trials

Acknowledgements

Kapur Lab Members

- Michele Esposito
- Xiaoying Qiao
- Vikram Paruchuri
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- Shiva Annamalai
- Yali Zhang
- Peter Natov
- Kevin Morine
- Emily Mackey
- Lyanne Buitten

Collaborators:

- Richard Karas
- Noam Josephy
- Daniel Burkhoff
- Divaka Perrara
- Natalia Briceno
- William O'Neill

NIH National Heart, Lung, and Blood Institute

American Heart Association | American Stroke Association

life is why™

HFSA HEART FAILURE SOCIETY OF AMERICA

Herbert J. Levine Foundation Tufts Medical Center

ABIOMED

Recovering hearts. Saving lives.

Thank you

nkapur@tuftsmedicalcenter.org

To Learn More about Acute MCS & Hemodynamics

The Acute MCS Working Group

TEACH TRAINING & EDUCATION IN ADVANCED CARDIOVASCULAR HEMODYNAMICS

CHIP: Hemodynamic Support and Complex PCI

Tufts Medical Center
The CardioVascular Center

Interventional Heart Failure

ACURE

August 24-25, 2017: Barcelona, Spain

Device Therapies for Heart Failure
December 15-16 2017
Berlin, Germany

D-HF

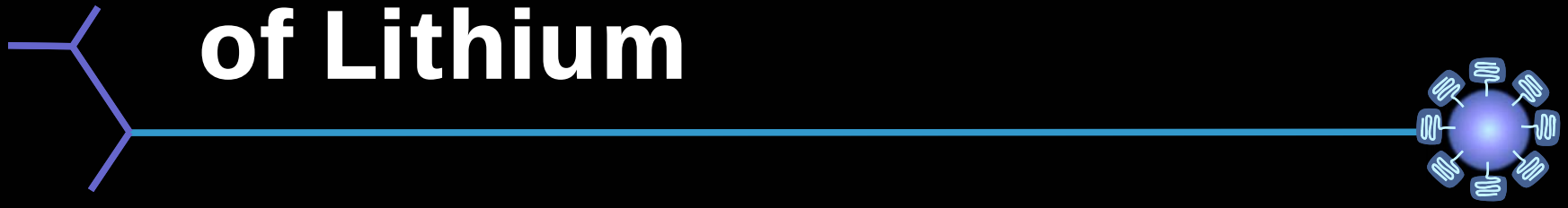
In Vivo Nanosensors and Imaging Technologies

Heather Clark, PhD

Professor
College of Engineering, College of Science
Northeastern University

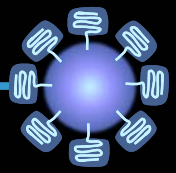
Tufts | CTSI
Tufts Clinical and Translational Science Institute

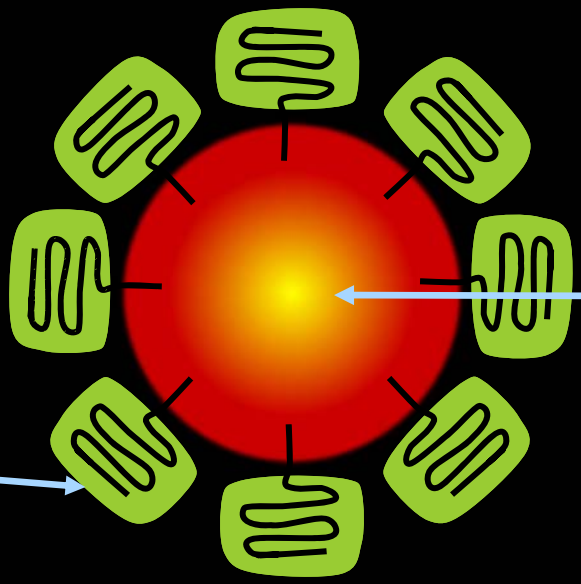
Building an Imaging Toolbox: *In Vivo* Pharmacokinetics of Lithium



Heather A. Clark
Department of Bioengineering
Department of Chemistry and Chemical Biology
Northeastern University

Nano-tools for bioanalysis





Hydrophobic core in which to incorporate:

- Dyes
- Chemistries
- Quantum dots
- Recognition molecules
- Etc.

Biocompatible outer layer (PEG)

Goal:	A new toolbox for biological analysis
Advantage:	Modular design leads to rapid development cycle
Approach:	Design, fabricate and characterize novel nanosensors; team with experts to apply the nanosensors to biological problems

Our projects

Nanosensor design: novel biomarker detection, new materials

Cellular Imaging

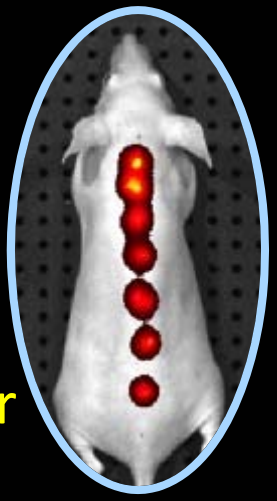
- Cellular imaging – the search for "hotspots" and "waves"
- Neurotransmitter release

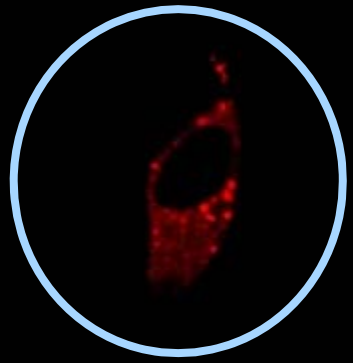
Development of the Nano Clinical Analyzer

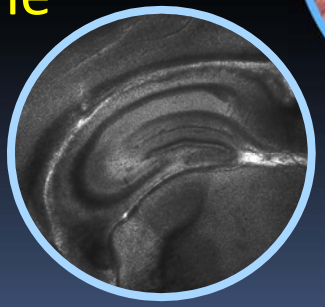
- nanosensors for physiological monitoring and personalized medicine

Deep tissue Imaging

- Photacoustic Imaging
- MRI



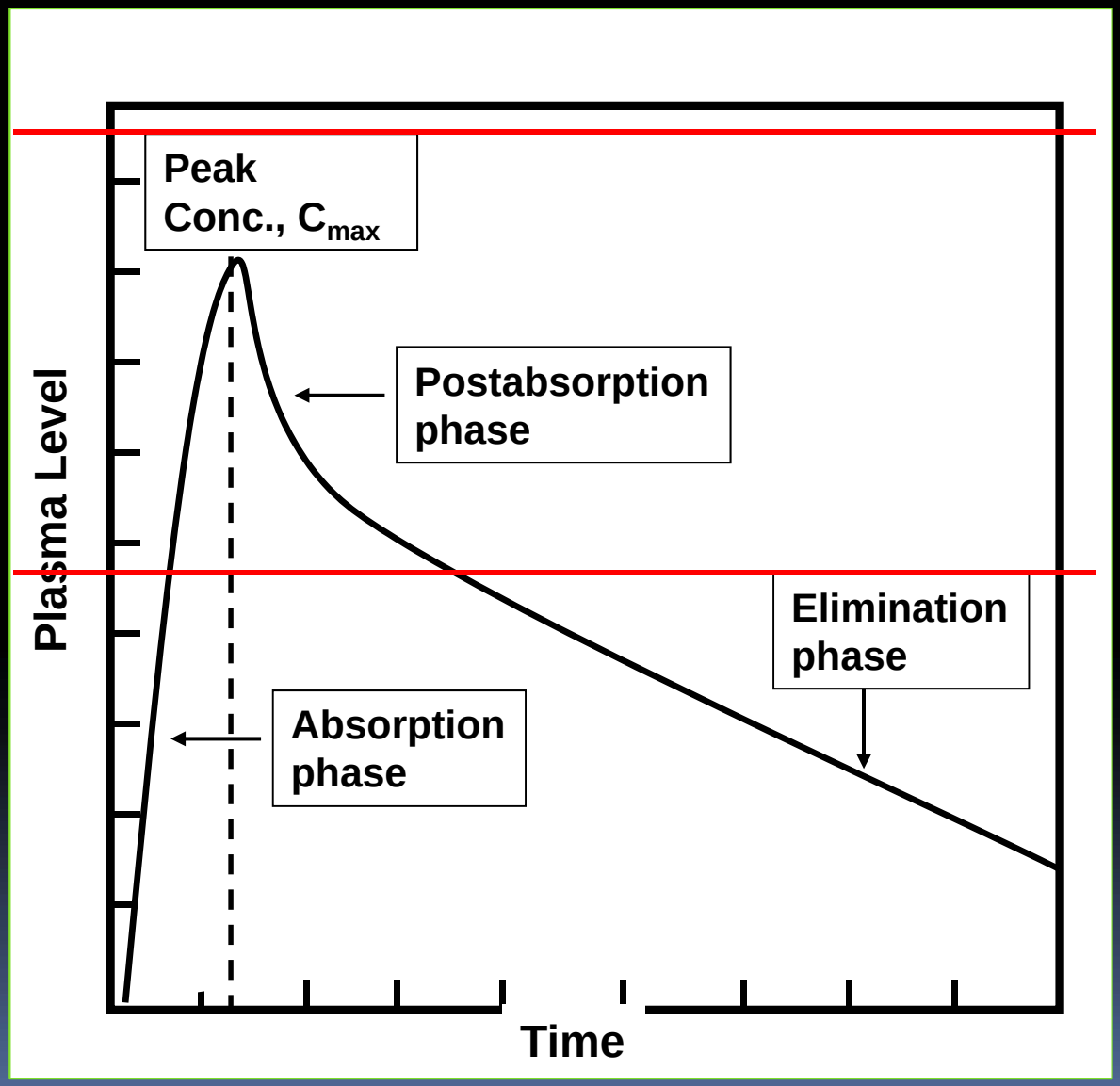




Clinical Analyzers

Current clinical analyzers:
are not continuous
Require a blood draw
Labor intensive
Require an office visit

Pharmacokinetics of Therapeutic Drugs

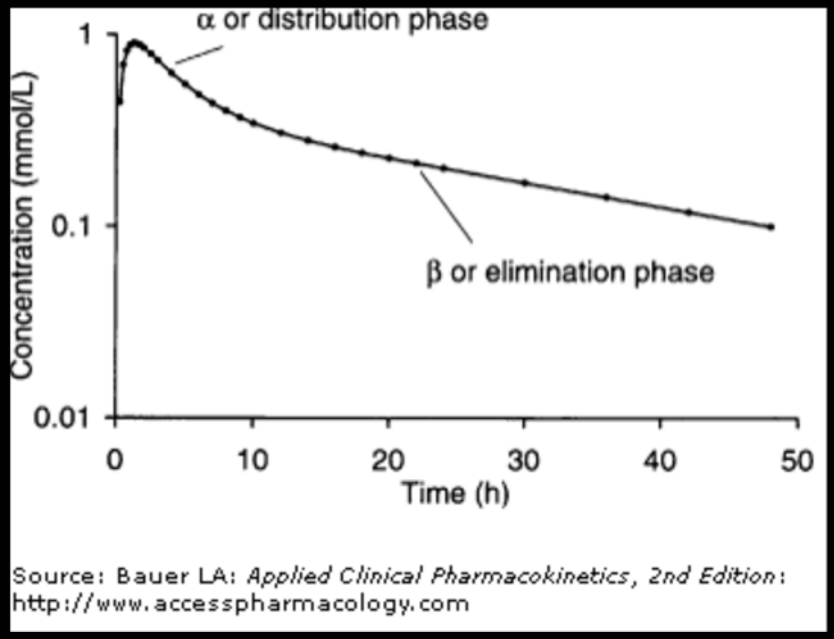


MTC

MEC

Plasma level time curve for a drug given in a single oral dose

The need: Lithium pharmacokinetics



Blood panel for lithium dosing:

- **Lithium**
- **Sodium**
- **Potassium**
- **Chloride**
- **pH**
- **creatinine**

- Lithium is used to treat bipolar disorder
- Recommended plasma concentrations: 0.6 - 1.5 mmol/L
- Toxic range: 2 – 3 mmol/L
- Toxic levels of lithium lead to renal impairment and decrease in lithium clearance

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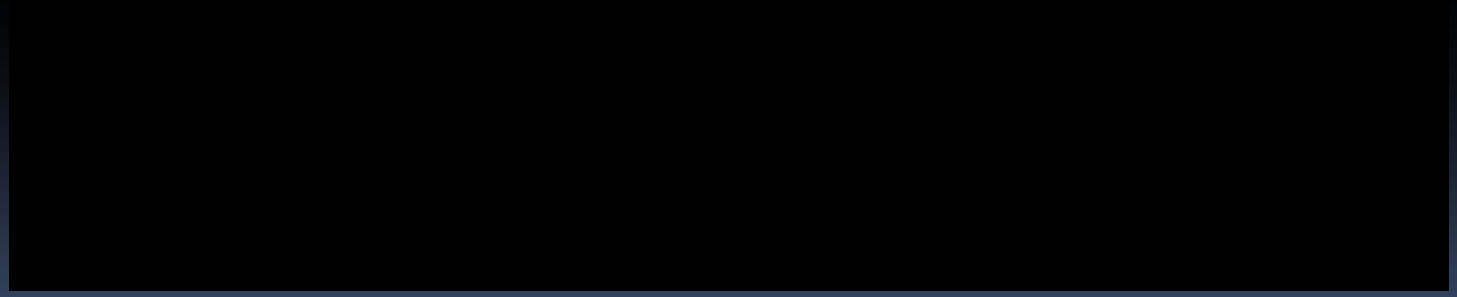
The concept: Nano Clinical Analyzer



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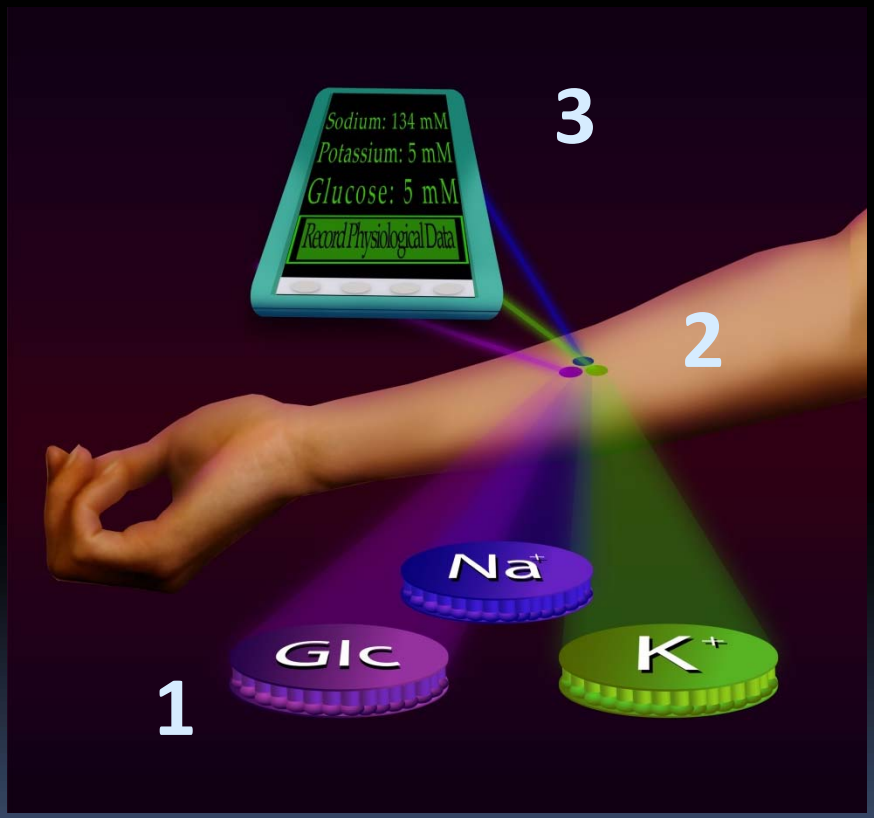
NanoClinical Analyzer components



Analytical Chemistry, 2014, 86 (3)

Hypothesis: personalized PK will enable individualized dosing by keeping patients within a therapeutic range

1. **Lithium-selective nanosensor development**
2. **Placement in skin**
3. **Fluorescence and Photoacoustic imaging**

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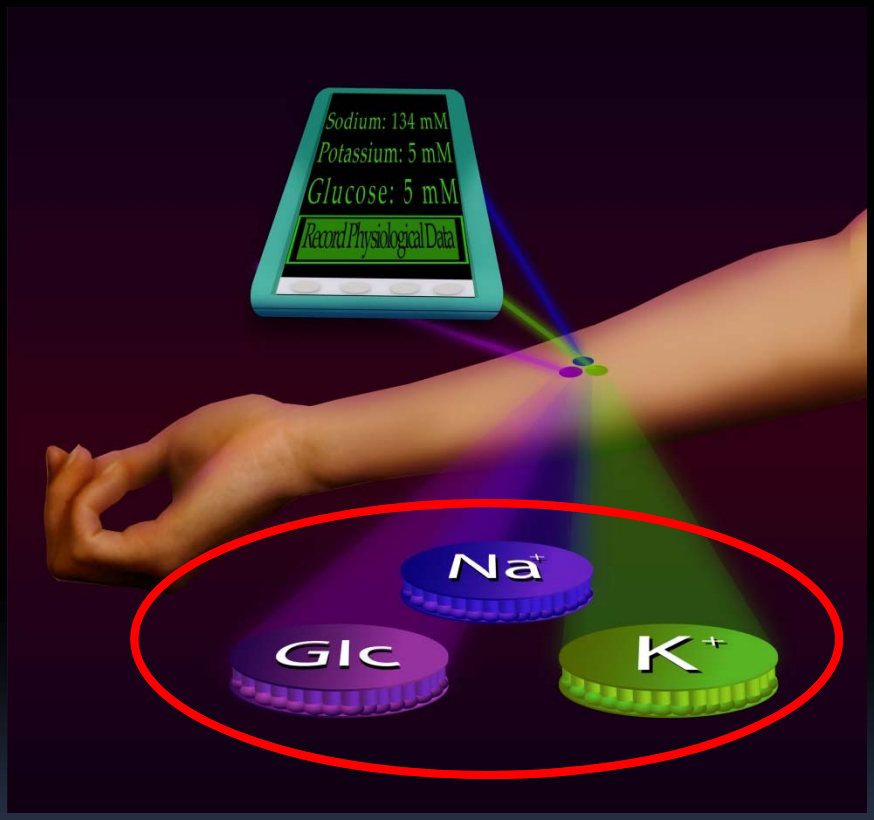
Nanosensor chemistry



Lithium-selective nanosensor development

Analytical Chemistry, 2014, 86 (3)

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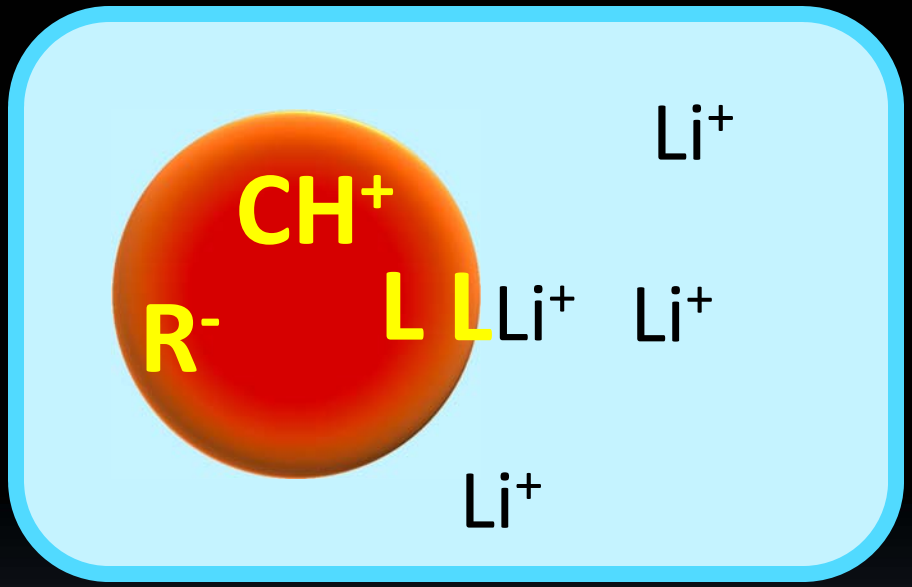
Sensor Mechanism - lithium



C = Neutral chromoionophore
L = Neutral ionophore
R = Negative additive

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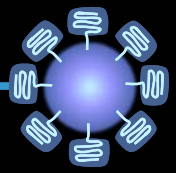
Nanosensor Synthesis



Plasticizer
PVC
Chromoionophore
Additive
Ionophore

① Optode cocktail

THF
CH_2Cl_2

Optode Solution

drop-wise addition

③ Add to aqueous solution

PEG-lipid in chloroform stock

Dried PEG-lipid

sonicator tip

evaporate

sonicate

PEG Solution

Nanosphere Solution

Redissolved PEG-lipid

② Dual solvent system

Water

④ Remove solvent

spray gun

⑤ Filter for size

Nanosensors

Nano Letters, 2007; 7(6); 1827-1831

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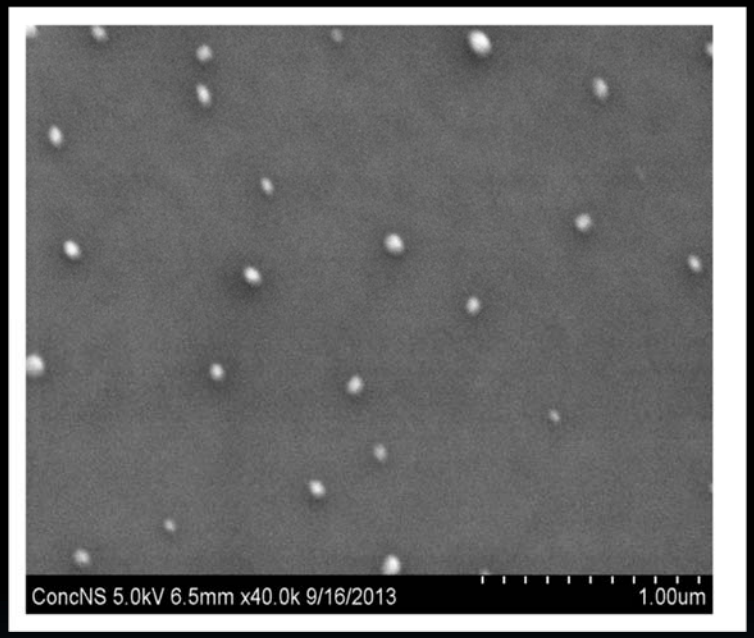
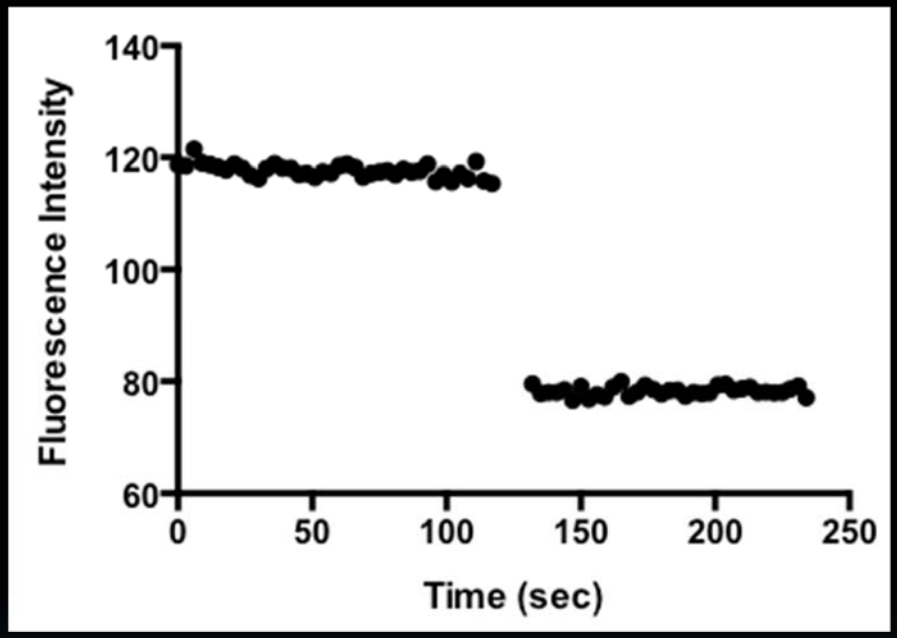
Design Requirements

- Analytical characterization (fluorescence):
  - Calibration/dynamic range: : 0.6 - 1.5 mmol/L
  - Sensitivity
  - Reversibility
  - Specificity/Selectivity: Na^+ ~140 mM
  - Size
- Analytical Characterization (photoacoustics)
- Cellular environment
  - *in vivo* calibration

Size/Response time





- 50 nm by SEM
- Small size leads to fast response time: 15 seconds or less

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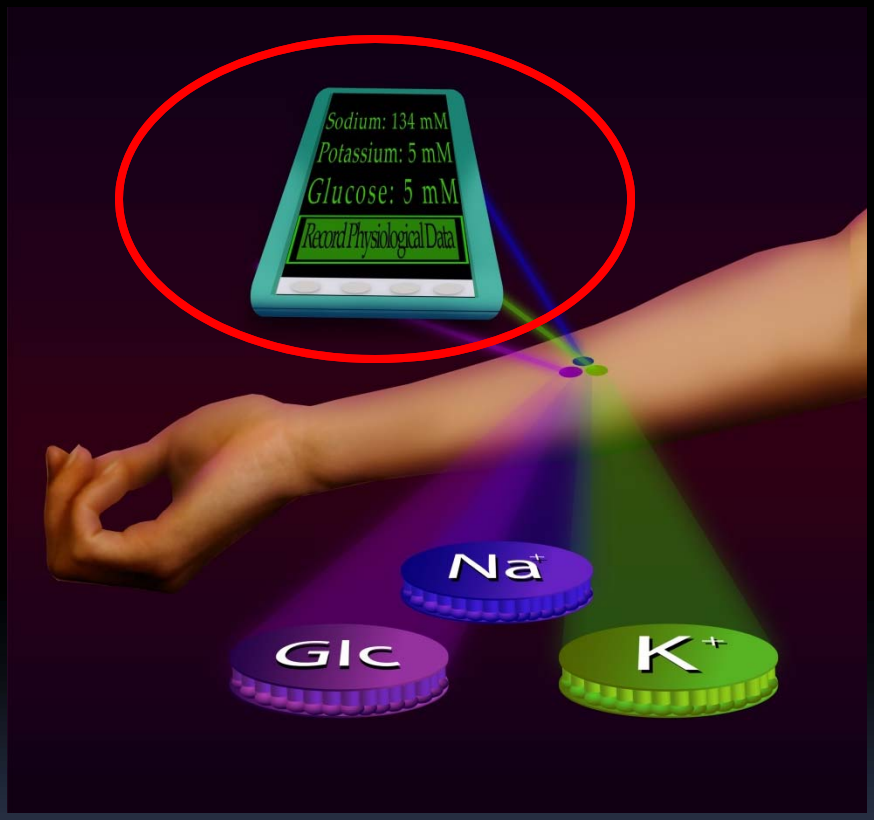
Imaging the sensors: photoacoustics

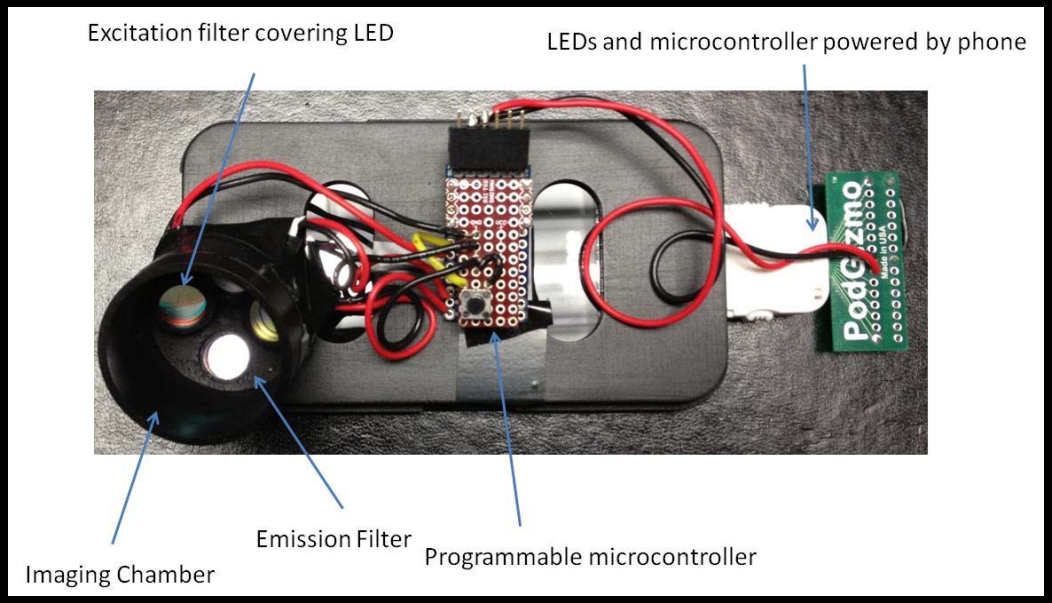


The goal: using ultrasound to detect deeper into tissue

Analytical Chemistry, 2014, 86 (3)

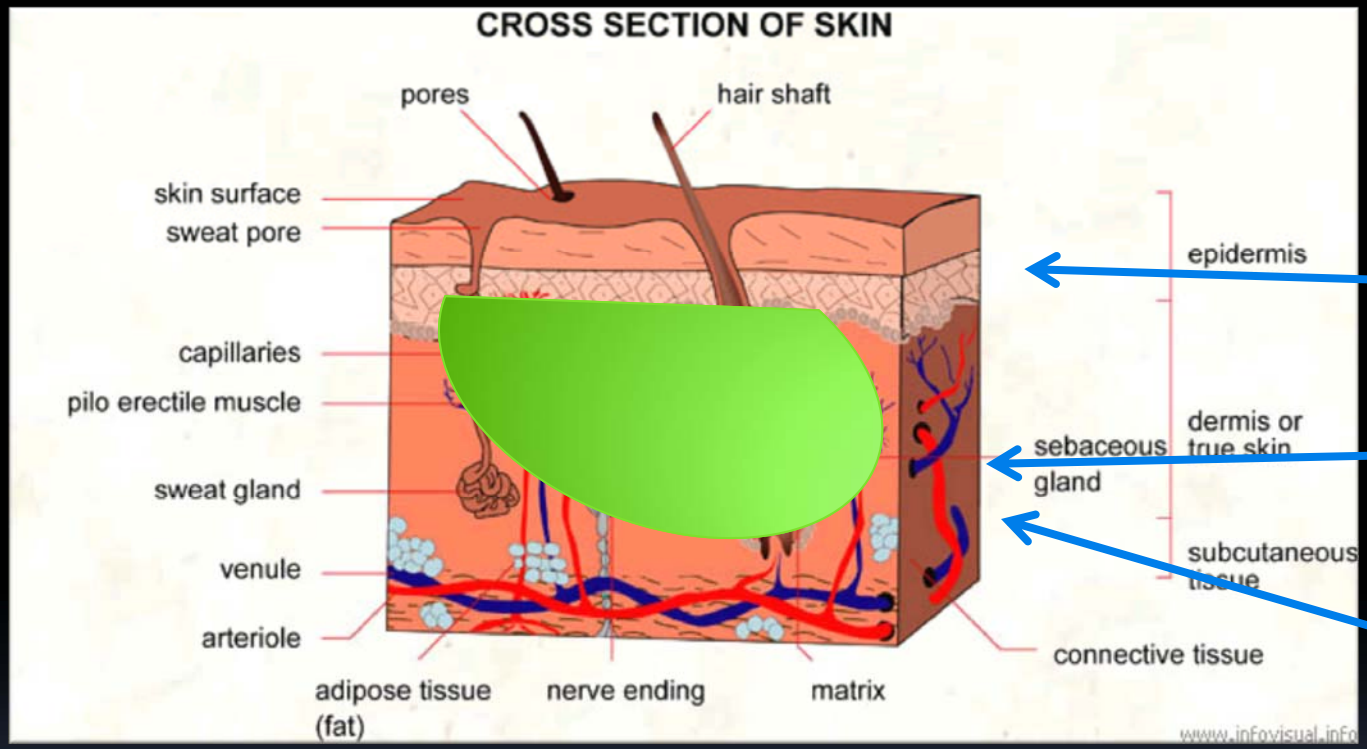
Handheld Reader Prototype

Analyst, 2014, 139, 5230-5238



- Fluorescence measurements have superior sensitivity
- Only a surface technique: scatter and aborption from tissue prevent depth measurements

Placement in skin



Original goal for nanosensor placement

tattoos

Current injection site

- Location of sensors in skin will determine permanence as well as lag time in measurement.
- Current method if injection is a fine gauge insulin needle.

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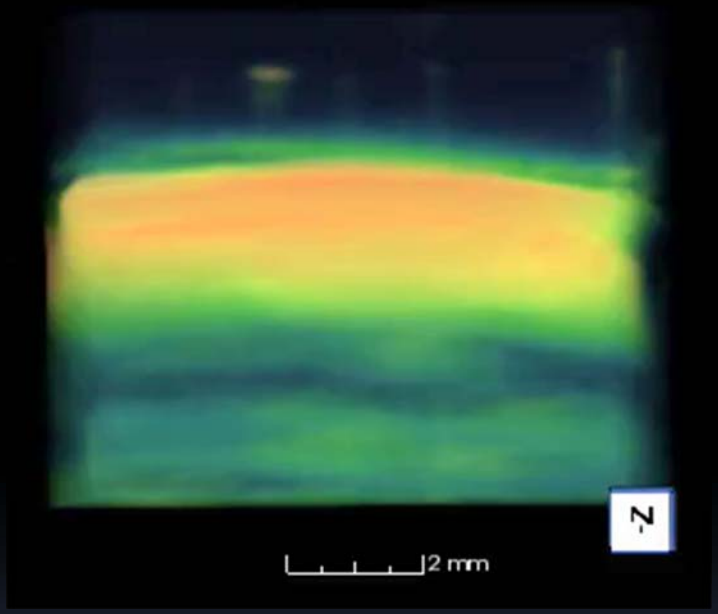
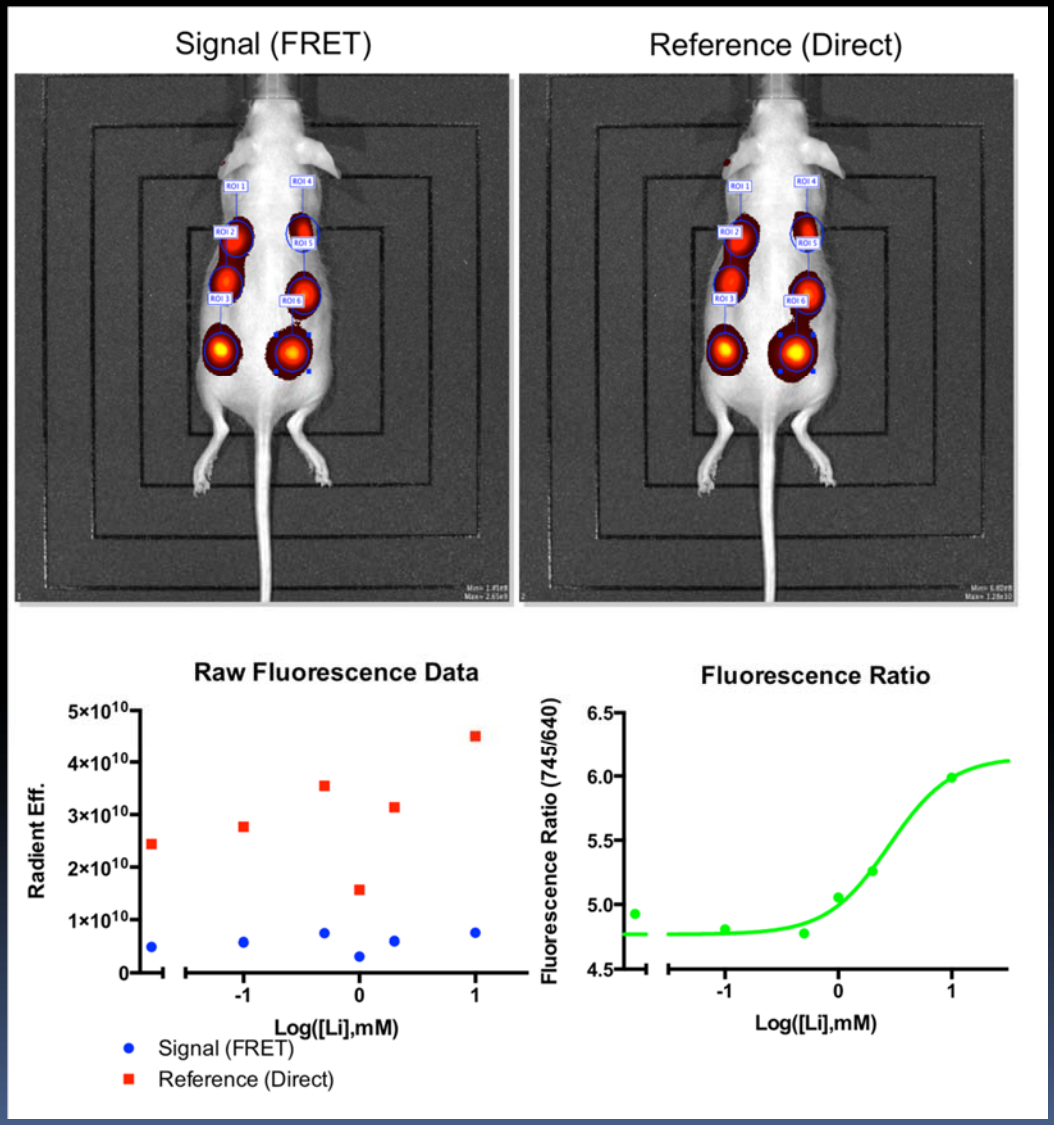
In vivo imaging



- Depth profile obtained by dual wavelength PA imaging of lithium sensitive nanosensors implanted in mice
- Deep reflection mode photoacoustic tomography, 10 MHz ultrasonic transducer

In vivo calibration



- Ratiometric imaging negates variations in particle concentration and depth
- Calibration similar to in vitro results

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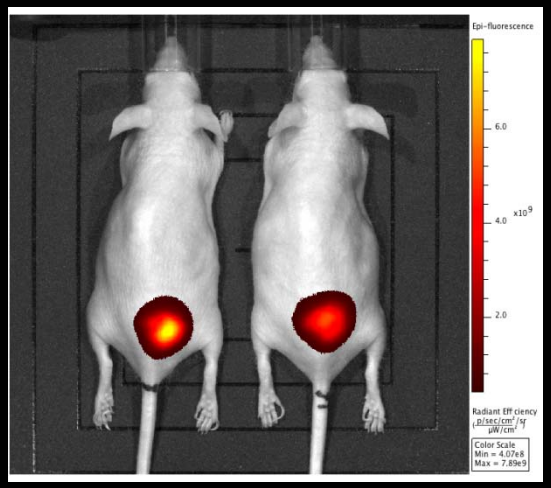
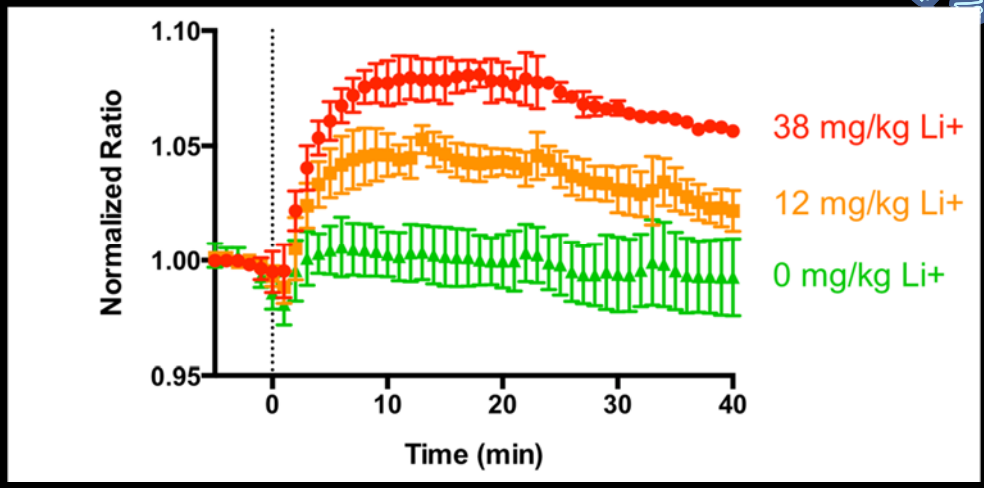
Drug Kinetics: fluorescence





- Magnitude of signal change: 8%
- Clear dose response
- ADME phases distinct
- Lithium cleared faster in mice (18 minutes to peak) than in humans (2 hours)

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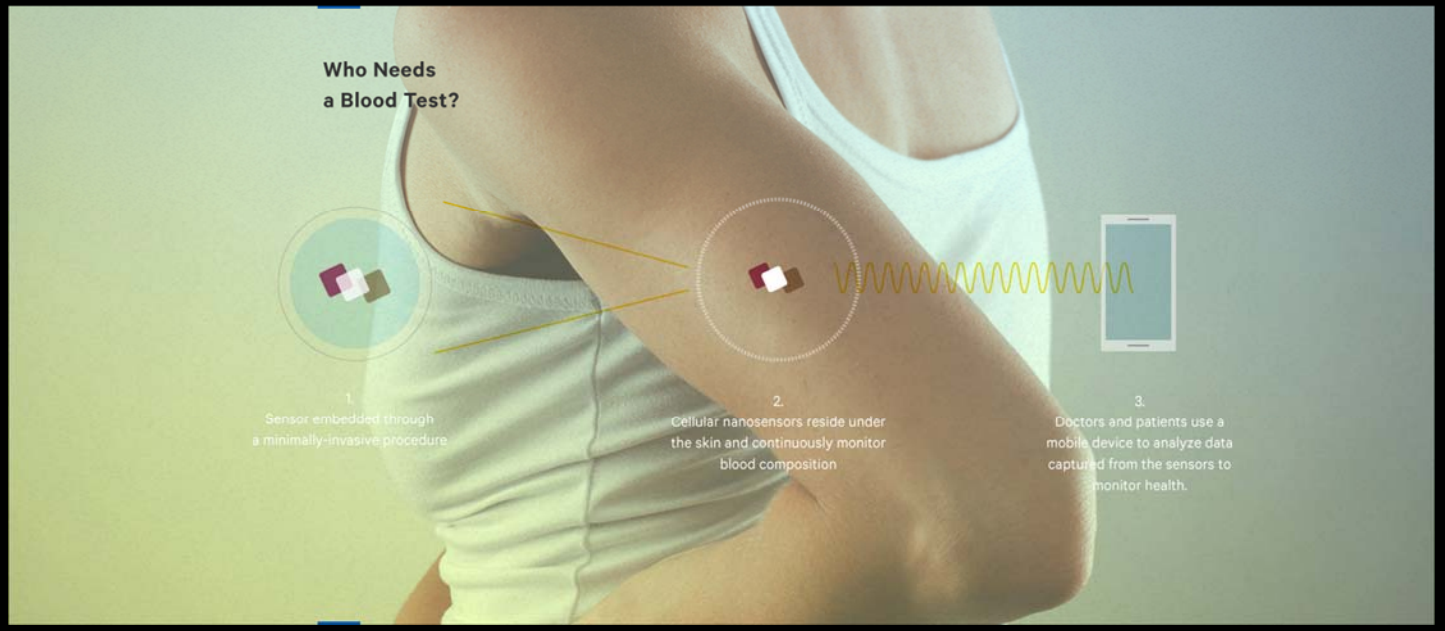
In summary: Continuous Monitoring



http://www.theatlantic.com/sponsored/qualcomm/the-space-within/482/

Our nanosensor technology has significant advantages:

- Semi-invasive: The number of invasive procedures is minimized.
- Continuous: Quantitative measurements are real-time and trends can be determined.
- Portable: detection can be paired with hand held device for personalized dosing information

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Acknowledgments

Collaborators

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Alumni: Kevin Cash, Tim Ruckh, Kelvin Billingsley, Kate Balaconis, Matt Dubach, Ankeeta Mehta, Ryan Walsh, Chris Skipwith, Lia Hondroulis,

DARPA

National Institutes of Health

CIMIT® Center for Integration of Medicine & Innovative Technology

NASA

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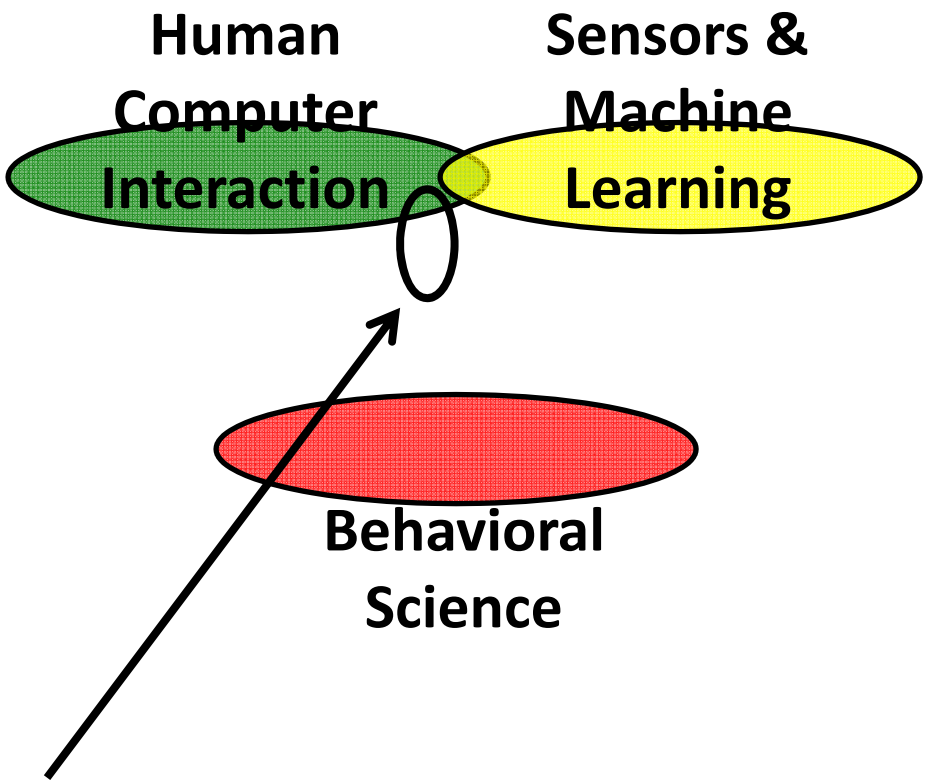
Improving Behavioral Measurements from Mobile Devices

Stephen Intille, PhD

Associate Professor
College of Computer and Information Science
Health Sciences Department, Bouvé College of Health Sciences
Northeastern University

Tufts | CTSI
Tufts Clinical and Translational Science Institute

Opportunity



Leverage:

Mobile and ubiquitous technologies

Focus:

- **Computational models for real-time measurement of behaviors, states, & contexts**
- **Just-in-time adaptive health interventions**
- **Real-world validation**

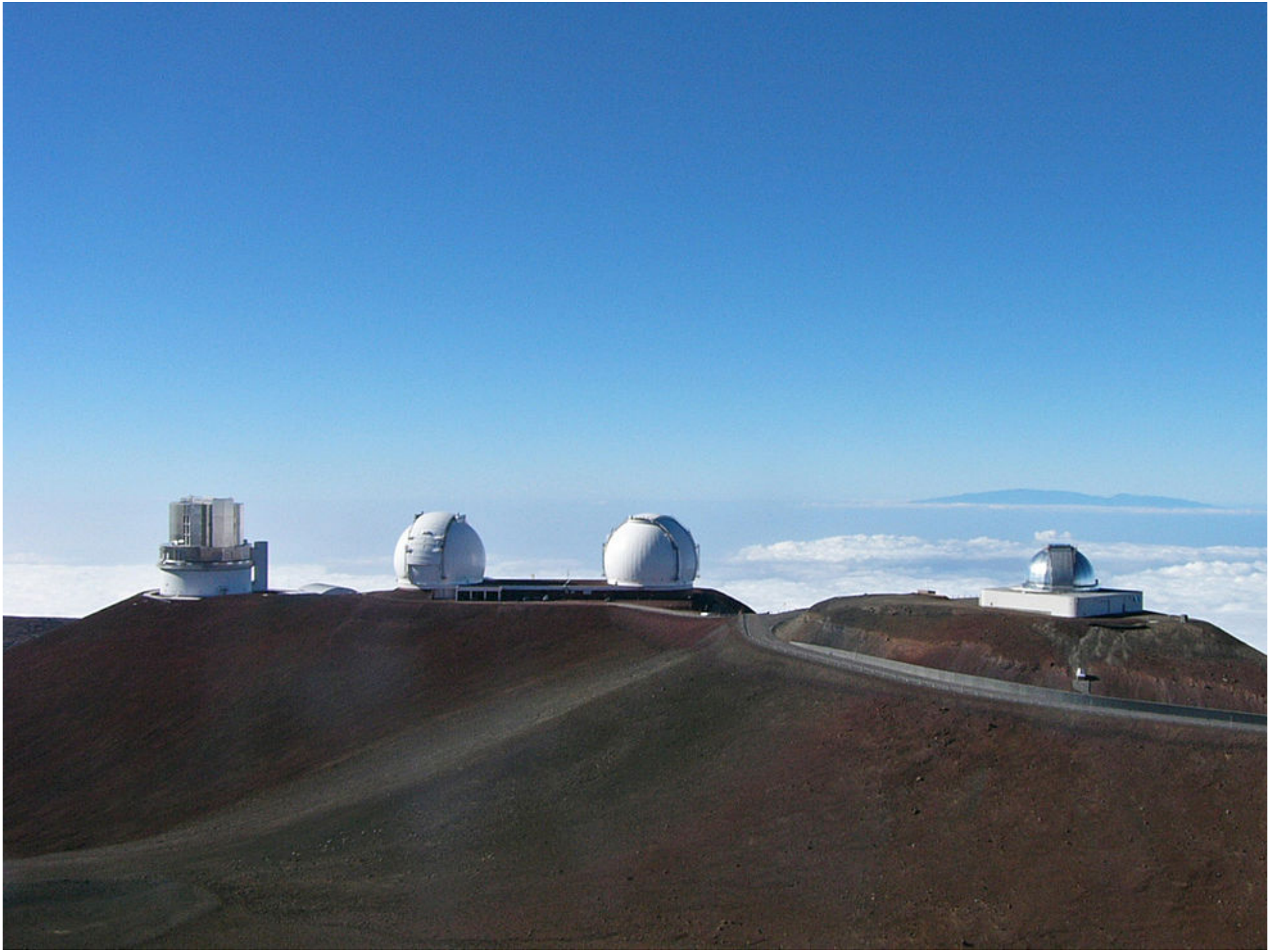
Take away

- Tools for measuring behavior, states, and context of people are poor
- Smartphones, smartwatches, and other wearable sensors provide new sensor data
- These “digital breadcrumbs” can be used by algorithms to infer behavior, states, and contexts
- This also enables context-sensitive self-report, which may further improve our behavioral measures

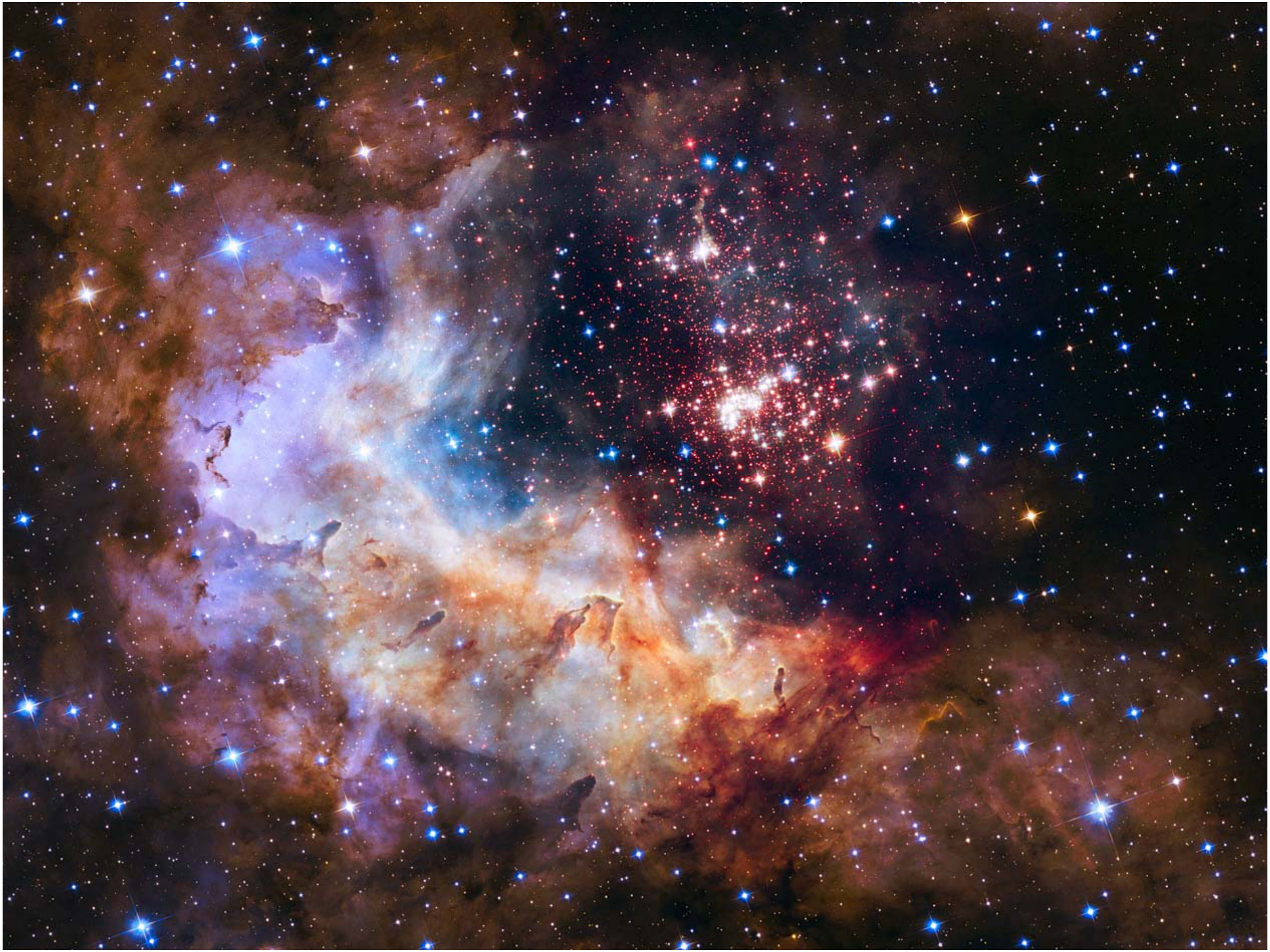
New measurement tools accelerate scientific discovery

At massive scale

Telescopes

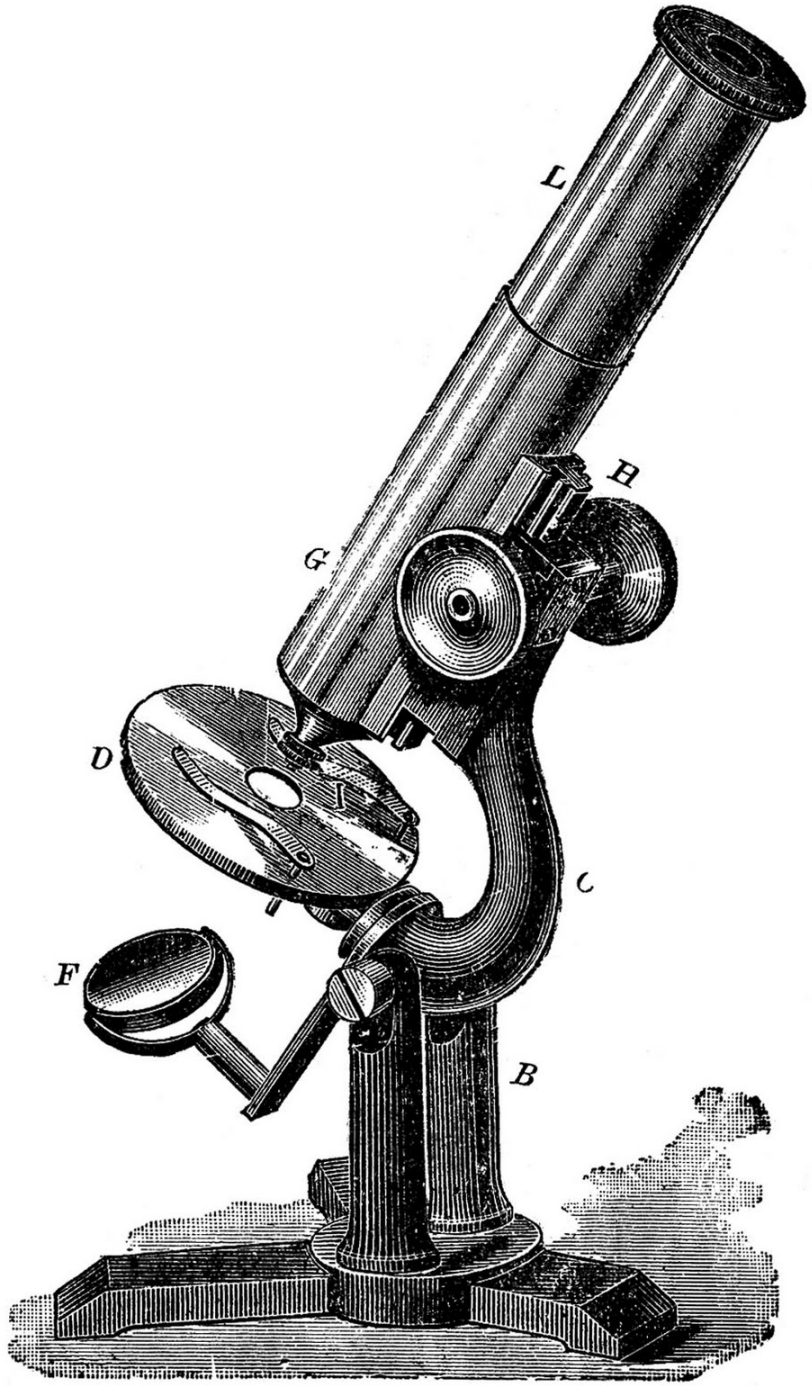



ESA



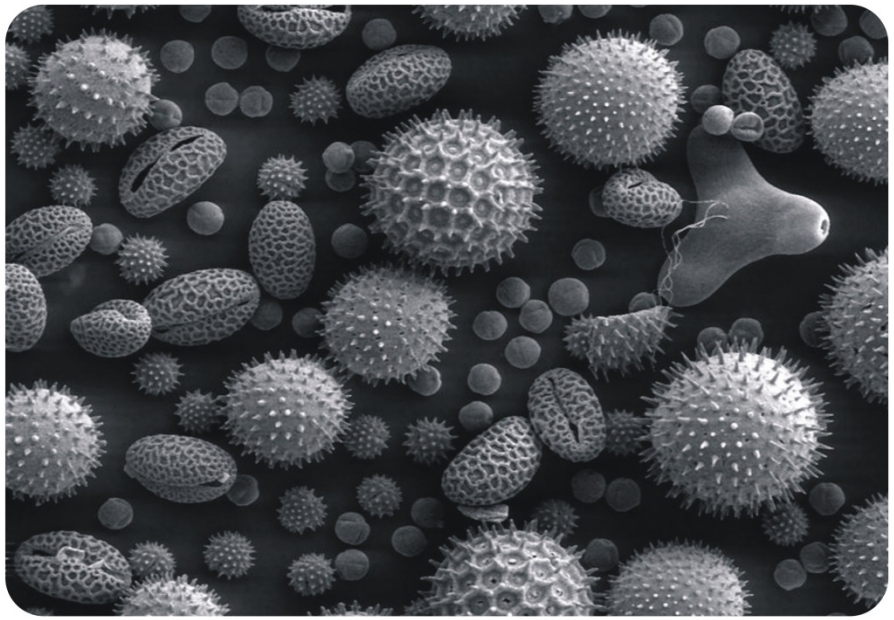
At micro scale

Microscopes




40X


HITACHI




http://www.dna-rainbow.org

At behavioral scale?

A barrier

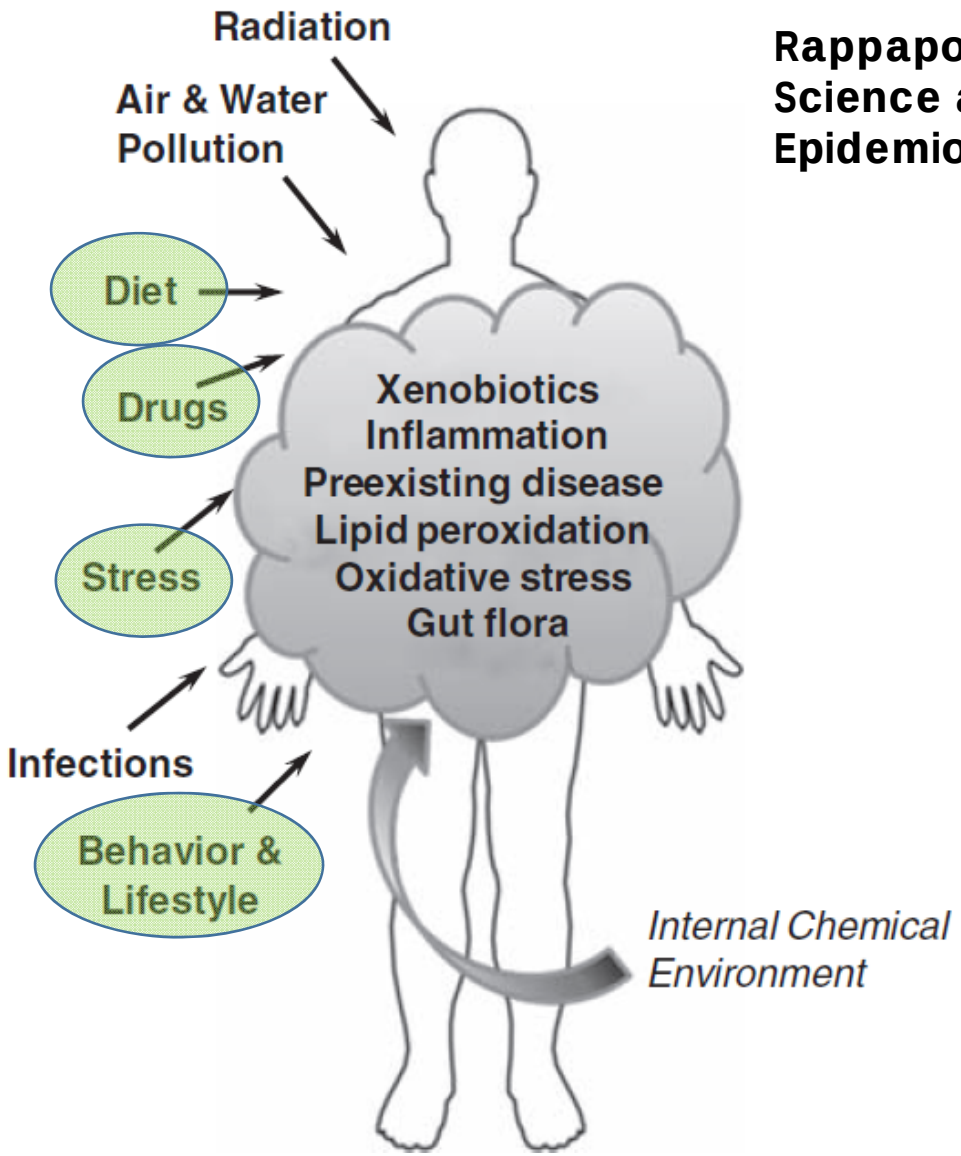
Typical NIH grant review meeting on research related to health behavior ...

Exposure and disease

"familial and twin studies suggest that roughly 90% of cancer deaths and half of heart disease mortality cannot be explained by the genes and, therefore, point to environmental factors"

Rappaport, J. of Epidemiology and Community Health 2012;66:99-102

Exposome



Rappaport, J. of Exposure Science and Environmental Epidemiology, 2011

Important behaviors/states

- Diet (what is eaten … also when and how)
- Physical activity and sedentary behavior
- Risky behavior
- Medication adherence
- Social context/socialization
- Assessment of pain
- Stress/stressors
- Affective state

At behavioral scale?

- Automatically detect patterns of behavior by computer from “digital breadcrumbs”
- Simultaneously **measure across health research silos to obtain a holistic view of behavior**
- Find unexpected relationships between behavior and health outcomes
- Develop computation models of behavior change

Reduce measurement noise ⇨ **Advance science**

The need

NHANES (National Health and Nutrition Examination Survey)

Self-report: ≈45% of U.S. adults meet the physical activity guidelines

Measurement: <5% of meet guidelines

Troiano *et al*., "Physical activity in the United States measured by accelerometer"
Med Sci Sports Exerc. 2008 Jan;40(1):181-8.

Better measures

Better questions

E.g., Are short bouts of activity as protective against disease as continuous long bouts?

Thinking long term

Two motivations for measurement

- Scientific inquiry (Better tools for scientists)

This requires longer-term, less invasive measurement than scientific inquiry might

- Building effective interventions
  - Measure changes in behavior/state
  - Use measurement to intervene with just-in-time support for health/wellness tailored to behavior/state

Digital models of behavior

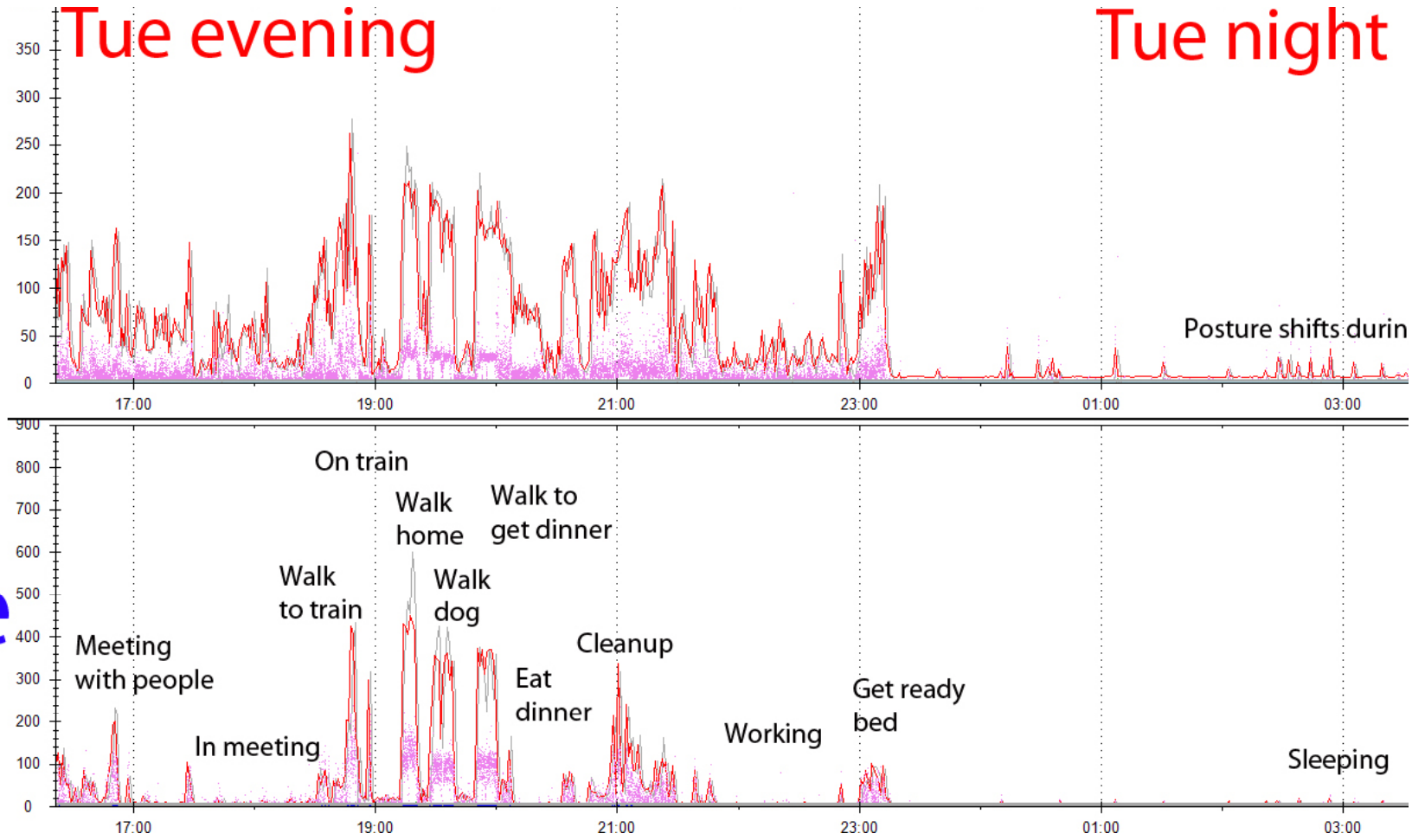
Incorporate real-time behavior, state, & context

Want probabilistic models of:

- Current behavior
- Next likely behavior
- Receptivity to information
- Decision-making & cognitive reserve
- Habits and habit formation

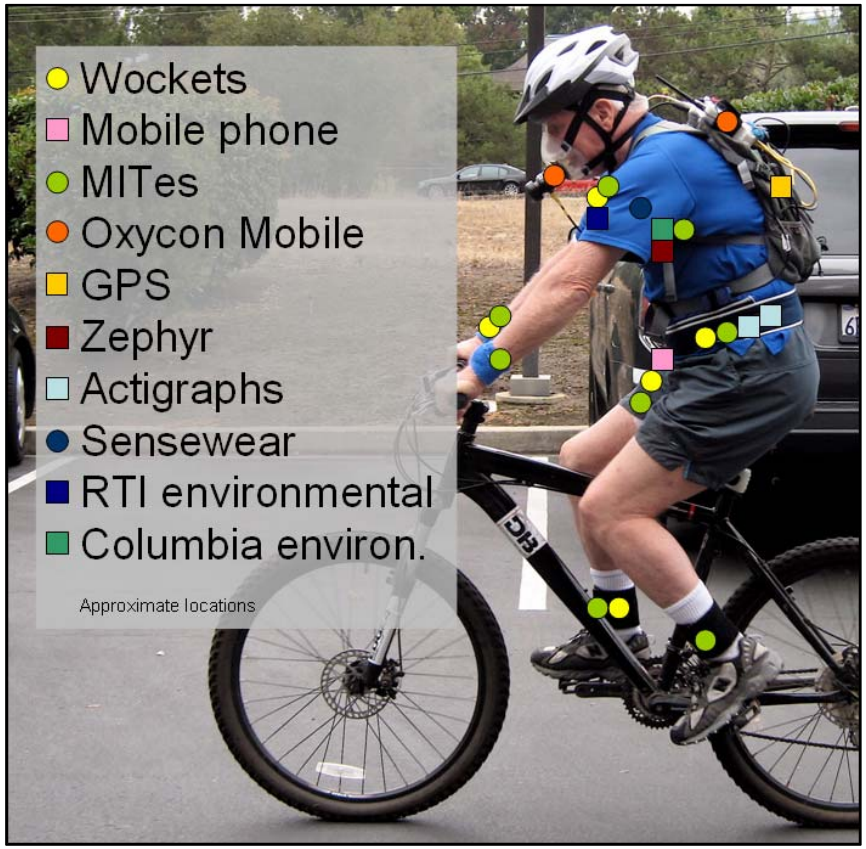
Wrist

Ankle


Tue evening
Tue night
Posture shifts durin
Meeting with people
In meeting
Walk to train
On train
Walk home
Walk dog
Walk to get dinner
Eat dinner
Cleanup
Working
Get ready bed
Sleeping
17:00
19:00
21:00
23:00
01:00
03:00

This type of info, plus social interaction, location, and more ... for long time periods ... might change research methods and research questions and lead to new interventions

Lab validation experiments



- Lab & simulated free-living
- Variety of sensors (including smartphone/smartwatch)

Lab performance: Activity recognition

		Subject Dependent	Subject Independent
Activities to recognize	**Random Guess (%)**	**Total Accuracy (%)**	**Total Accuracy (%)**
All (51)	1.9%	87.9	50.6
All with no intensities (31)	3.2%	91.4	72.0
Postures, ambulation and two MET intensity categories (11)	9%	96.5	81.3
Postures and Ambulation with no intensity (8)	12.5%	98.4	92.9
Postures (4)	25%	99.3	98.0

Single sensor: wrist vs. ankle

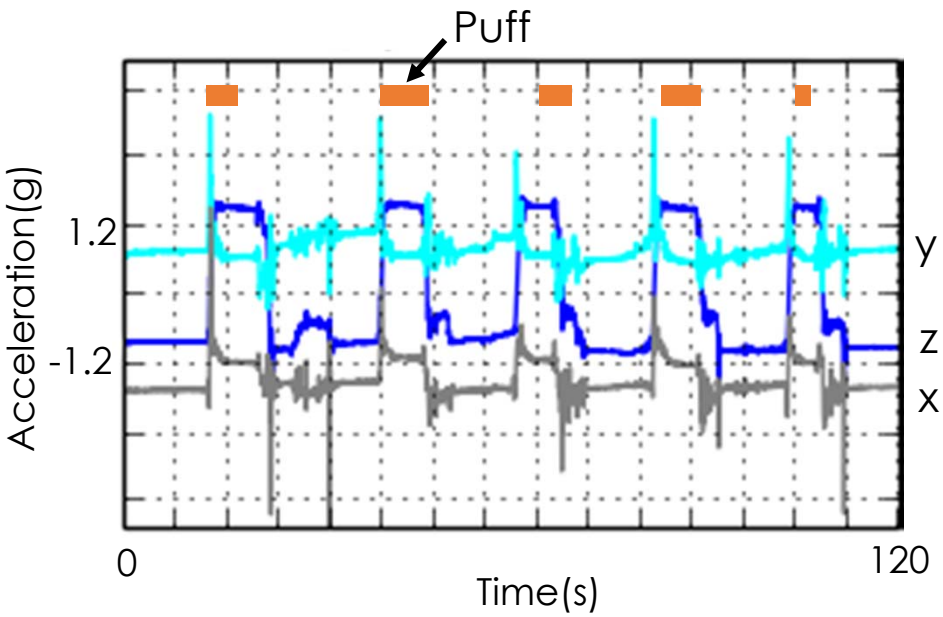
33 subjects: wrist vs. ankle ambulation detection

Wrist			Ambulation	Cycling	Other activities	Sedentary
	Actual label	Ambulation	**2263 (90.6 %)**	79 (3.2 %)	60 (2.4 %)	95 (3.8 %)
		Cycling	72 (6.9 %)	**672 (64.5 %)**	20 (1.9 %)	278 (26.7 %)
		Other activities	66 (6.9 %)	10 (1.0 %)	**806 (83.9 %)**	79 (8.2 %)
		Sedentary	45 (1.5 %)	150 (5.0 %)	61 (2.0 %)	**2756 (91.5 %)**
			Overall accuracy = 86.5%			
Ankle			Ambulation	Cycling	Other activities	Sedentary
	Actual label	Ambulation	**2547 (99.6 %)**	5 (0.2 %)	6 (0.2 %)	0 (0.0 %)
		Cycling	8 (0.8 %)	**993 (94.8 %)**	26 (2.5 %)	21 (2.0 %)
		Other activities	6 (0.6 %)	15 (1.5 %)	**817 (82.4 %)**	153 (15.4 %)
		Sedentary	1 (0.0 %)	11 (0.4 %)	89 (2.9 %)	**2928 (96.7 %)**
			Overall accuracy = 95.5%			

Mannini, Intille, et al., Med Sci Sports Exerc., 2013.

E.g.: Detecting smoking behavior

Data from accelerometer on the right wrist



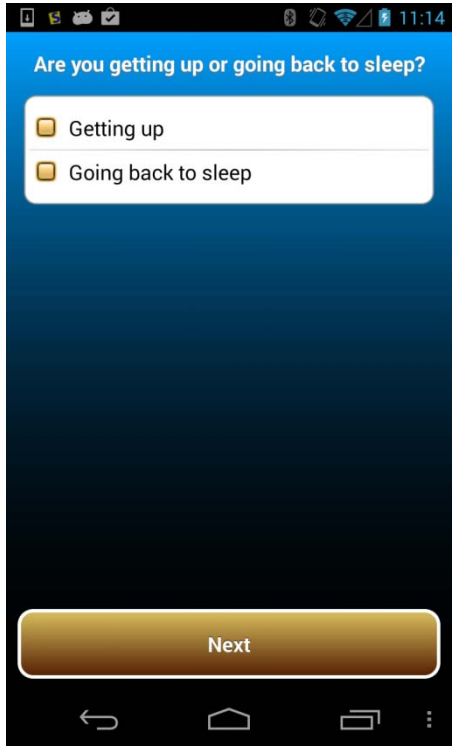
(While standing)

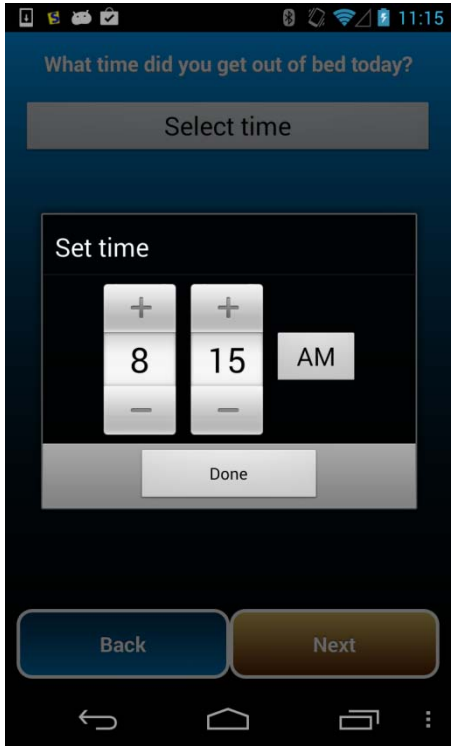
- "Easy" when no other activities
- On "real data" much more challenging (eating vs. smoking)

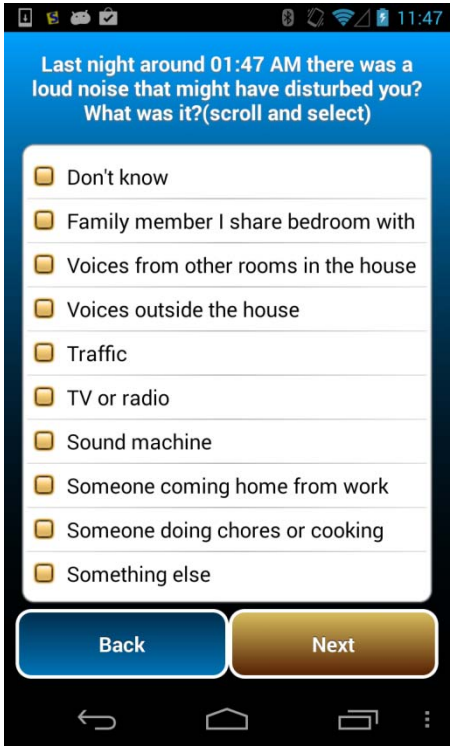
Tang, Vidrine, Crowder, and Intille, "Automated Detection of Puffing and Smoking with Wrist Accelerometers," Pervasive Health, 2014.

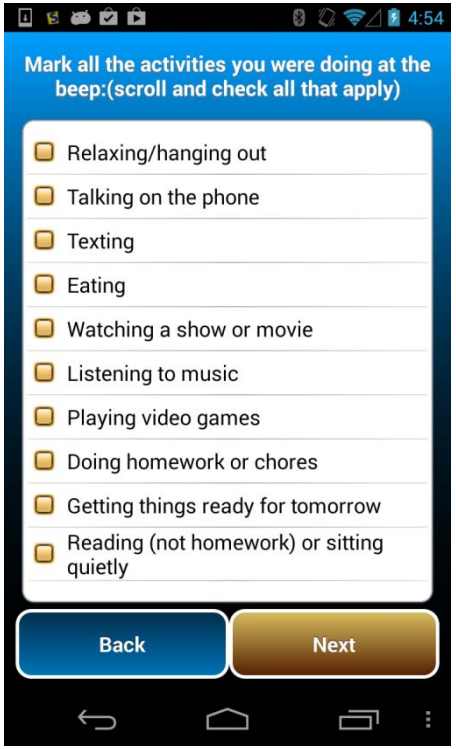
E.g. : Sleep quality and disturbances

J. C. Spilsbury, S. R. Patel, N. Morris, A. Ehyaei, and S. S. Intille, "Household chaos and sleep-disturbing behavior of family members: Results of a pilot study of African American early adolescents," Sleep Health, vol. 3, pp. 84-89, 2017.









But, need some self-report:

EATING

RELATIONSHIPS

PAIN

MOOD

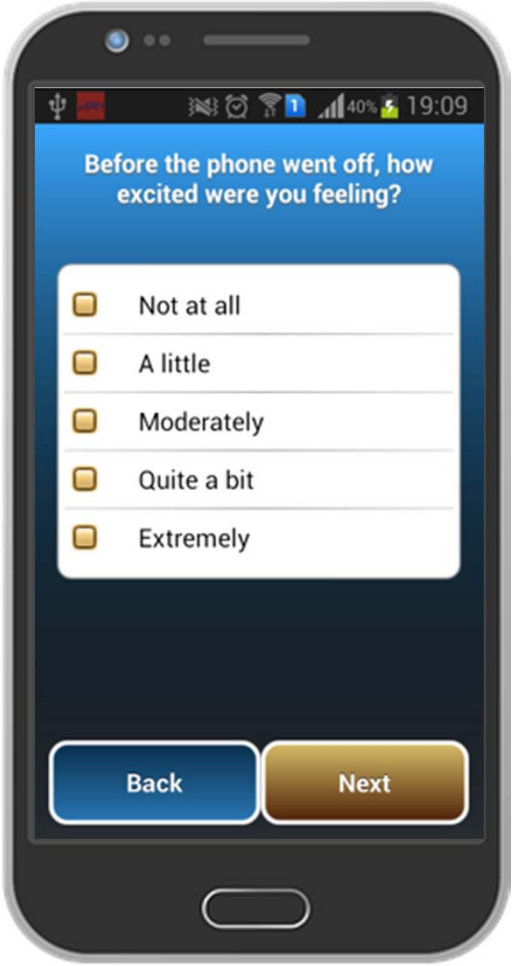
PERCEIVED EXERTION

...

What is EMA?

EMA or Ecological momentary assessment is an ***in situ*** **self-report data collection method** to assess behavior

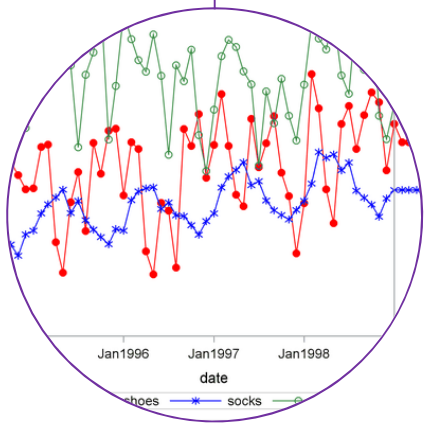
– *Shiffman & Stone, 1998; Smyth & Stone, 2013*



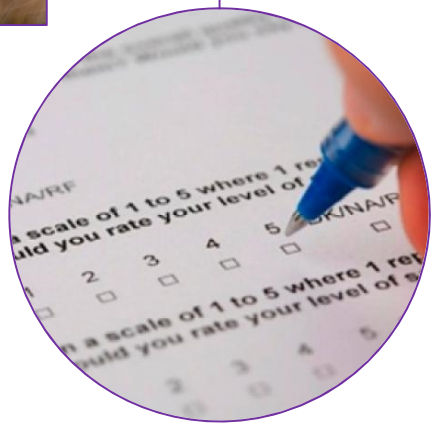
What is EMA?

Real world = Ecological validity

Prompted several times a day on mobile phone

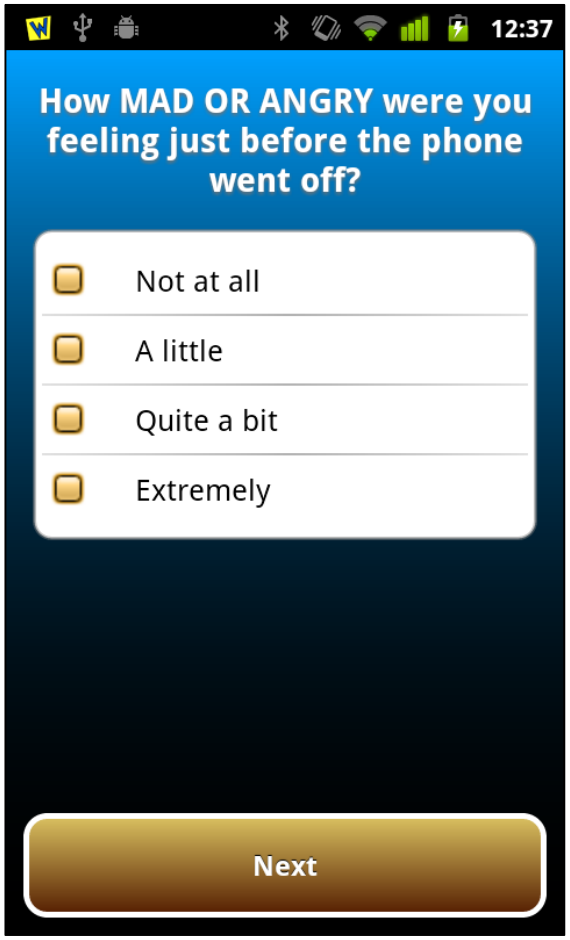


Explain missing sensor data

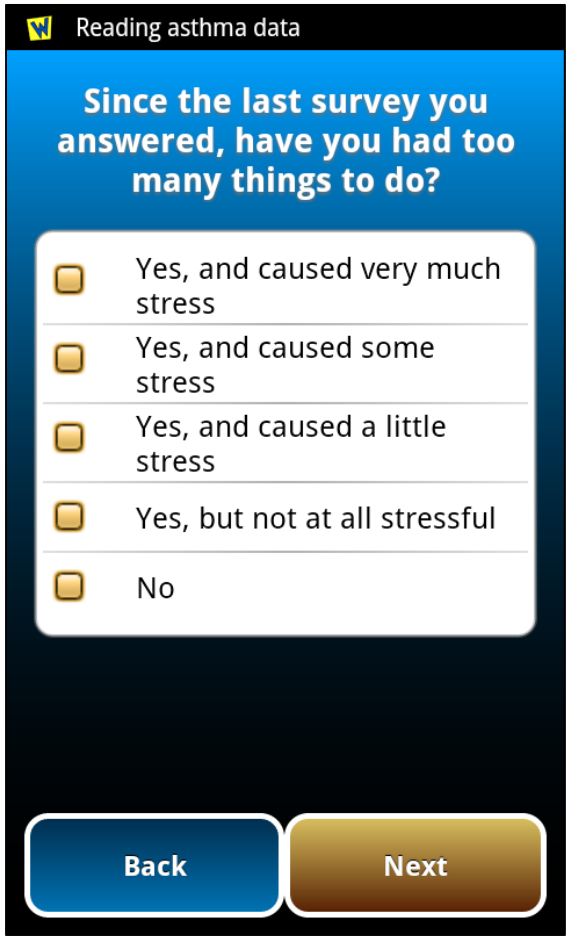


Reduces recall biases

EMA

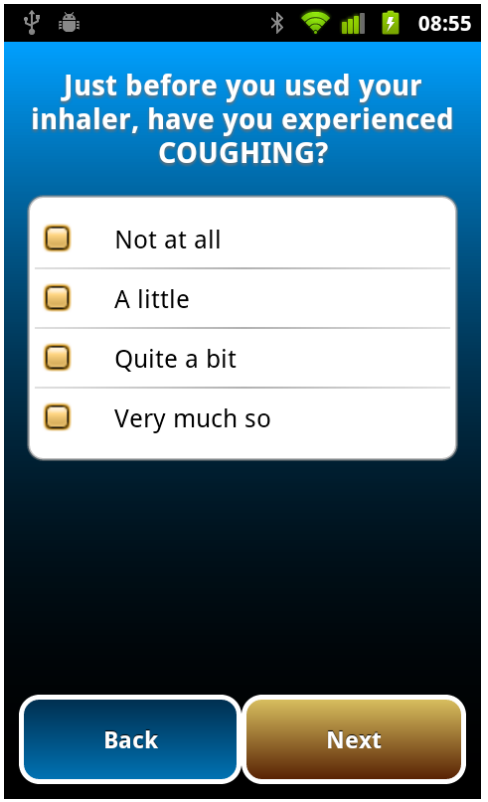

12:37
How MAD OR ANGRY were you feeling just before the phone went off?
Not at all
A little
Quite a bit
Extremely
Next


12:52
What were you DOING just before the phone went off? (Choose all that apply)
Reading/Computer/ Homework
Using technology (TV, phone)
Active Play/Sports/ Exercising
Eating/Drinking
Going somewhere
Sleeping
Something else
Back
Next


Reading asthma data
Since the last survey you answered, have you had too many things to do?
Yes, and caused very much stress
Yes, and caused some stress
Yes, and caused a little stress
Yes, but not at all stressful
No
Back
Next

Context-sensitive sampling

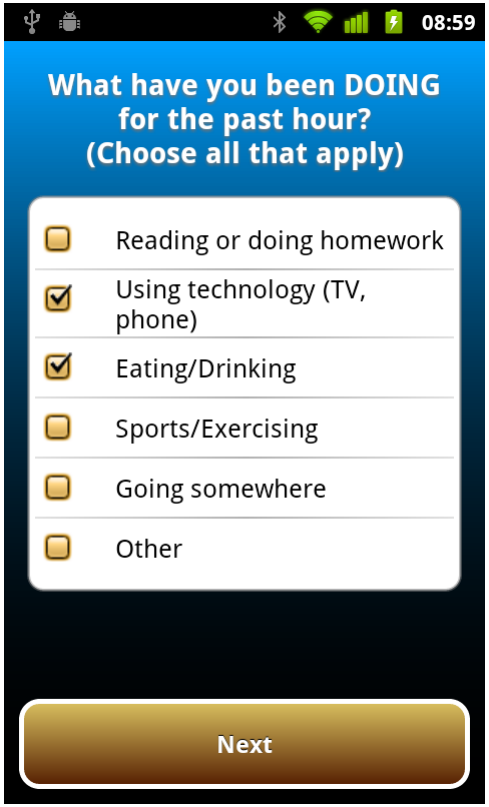
Teen asthma measurement prompted just after inhaler used:



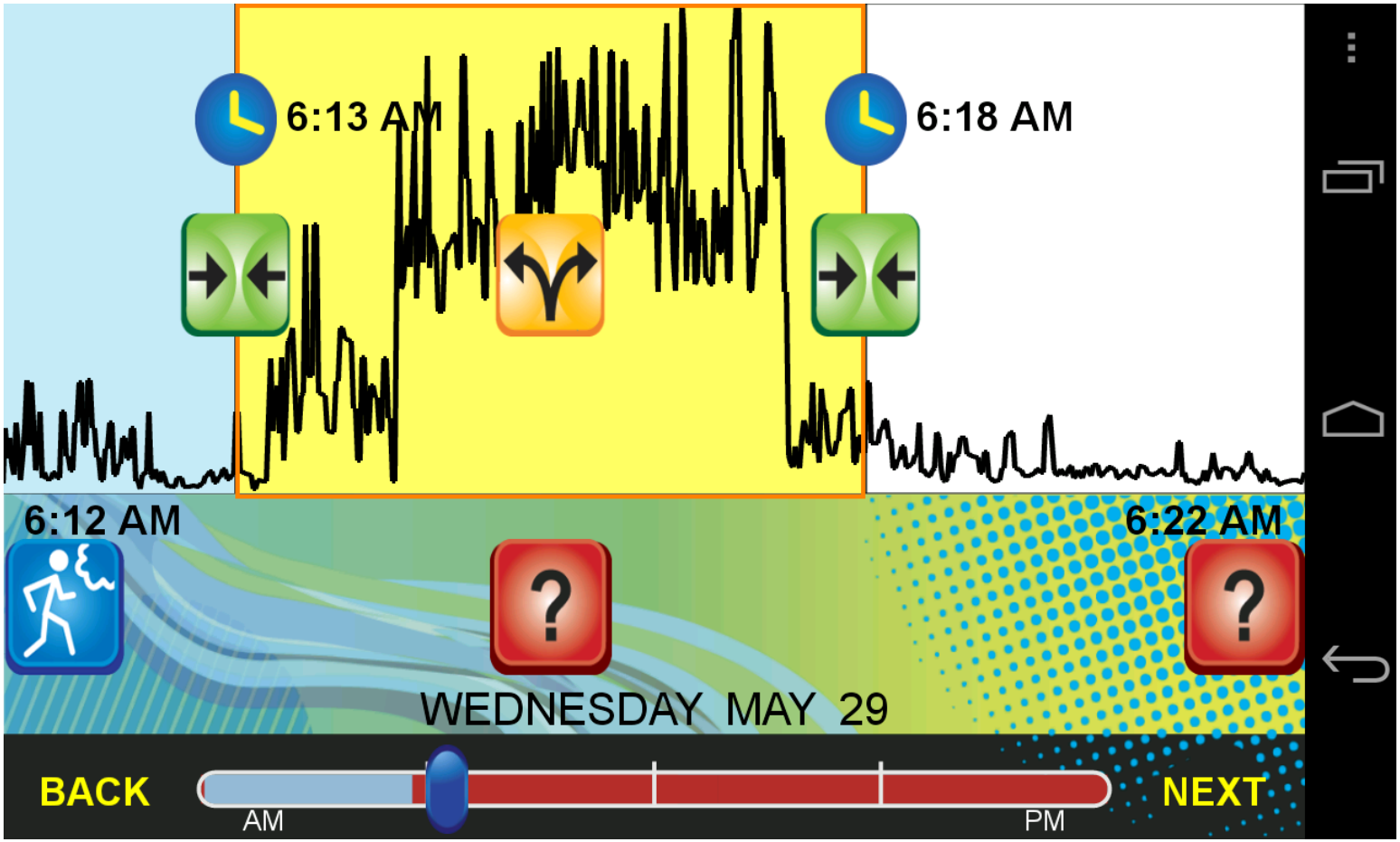
E. Dzubur, M. Li, K. Kawabata, Y. Sun, R. McConnell, S. Intille, and G. F. Dunton, "Design of a smartphone application to monitor stress, asthma symptoms, and asthma inhaler use," Ann Allergy Asthma Immunol, vol. 114, pp. 341-342, 2015.

Context-sensitive sampling

Prompted after 60 min of phone motion or no motion:

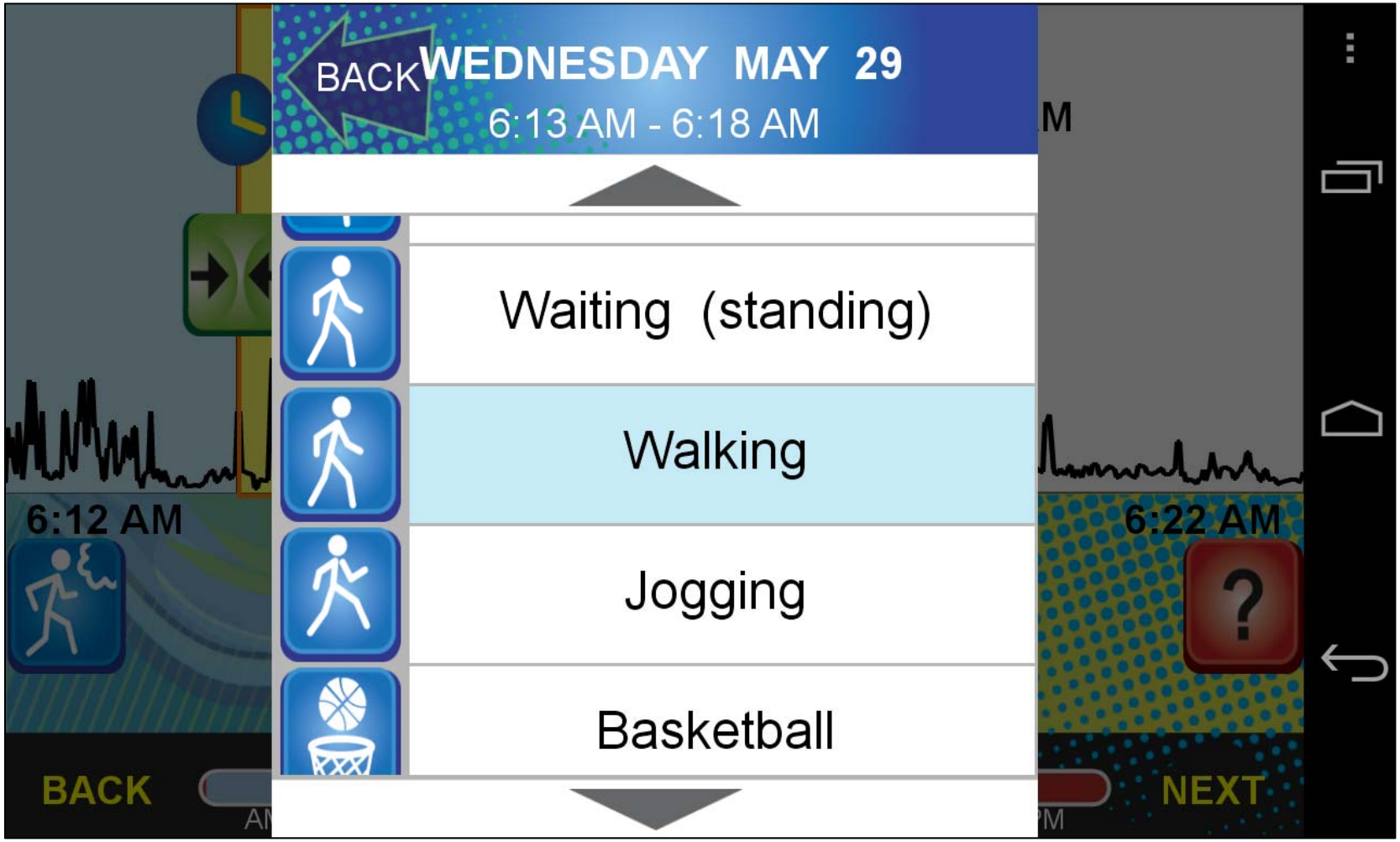


Semi-automated self-report

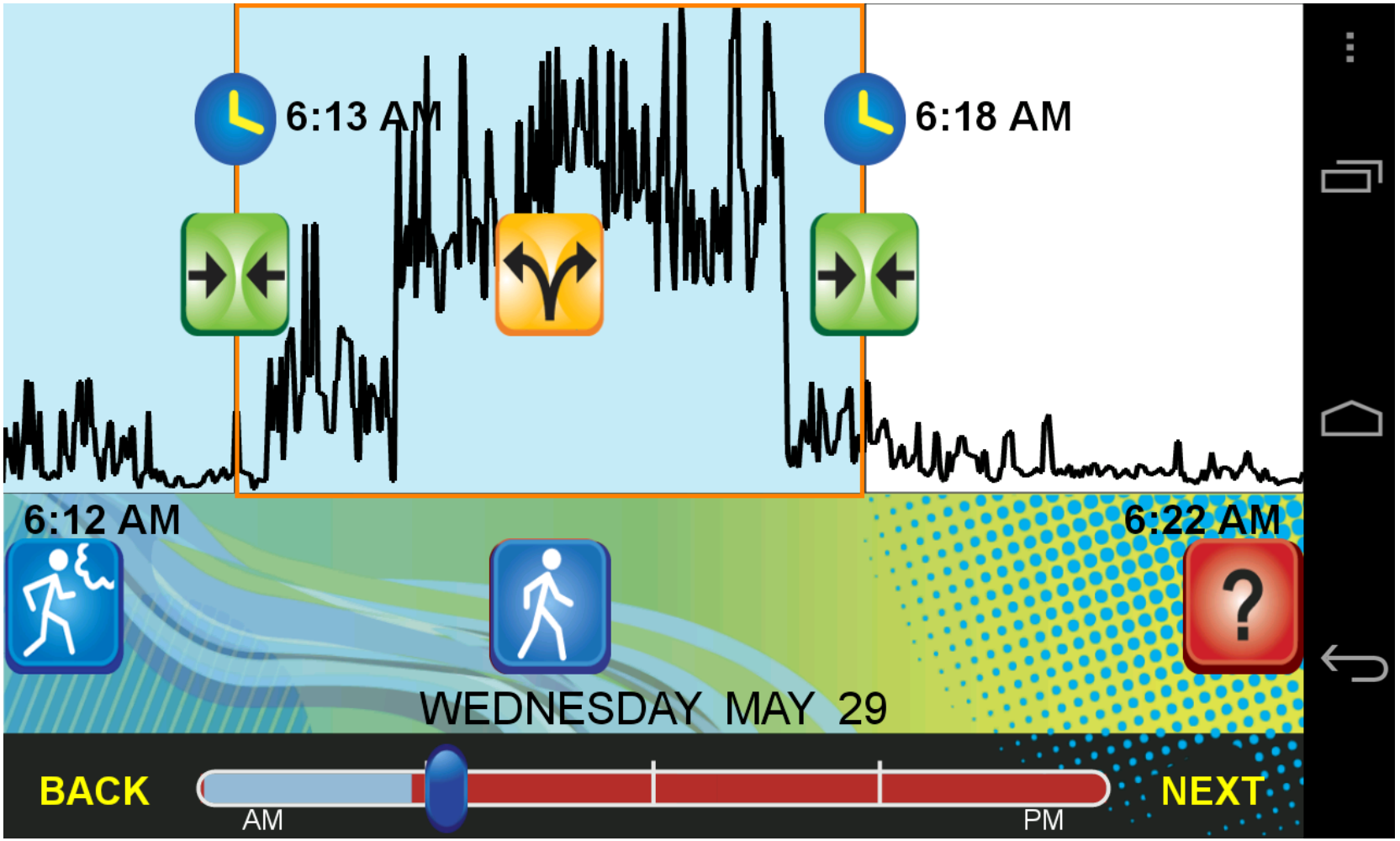


Dunton, Dzubur, Kawabata, Yanez, Bo, and Intille, "Development of a smartphone application to measure physical activity using sensor-assisted self-report," Front. Public Health, 2014, Feb 28, 2:12.

Semi-automated self-report



Semi-automated self-report



EMA limitation

Interruption burden

- Long question sets
- Frequent questionning
- Obtaining device access
- Prompt disruptiveness

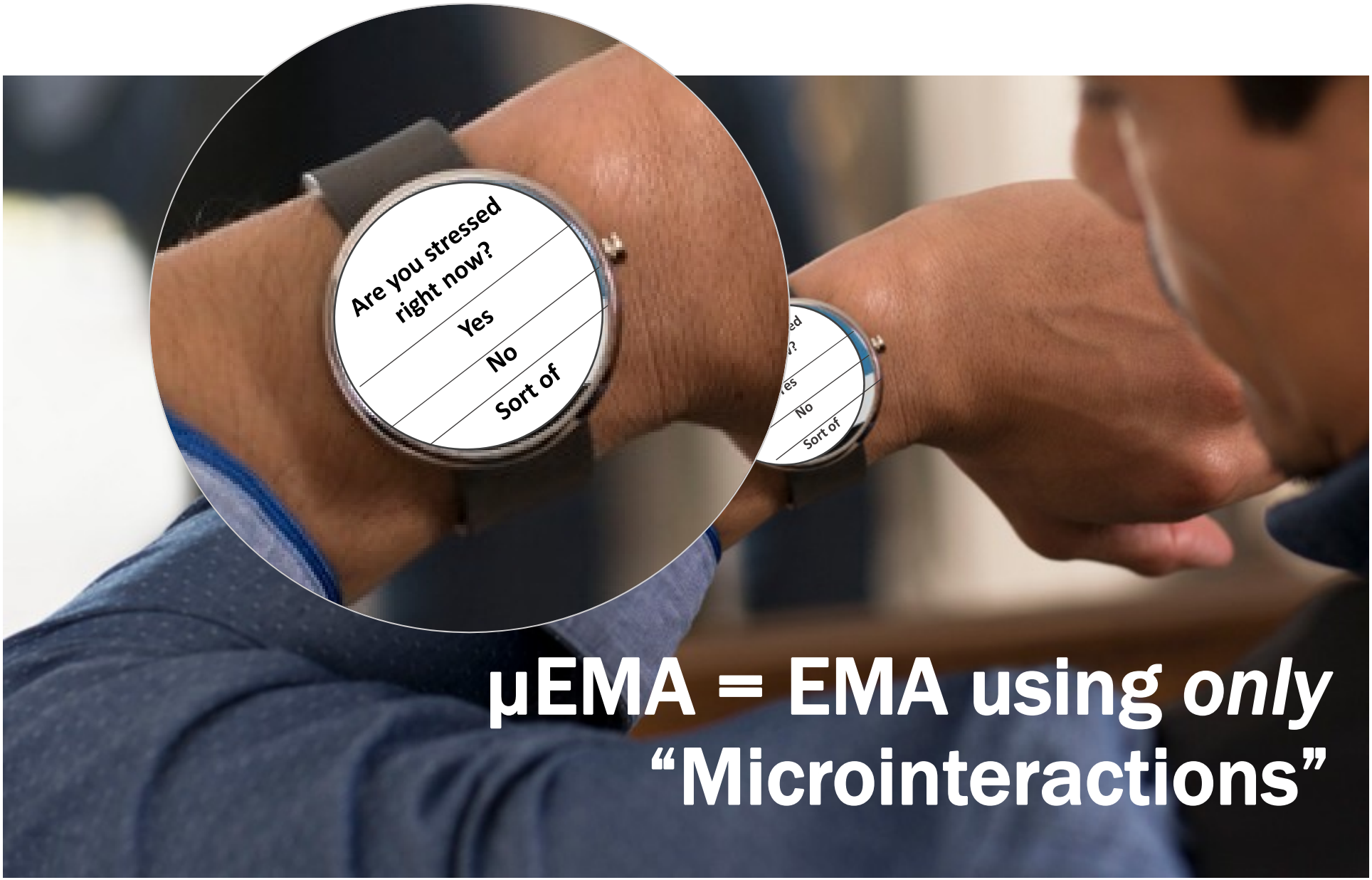
!

Resulting in high perceived burden and lower study compliance

EMA challenge

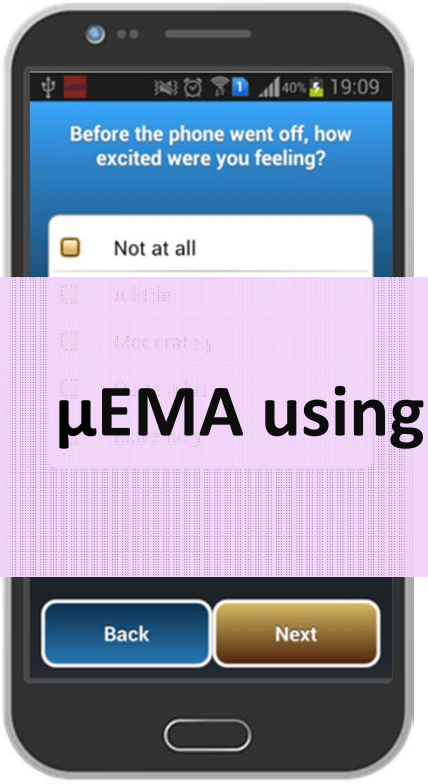
How might we reduce interruption burden, but still achieve high temporal density in EMA?

“At a glance” microinteractions

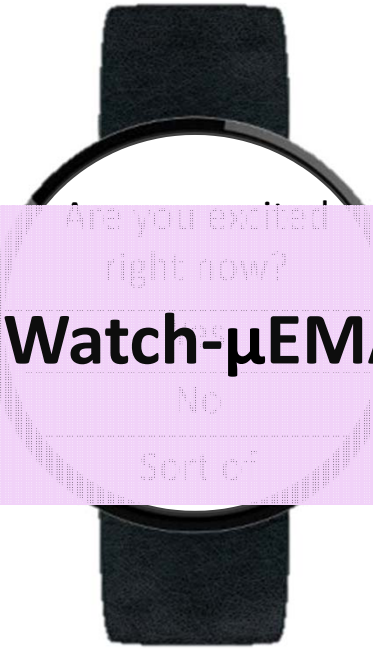


Use microinteractions

mobile-EMA



Watch-µEMA



µEMA using a smartwatch → Watch-µEMA

Interrupt less, ask more

Interrupt more, ask less

Recent pilot results

- **Despite ~8 times more interruption**, watch-µEMA had **higher response rates and study compliance** than mobile-EMA

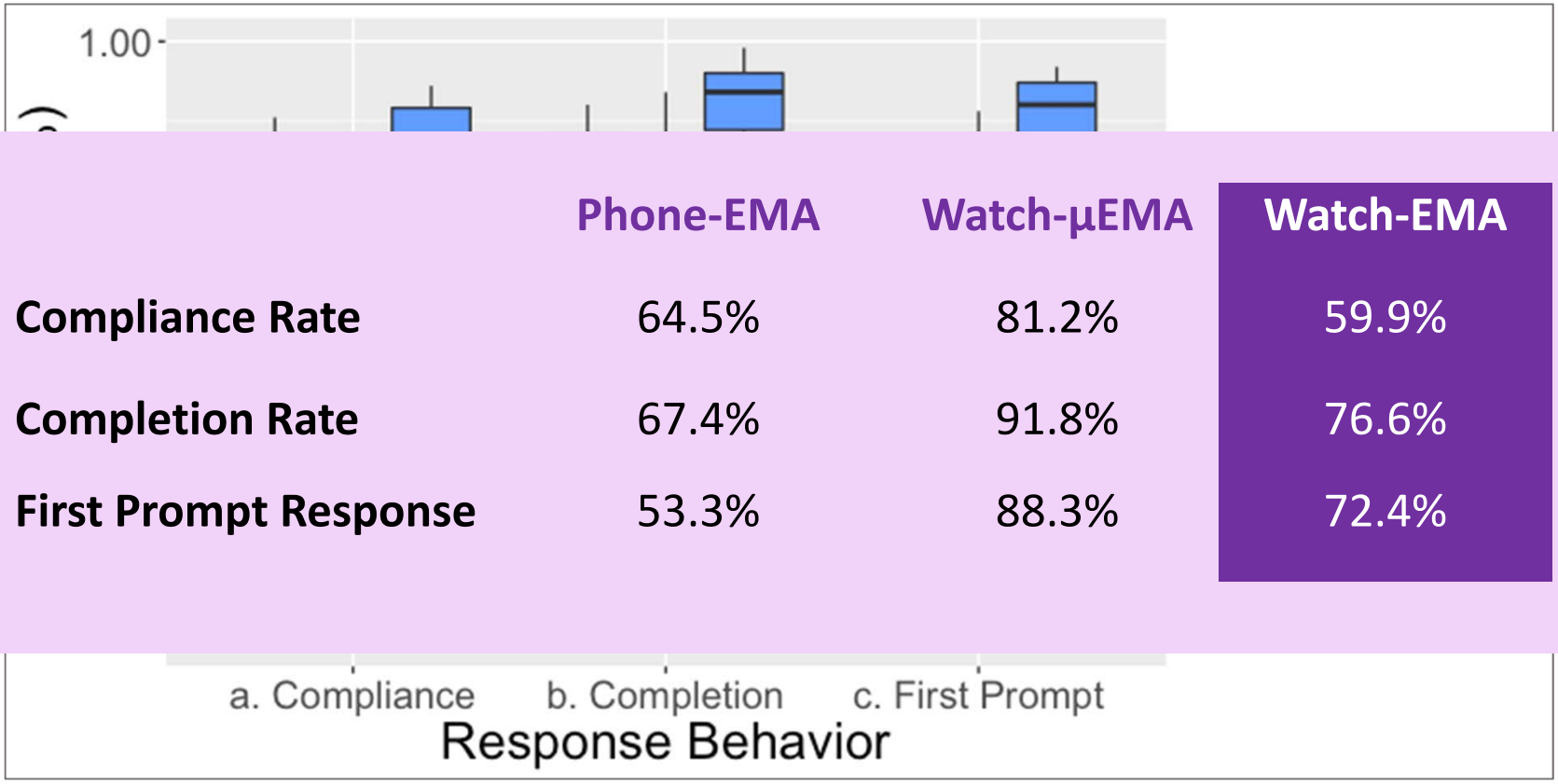
- Despite **interruption rates as high as 8 per hour**, watch-µEMA was **perceived as more tolerable** than mobile-EMA

?

Is the effect due to microinteractions or the smartwatch alone?

Results – All response rates

Response rates summary



	Phone-EMA	Watch-µEMA	Watch-EMA
Compliance Rate	64.5%	81.2%	59.9%
Completion Rate	67.4%	91.8%	76.6%
First Prompt Response	53.3%	88.3%	72.4%

Microinteractions

The novelty of a smartwatch and its easy access alone are **not sufficient to drastically improve EMA compliance** and reduce burden

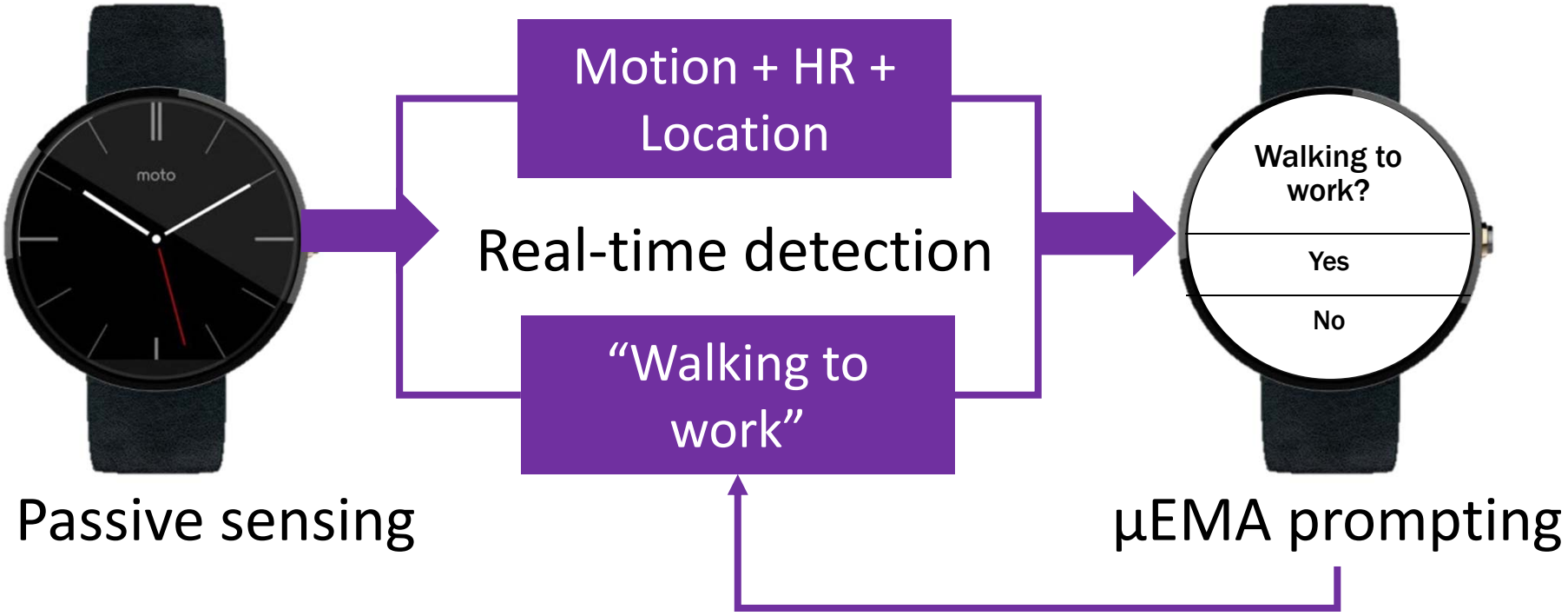
Microinteractions appear to be necessary

Intille et al., "µEMA: Microinteraction-based ecological momentary assessment (EMA) using a smartwatch," in Proc. of the 2016 ACM Int'l Joint Conf. Pervasive and Ubiquitous Computing: ACM, 2016, pp. 1124-1128.

Ponnada et al., "Microinteraction ecological momentary assessment response rates: Effect of microinteractions or the smartwatch?," Proc. ACM J. Interactive, Mobile, Wearable, and Ubiquitous Technology, vol. 1, 2017.

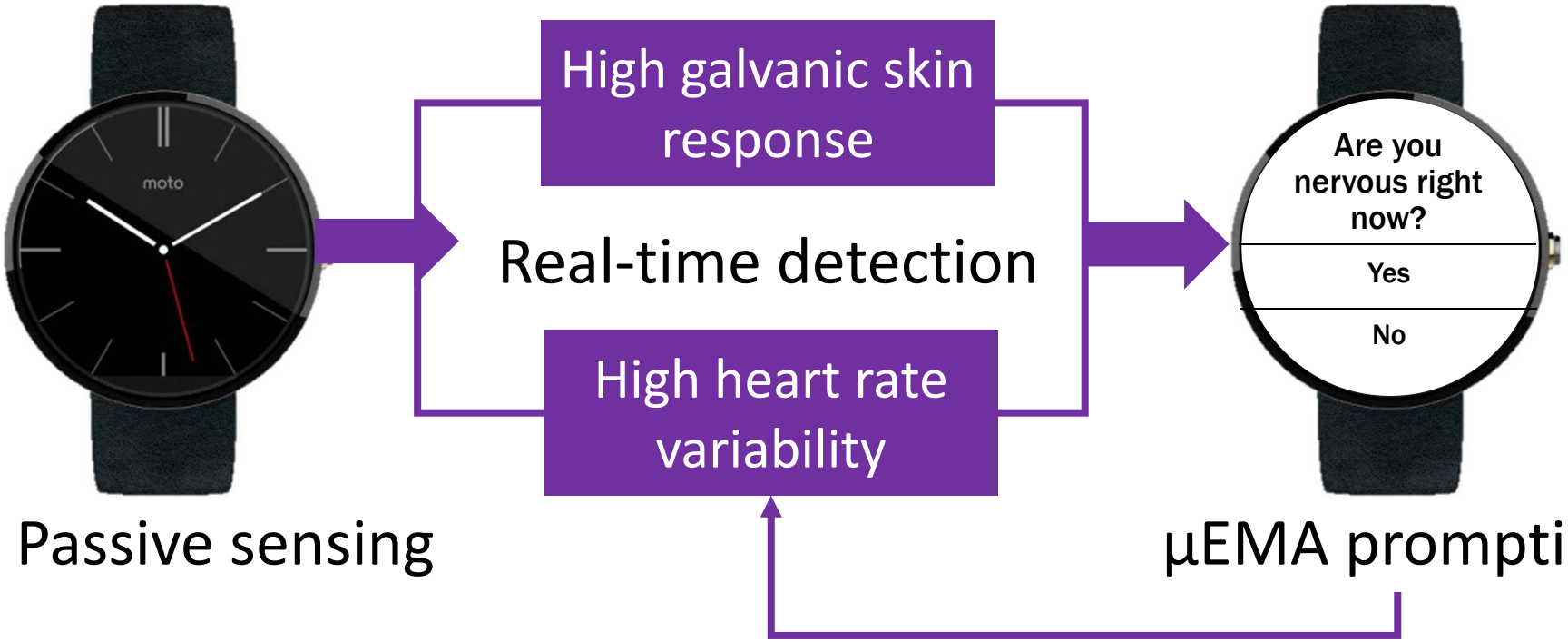
Future: Sensing + µEMA

Validate activity/state recognition



Future: Sensing + µEMA

Validate activity/state recognition



Take away

- Tools for measuring behavior, states, and context of people are poor
- Smartphones, smartwatches, and other wearable sensors provide new sensor data
- These “digital breadcrumbs” can be used by algorithms to infer behavior, states, and contexts
- This also enables context-sensitive self-report, which may further improve our behavioral measures

Stephen Intille
Contact: s.intille@northeastern.edu

Thanks to:

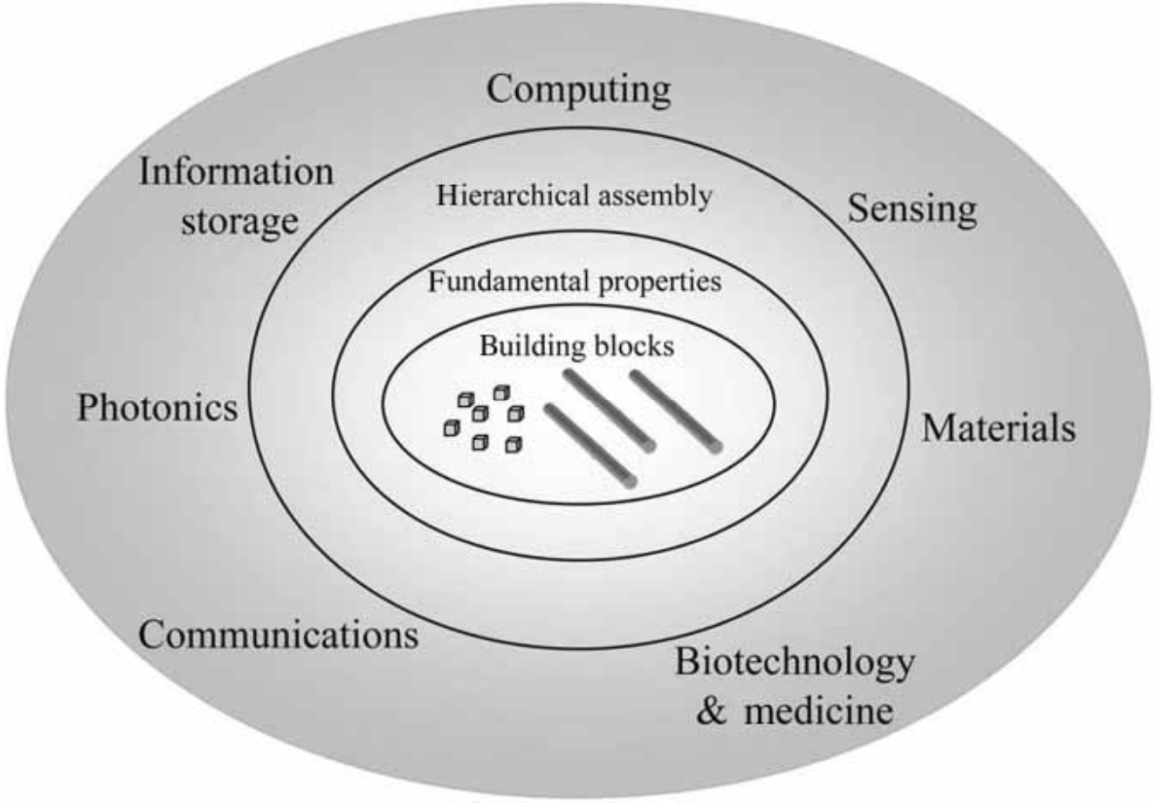
- NIH (R21 HL108018)
- NIH (UO1 HL091737)
- Google Glass Research Award

Nanoelectronic Devices for Cellular Interfaces and Hybrid Tissues

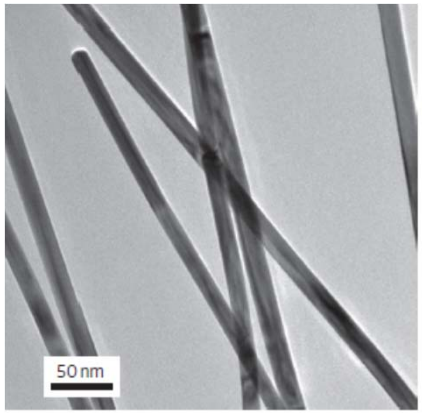
Brian P. Timko, Ph.D.
Assistant Professor
Tufts University Department of Biomedical Engineering

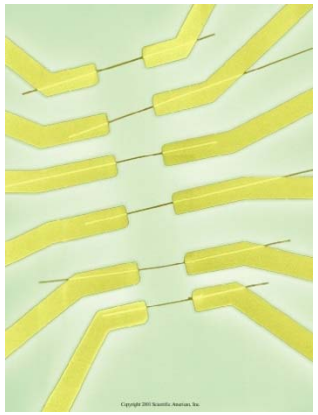
Tufts | CTSI
Tufts Clinical and Translational Science Institute

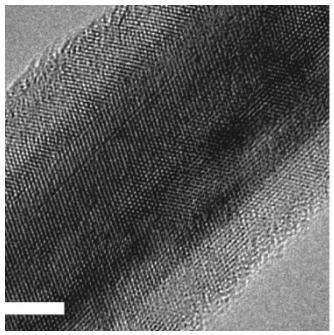
Bottom-up Paradigm

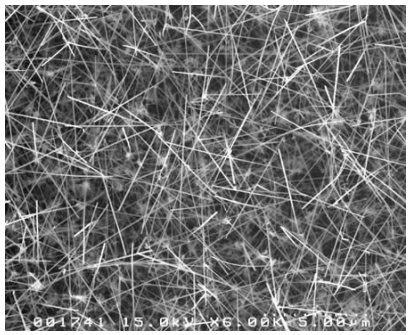


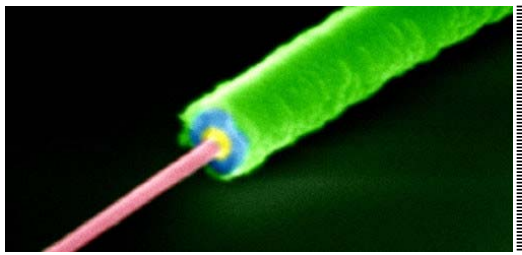
Nanowires: An Overview

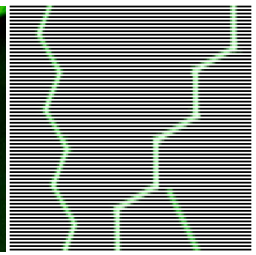












- **1D**: 10-100 nm wide
- Ca. 10 um long
- Single crystalline
- Function as building blocks for **active** or **passive** nanoelectronics

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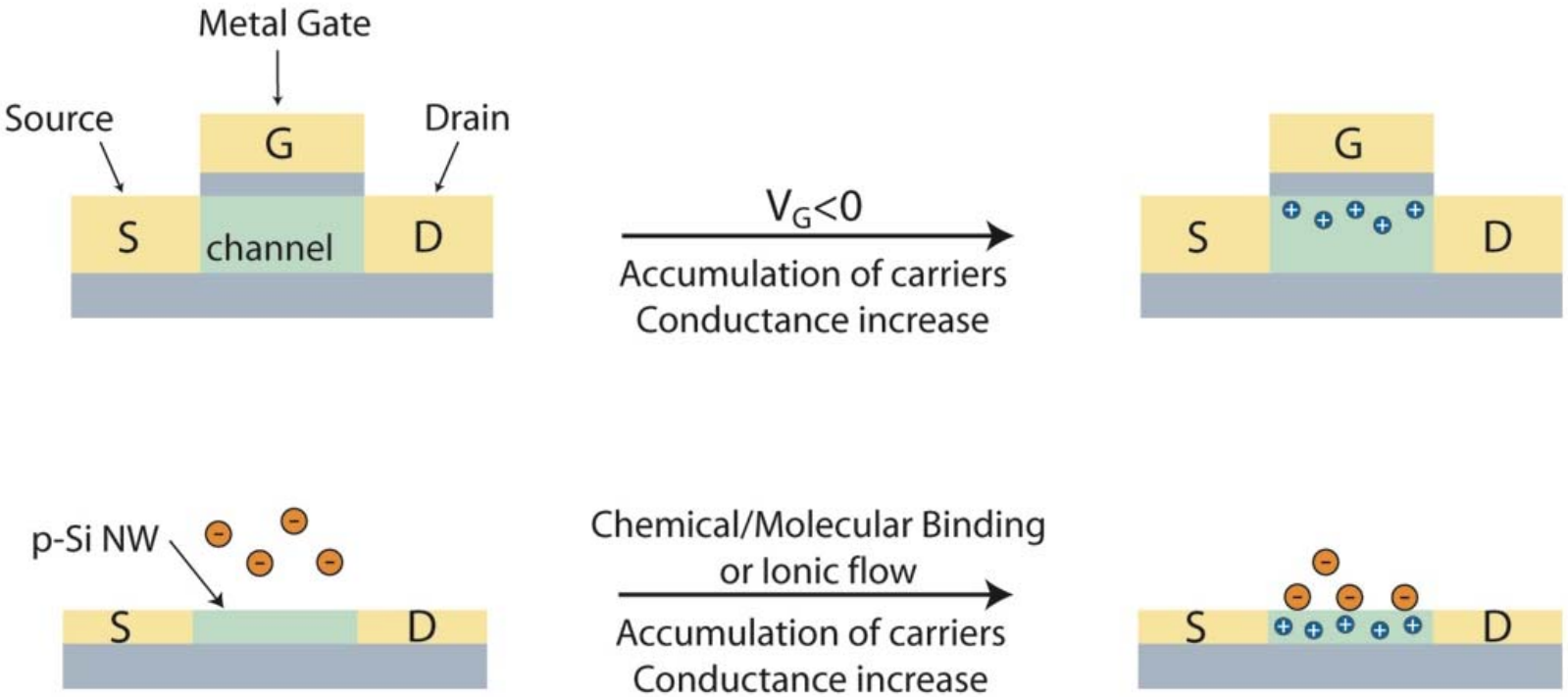
Tufts Clinical and Translational Science Institute

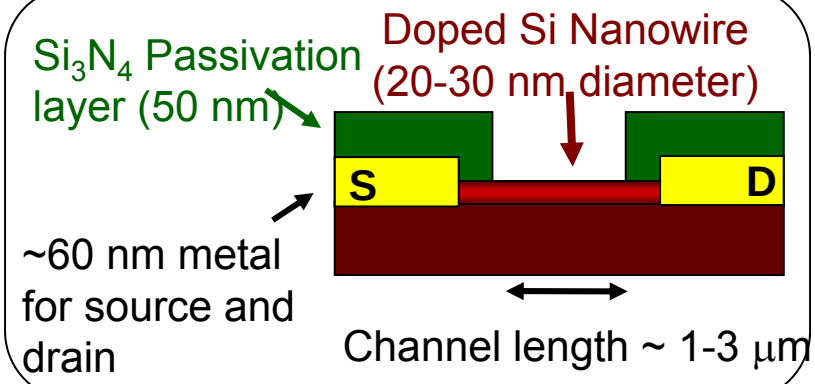
Nanowire FETs as Biosensors

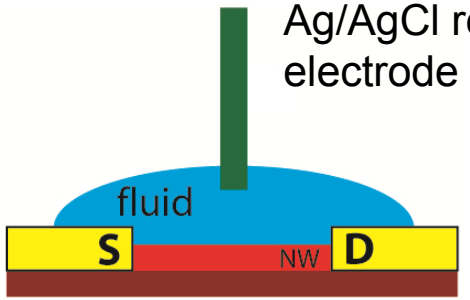


Tufts | CTSI

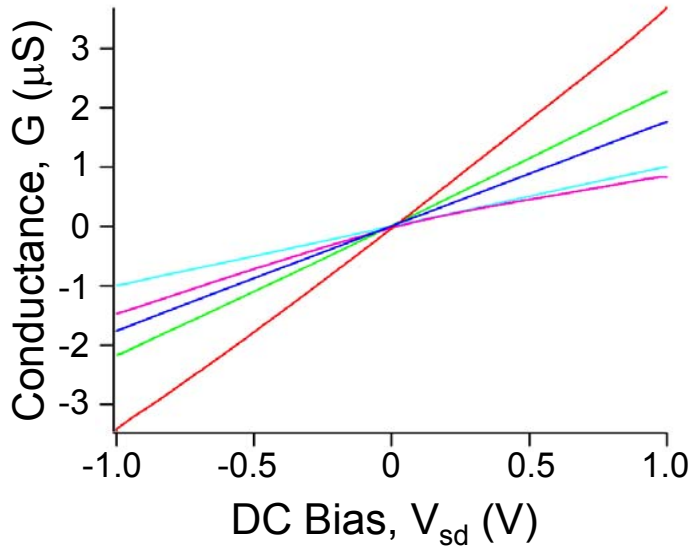
Tufts Clinical and Translational Science Institute

Water Gate Experiments Reveal FET Behavior



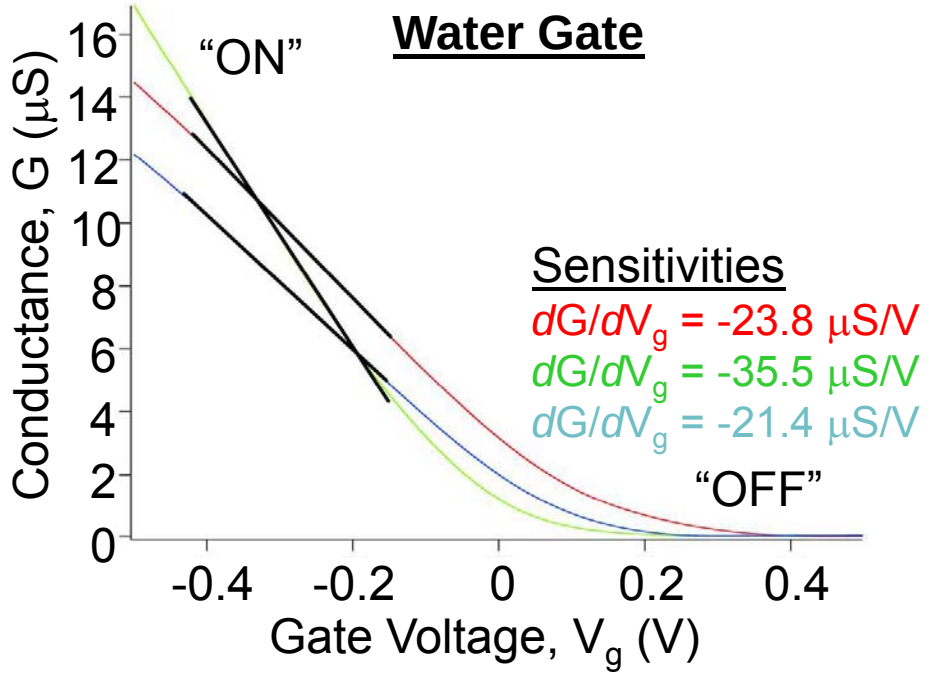


Dry State IV



- Contacts metalized with **Ni** or **Ti/Pd/Ti** are Ohmic.

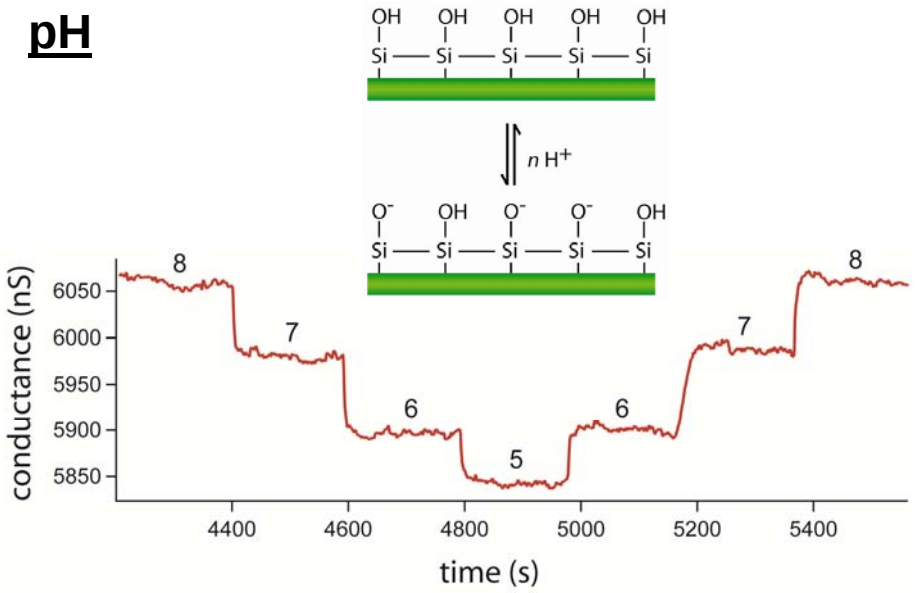
Water Gate



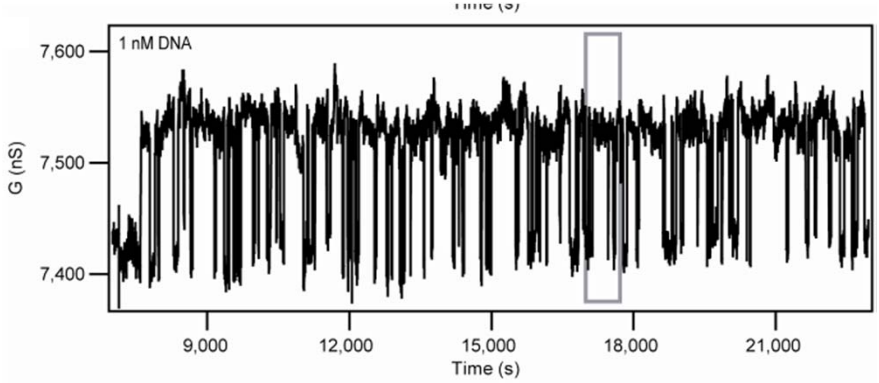
- Sensitivities (dG/dV_g) in the linear regime range from **10 μS/V to 30 μS/V.**

NW-FETs Achieve Biosensing

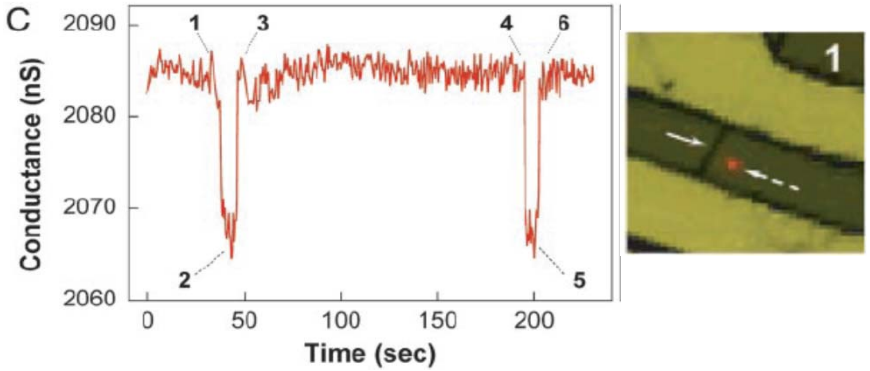
pH



DNA

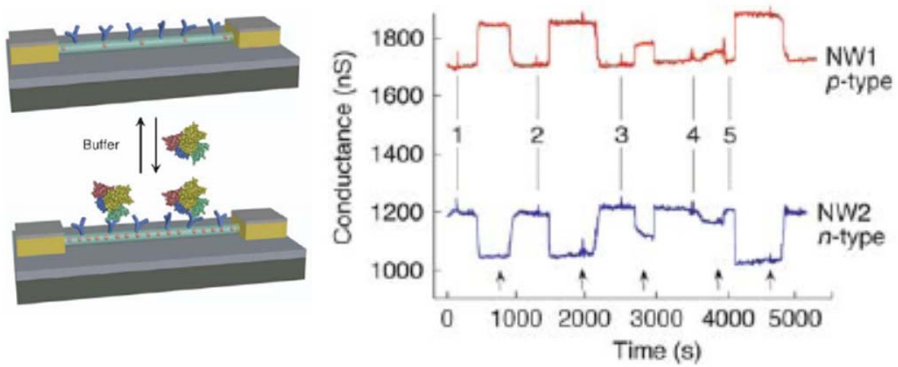


Virus



Single virus sensitivity

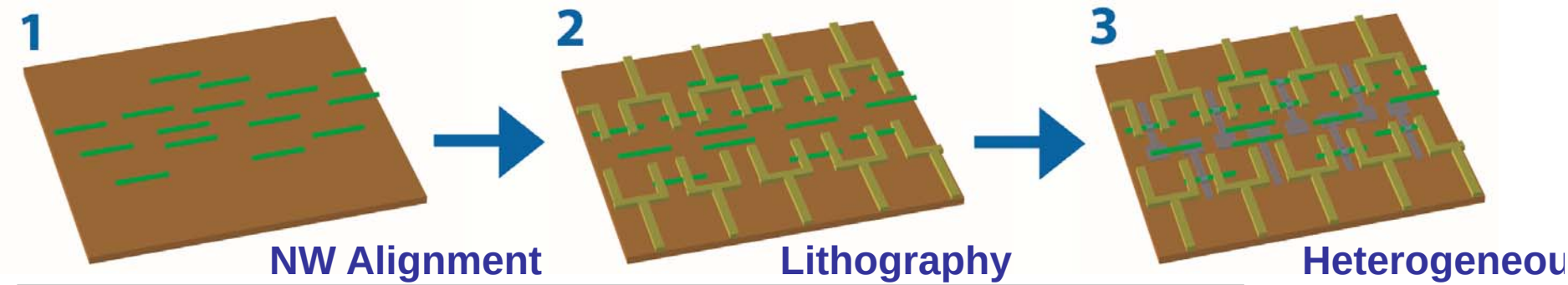
Proteins



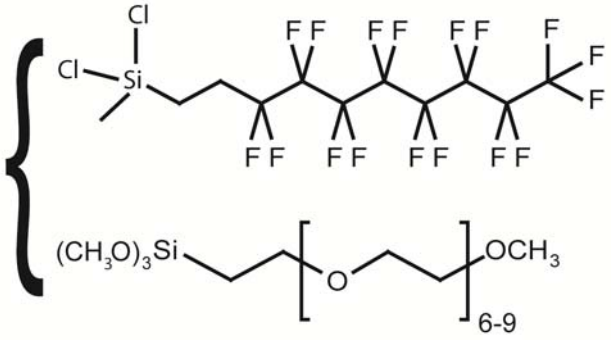
fM PSA sensitivity

F. Patolsky, **B. P. Timko**, G. Zheng, C. M. Lieber, *MRS Bull.* **32,** 142 (2007). (review)
B. P. Timko et. al., *IEEE Trans. Nanotechnol,* 9, 269 (2009). (review)

Heterogeneous patterning achieves neuronal guidance

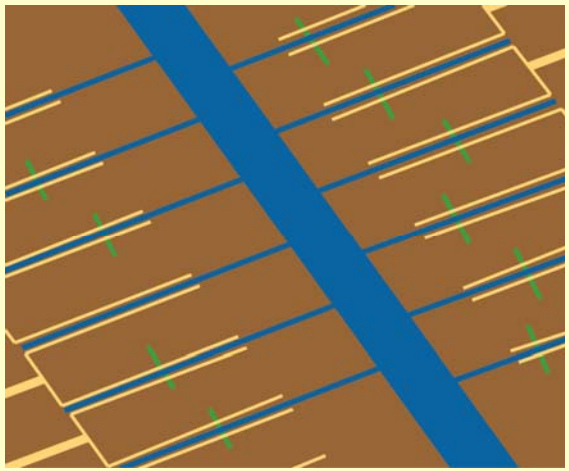


silane for SAM =

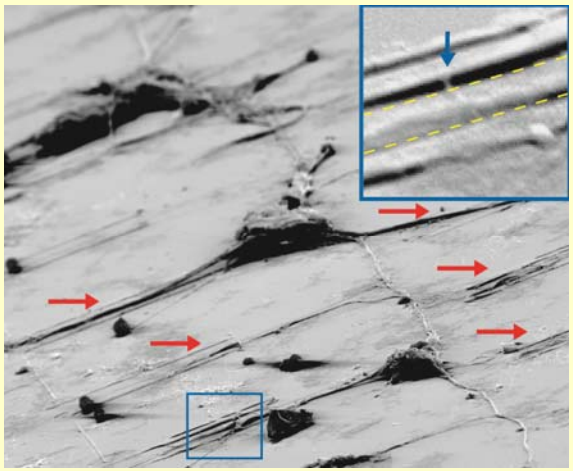


Adhesion factor = poly-d-lysine

Patterning scheme



SEM of patterned neurons

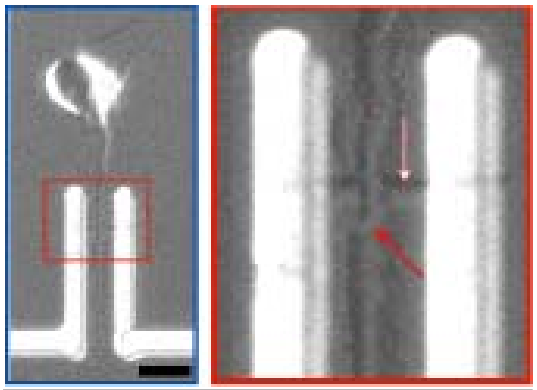


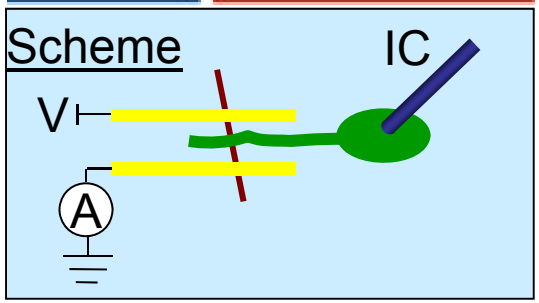
- SEM of fixed neurons indicates good alignment.
- Neurons can be patterned to cross one or multiple NW devices.

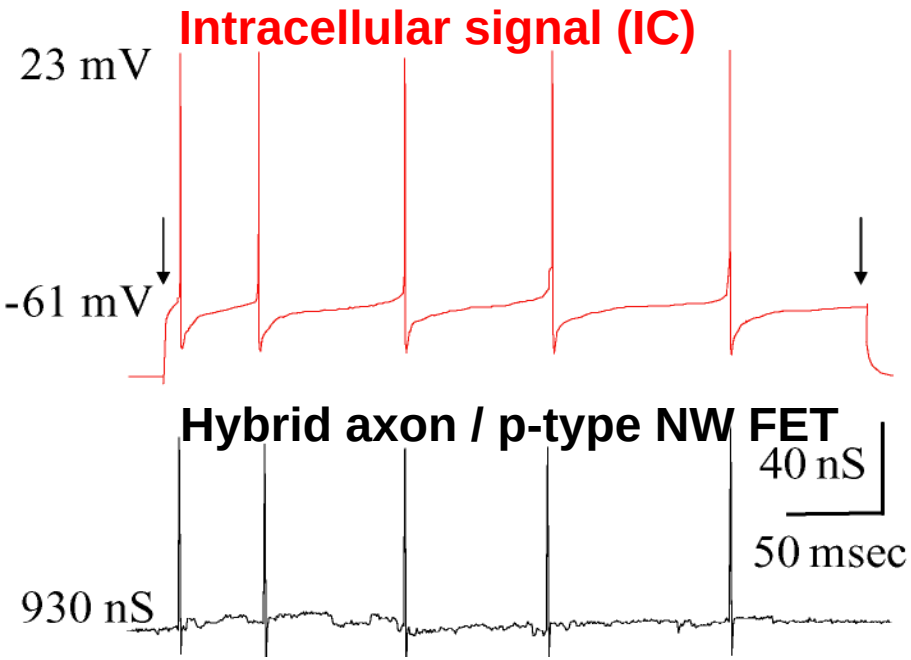
Axon / Nanowire Interface

Can we use NW interfaces to measure action potential signals from neurons?

- Neurons were cultured in a **1 axon / 1 NW device motif.**
- Small device-axon interface area (ca. 20 nm x 1 μm) represents **first-ever "artificial synapse"!**
- **NW** and **IC** signals were measured simultaneously.





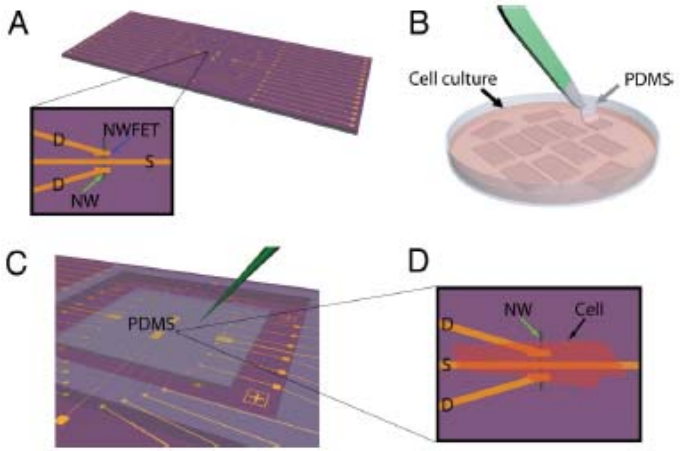


- **IC** and **NW** signals are **correlated in time.**
- Positive signals from the p-type NW represent a **negative potential in the junction.**

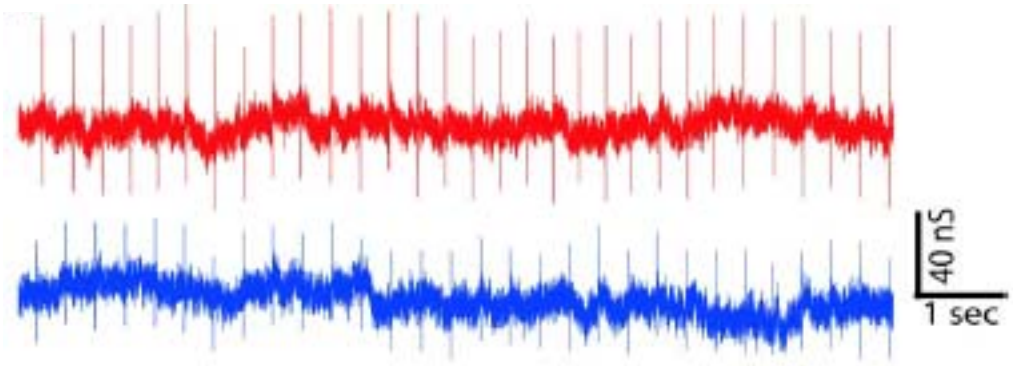
B.P. Timko,* F. Patolsky,* G. Yu, Y. Fang, A.B. Greytak, G. Zheng & C.M. Lieber, *Science* **313,** 1100 (2006).

Neuron / Substrate Coupling: Qualitative View

Cardiac myocytes were cultured on PDMS slabs



Spontaneous beating

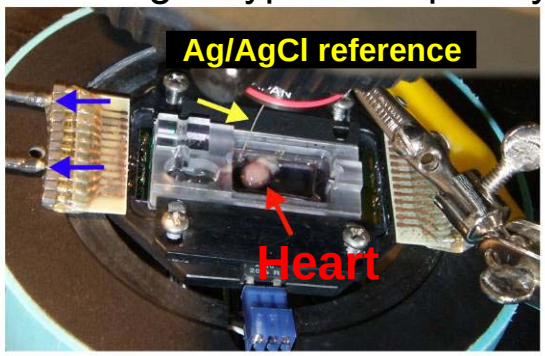


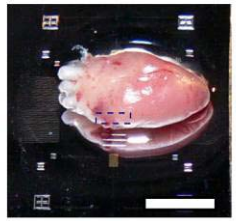
T. Cohen-Karni,* **B.P. Timko,*** L. Weiss & C.M. Lieber, *PNAS* **106,** 7309 (2009).

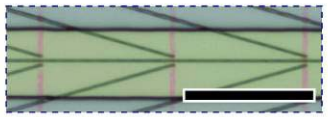
Heart-Nanowire Interfaces

Can the NW-neuron approach be extended to entire organs?

- Embryonic chicken hearts (E11-15) were isolated. They beat spontaneously on the heated stage. Typical frequency was 1-3 Hz.

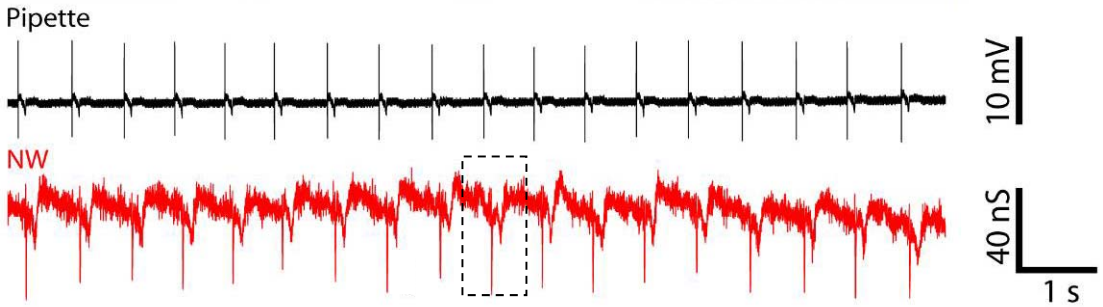


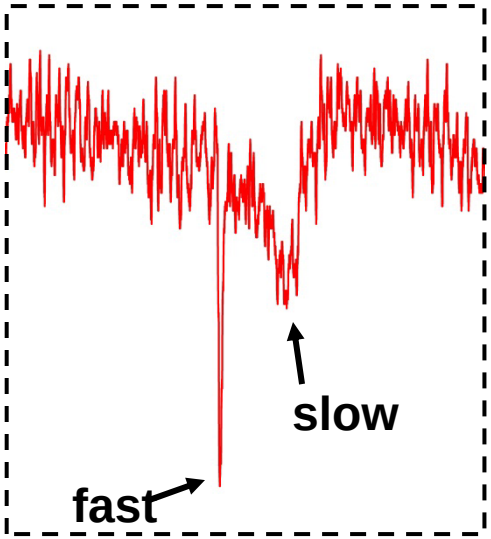




Active device region is located beneath tissue

Device spacing is 150 μm



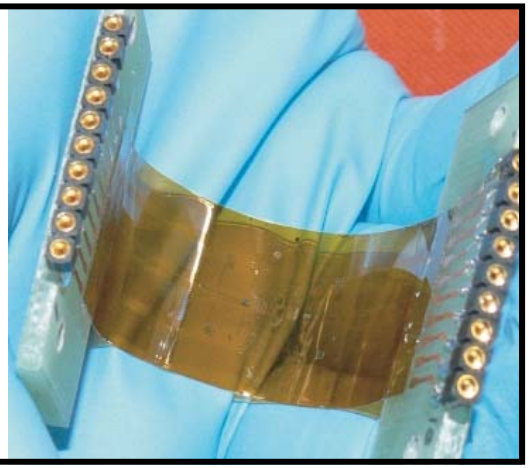


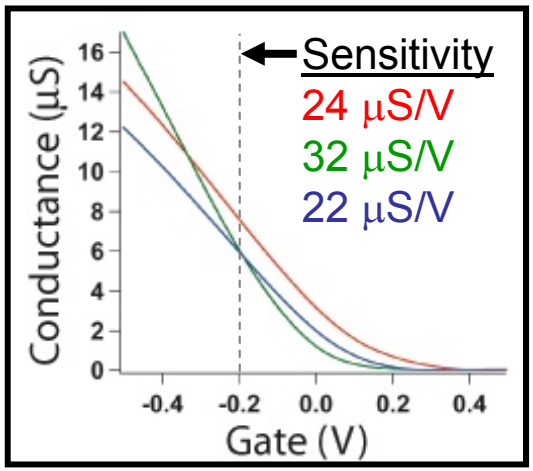
- NW recording is correlated to conventional IC electrode.
- Signals have two phases:
  - **Fast phase** (6.8±0.7 ms)
  - **Slow phase** (31±9 ms)

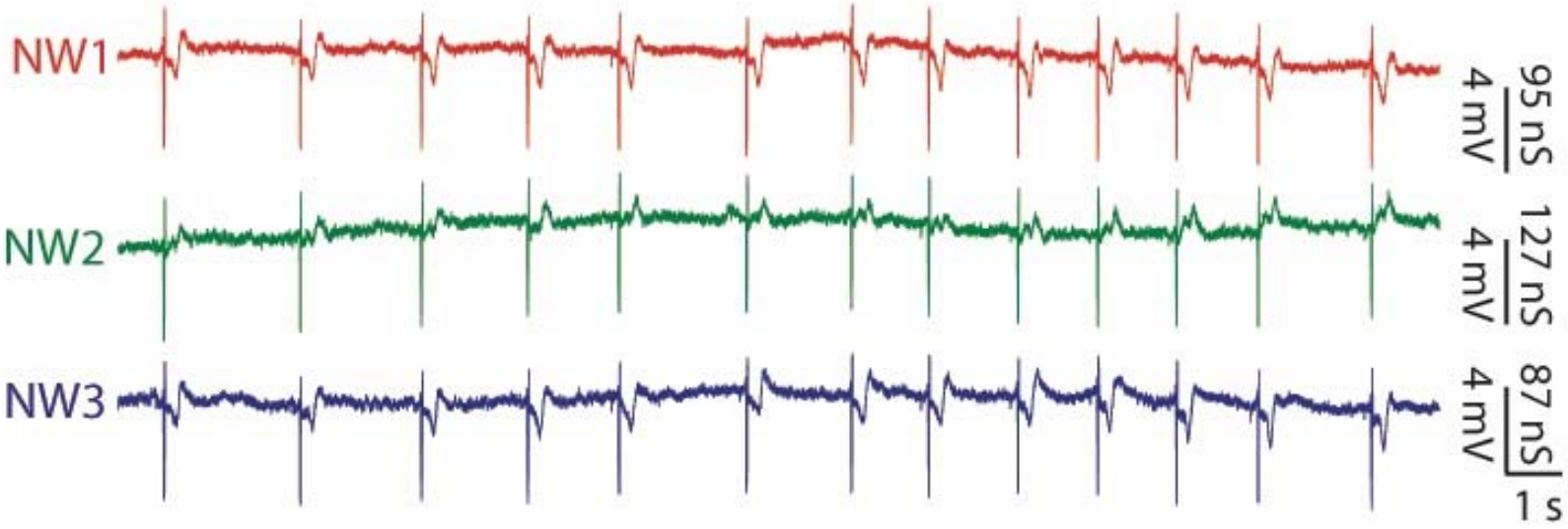
B.P. Timko,* T. Cohen-Karni,* G. Yu, B. Tian, Q. Qing & C.M. Lieber, *Nano. Lett.* **9,** 914 (2009).

Flexible, Multiplexed Electronics

- Kapton polymer substrates are **transparent, flexible, and biocompatible.**
- We fabricated devices on **50-μm thick Kapton.**

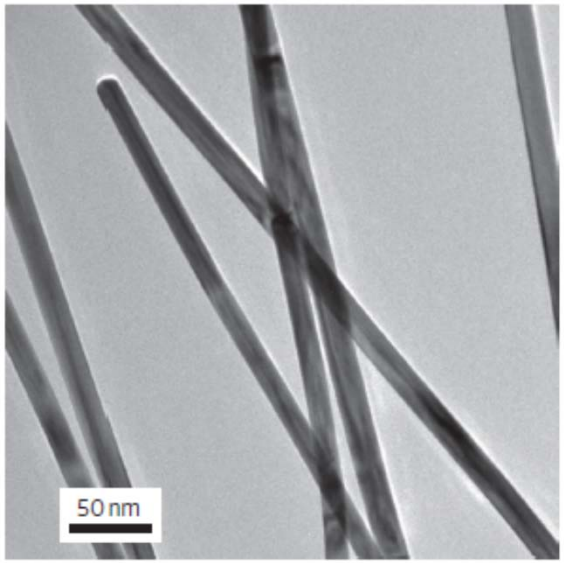


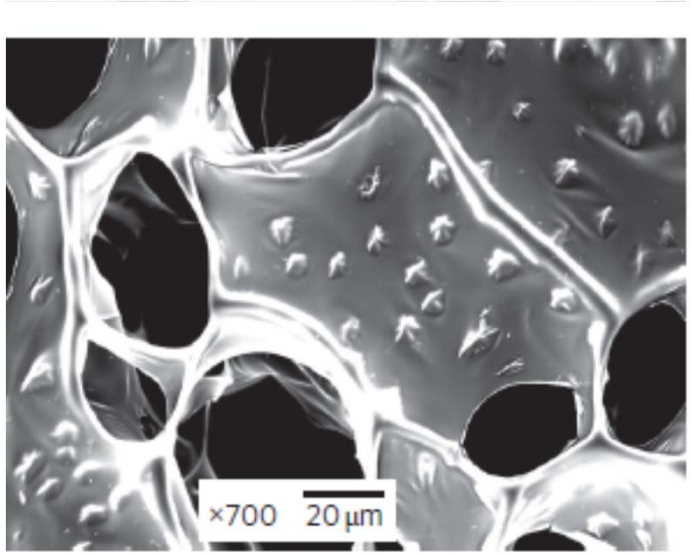




- Conductance magnitudes are **127±4 nS, 146±4 nS** and **114±4 nS.**
- Calibrated peak magnitudes are **5.3±0.2 mV, 4.6±0.1 mV** and **5.3±0.2 mV.**

Materials: Gold Nanowires and Composite Scaffolds



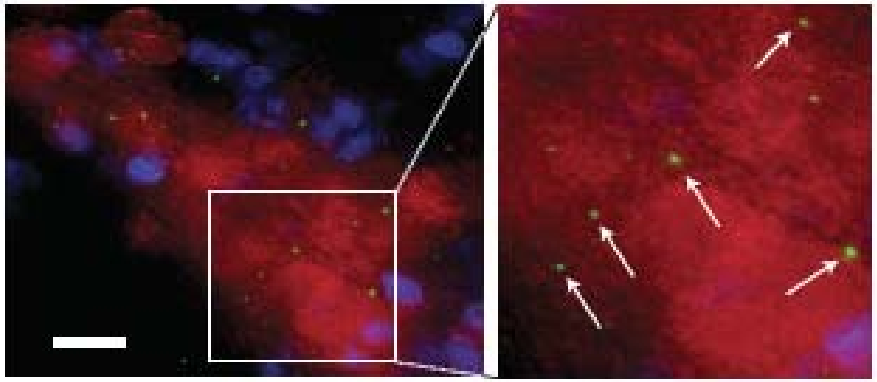


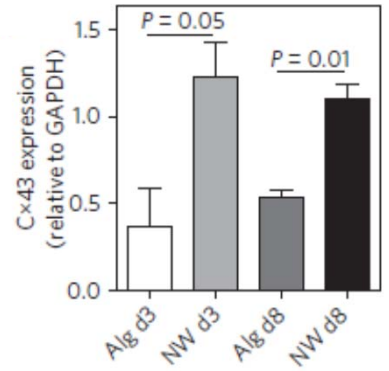
Gold Nanowires

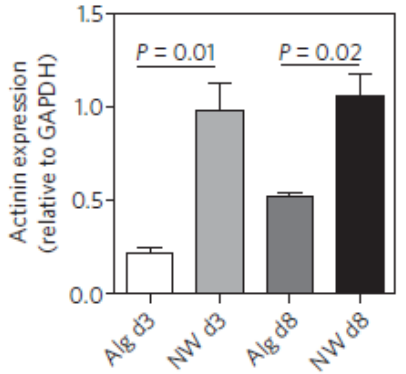
- Diameter: **10-30 nm**
- Length: ca. **1 micron**

Composite Scaffolds

- Concentration of AuNWs in hydrogel: **1-5 mg/ml**
- Avg. pore size in lyophilized material: **100 µm.**







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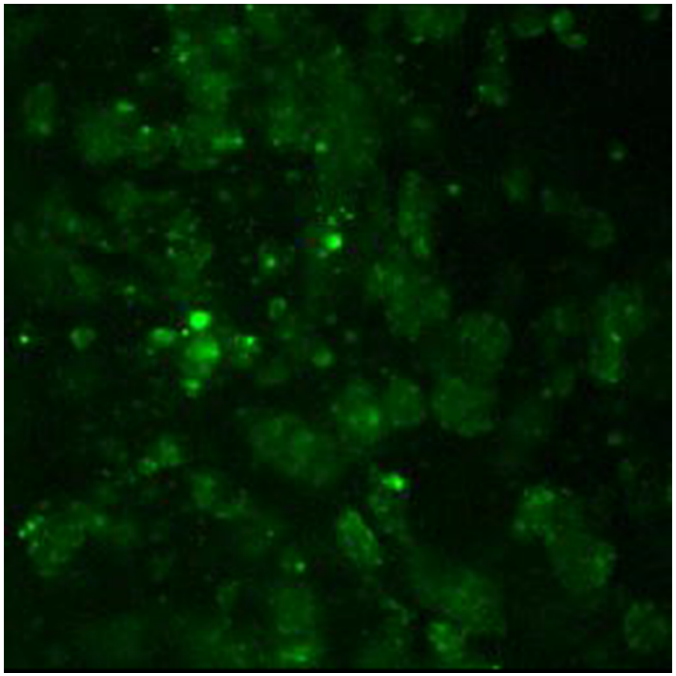
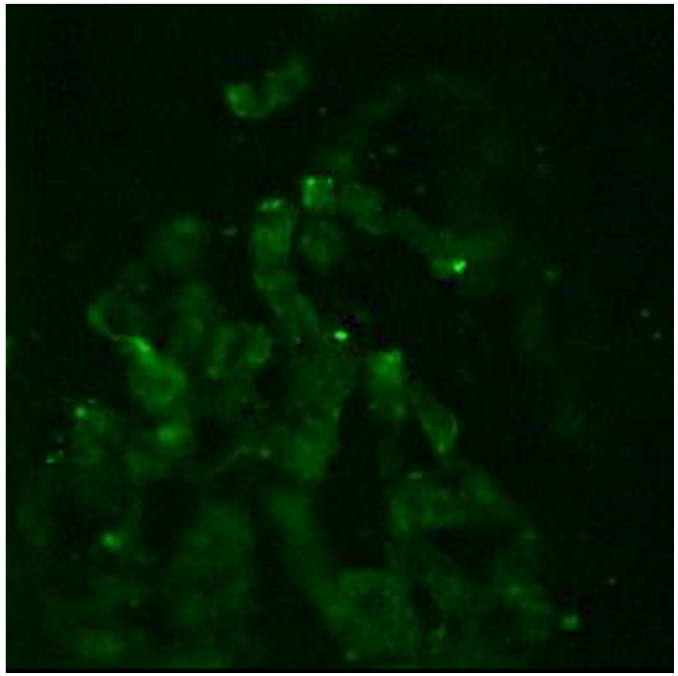
Protein Expression and Electrophysiology

Calcium-sensitive dyes *reveal electrical conductivity of engineered tissue.*

Pristine Alginate



Alginate-NW Composite

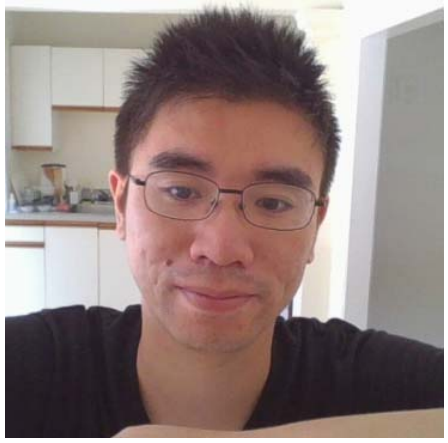


Pristine Alginate: Transients do not travel more than **100 μm**. Cells form **isolated clusters.**

Alg-NW Composite: Transients travel on the order of **millimeters.**




Questions?

Sensors & Devices

Q&A

Navin Kapur, MD
Heather Clark, PhD
Stephen Intille, PhD
Brian Timko, PhD

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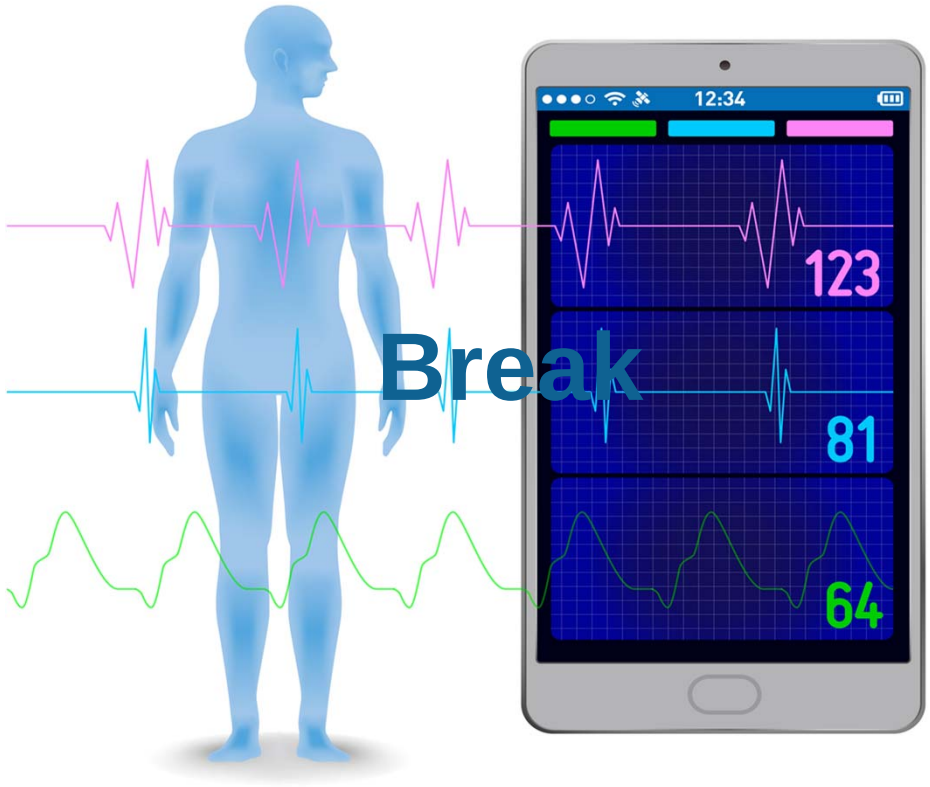

Break

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Biomarker Development and Application

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Harmonizing Biomarker Terminology: NIH-FDA BEST (Biomarkers, EndpointS, and other Tools)

Joining via WebEx

Christopher Leptak, MD, PhD

Director, OND Regulatory Science Program
Director, Biomarker Qualification Program
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
US Food and Drug Administration (FDA)

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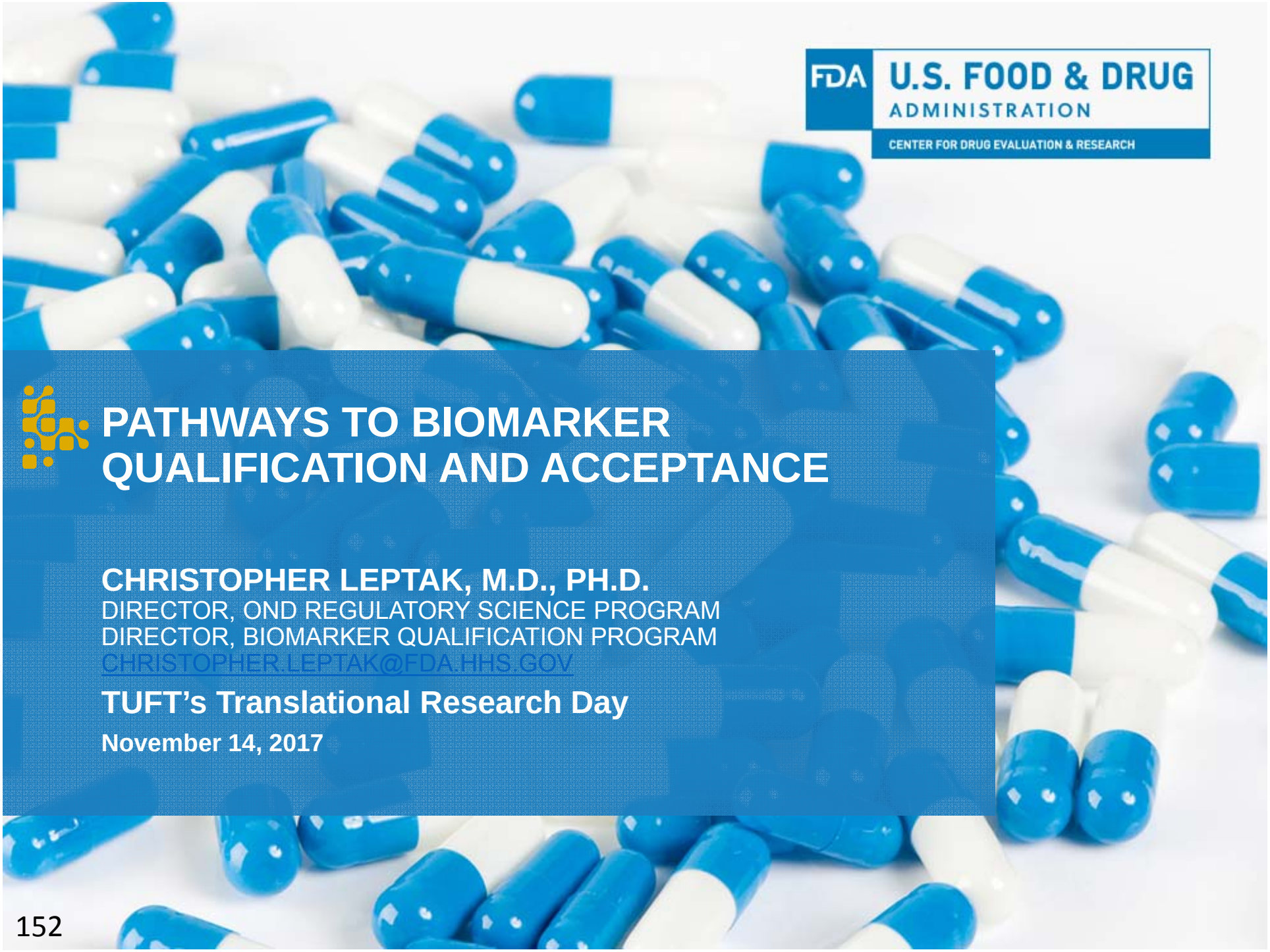


PATHWAYS TO BIOMARKER QUALIFICATION AND ACCEPTANCE

CHRISTOPHER LEPTAK, M.D., PH.D.
DIRECTOR, OND REGULATORY SCIENCE PROGRAM
DIRECTOR, BIOMARKER QUALIFICATION PROGRAM
CHRISTOPHER.LEPTAK@FDA.HHS.GOV

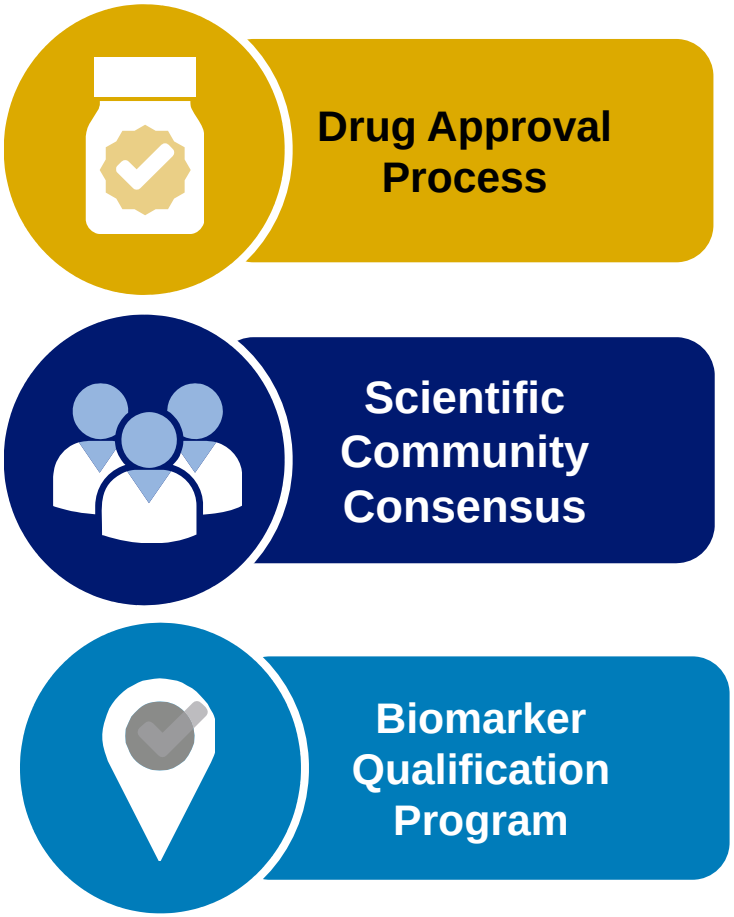
TUFT's Translational Research Day

November 14, 2017

FDA Regulatory Approach to Biomarkers

- *Biomarker*: a defined characteristic that is measured as an 1) indicator of normal or pathogenic biological processes or 2) response to an intervention.
- Broadly defined, with multiple biomarker types including molecular, histologic, radiographic, and physiologic. (i.e., serum protein, change in tumor size by imaging study, algorithm for QT determination on ECG)
- Characteristic is not a *clinical* assessment of how a patient feels, functions, or survives (contrasted with Clinical Outcome Assessments [COAs])
- Basic science research, clinical, and regulatory communities all use biomarkers, but each has unique requirements for acceptability. For regulators, drug approvals for patient populations consider data reproducibility, strength of association with clinical outcome, and feasibility of use.

BIOMARKER INTEGRATION INTO DRUG DEVELOPMENT



Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

DRUG APPROVAL (IND/NDA/BLA) APPROACH FOR BIOMARKER DEVELOPMENT

Drug Approval Process

Strengths

- Generally, biomarker use has a well-defined purpose
- Data (clinical trial information) available to the biomarker developer
- Opportunities to bring in outside experts
- Company maintains proprietary rights

Limitations

- Biomarker may not be generalizable
- Limited opportunities for additional data sources
- Company responsible for development costs
- Limited opportunities for engagement with outside stakeholder groups
- Biomarker information in drug labels and reviews are available only upon drug approval

SCIENTIFIC COMMUNITY CONSENSUS APPROACH FOR BIOMARKER DEVELOPMENT

Strengths

- Extensive knowledge base of exploratory biomarker data in published literature
- Opportunity for broad and multiple community inputs
- Public access and cost-sharing approach (e.g., NIH and other grant funded research)

Limitations

- Published data may not be not reproducible
- Protracted time for consensus building
- Variability of study designs, populations, and analytics
- Applicability to regulatory paradigms

BIOMARKER QUALIFICATION APPROACH FOR BIOMARKER DEVELOPMENT

Biomarker Qualification Program

Strengths

- Context of use clearly established
- Opportunity to pool resources , share costs and bring outside experts
- Leverage outside stakeholder groups
- Outcome is a public guidance with supporting reviews

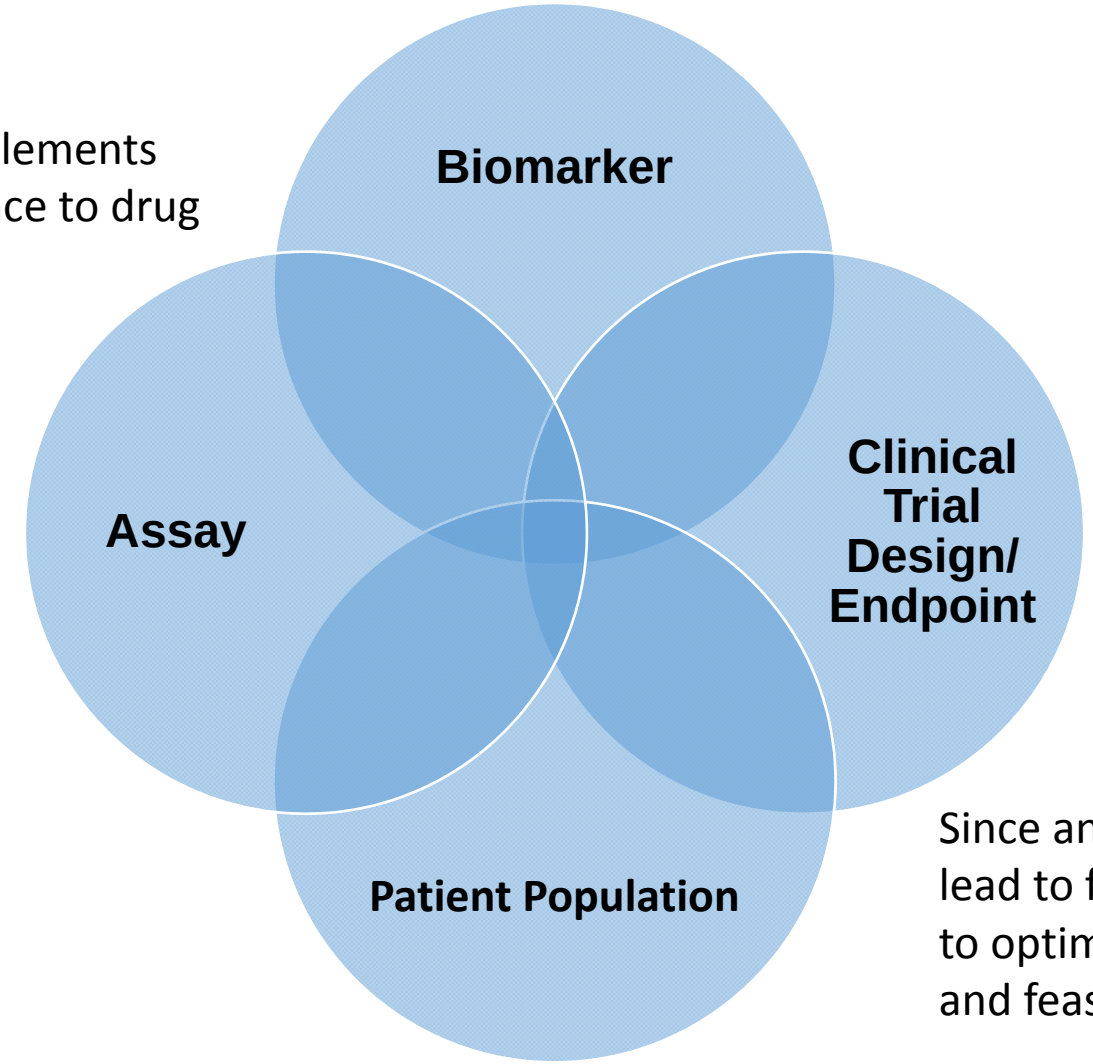
Limitations

- If part of a group effort, stakeholders may have differing goals, level of commitment, and engagement
- Data (clinical trial information) may not be readily available
- Data sharing and aggregation may be challenging

 https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm

COMPONENTS OF DRUG DEVELOPMENT SUCCESS

Each of these elements share importance to drug approval



Since any element can lead to failure, important to optimize as appropriate and feasible

Biomarkers: Speaking the Same Language…

"The BEST (Biomarkers, EndpointS, and Tools) Resource"

FDA-NIH Working Group

FDA-NIH JOINT EFFORT

- In the spring of 2015, the FDA-NIH Joint Leadership Council identified the harmonization of terms used in translational science and medical product development as a priority need, with a focus on terms related to biomarkers and study endpoints
- Goals of improving communication, aligning expectations, and improving scientific understanding
- The first phase of BEST comprises a glossary that clarifies important definitions and describes some of the hierarchical relationships, connections, and relationships among the terms
- Meant to be a living document with periodic updates and opportunity for public input

BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
- Publicly available at http://www.ncbi.nlm.nih.gov/books/NBK326791/
- BEST harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:

- Biomedical scientists
- Translational and clinical researchers
- Medical product developers
- Patient/disease advocacy groups

DEFINING A TERM: *GENERAL APPROACH*

1. Identify existing definitions
2. Identify related terms and definitions
3. Propose a definition
4. Discuss and revise definition
5. Finalize definition

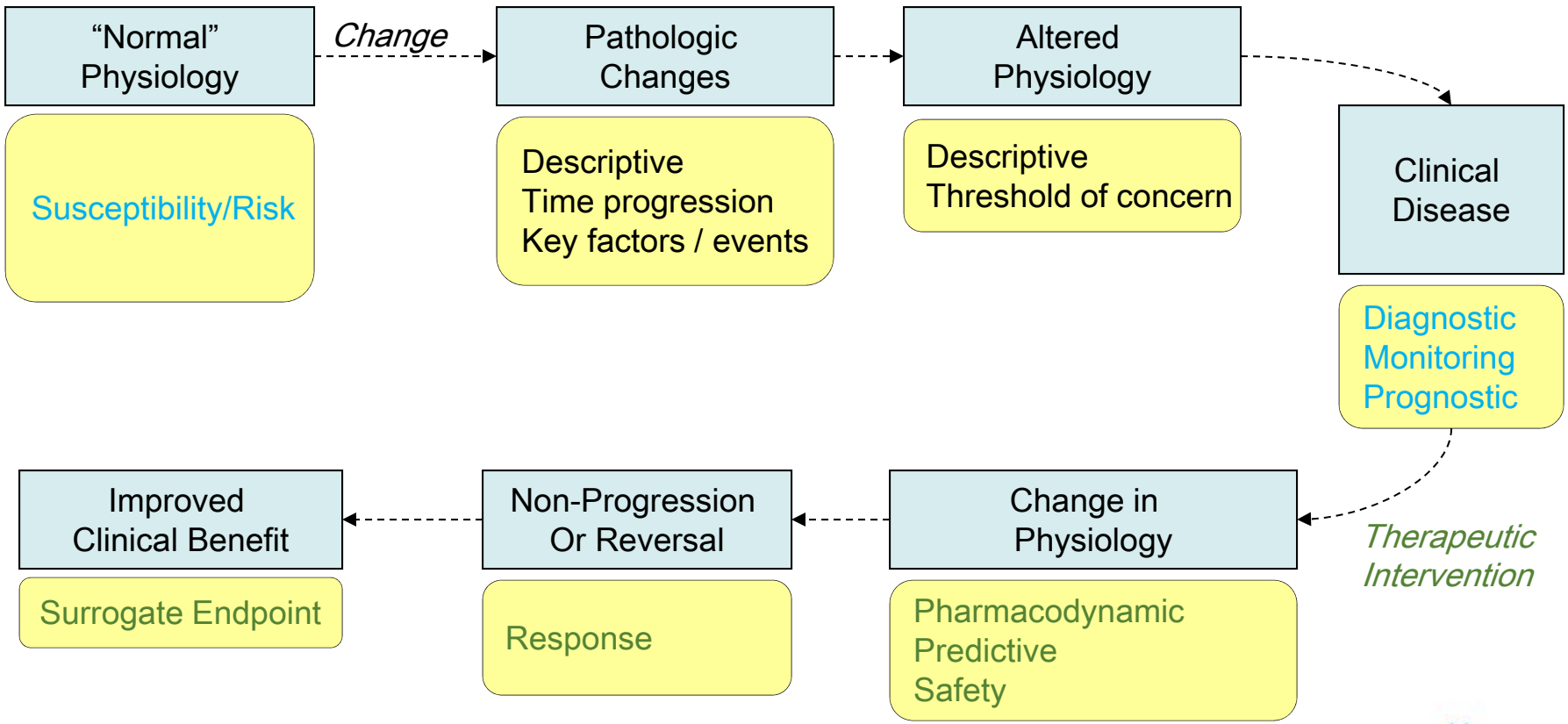
BIOMARKER CATEGORIES: *GUIDING PRINCIPLES*

- **Flexibility to accommodate** new concepts, methodologies, technologies and regulatory domains
- **Preserve distinctions** which are useful in achieving alignment with types of evidence and evidentiary standards
- **Amenable to unification** across stakeholder communities

Biomarker Classes from a Drug Perspective

- **Susceptibility/Risk:** Indicates potential for developing disease before it is clinically apparent (e.g., BRCA mutations and development of breast cancer)
- **Diagnostic:** 1) Detects presence of a disease or condition or 2) identifies patient subsets (e.g., HbA1c to aid in diabetes diagnosis)
- **Monitoring:** Assesses disease status, including degree or extent, through serial measurement (e.g., INR and anti-coagulation status)
- **Prognostic:** Identifies likelihood of a clinical event, disease recurrence, or progression, in in the absence of a therapeutic intervention (e.g., BRCA mutations and breast cancer recurrence)
- **Predictive:** Identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment (e.g., HLA-B5701 and risk of severe AE with Abacavir)
- **Pharmacodynamic/Response:** Indicates that a biological response has occurred in a patient who has received a therapeutic intervention. May become a clinical trial endpoint and for a very small subset, surrogate endpoint. (e.g., sweat chloride and response to CFTR agents)
- **Safety:** Indicates the likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention (e.g., QTc and Torsades)

"Fit for Purpose": BEST Biomarker Classes in Perspective



CONTEXT OF USE AND DEFINING A BIOMARKER'S UTILITY

COU Format: [BEST category] biomarker for [purpose in drug development] [proposed stage of drug development] in [patient population or targeted group/system].

- Purpose in drug development
  - Inclusion/exclusion criteria for prognostic or predictive enrichment?
  - Alter treatment allocation based on biomarker status?
  - Result in cessation of a patient's participation in a clinical trial because of safety concern?
  - Establish proof of concept for patient population of interest?
  - Support clinical dose selection?
  - Evaluate treatment response (e.g. pharmacodynamic effect)?
  - Support regulatory acceptability of a surrogate endpoint for accelerated or traditional approval?
- Proposed stage of drug development (e.g., early phase clinical trials, nonclinical safety studies)
- Population or model system (e.g., healthy normal volunteers, patients with chronic obstructive pulmonary disease, rats, cultured mouse fibroblasts)

:

THANK YOU FOR YOUR ATTENTION

Metatranscriptomic Approach to Salivary Biomarker Discovery in the Premature Newborn

Jill Maron, MD, MPH

Interim Executive Director
Mother Infant Research Institute
Tufts Medical Center

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Tufts Clinical and Translational Science Institute

Prematurity

- An estimated 15 million infants are born prematurely worldwide each year
  - 500,000 are born in the US

- These infants have increased mortality and are at great risk for wide range of morbidities that may impact their life course

- There is an important need to develop noninvasive biomarkers in the premature neonatal population
  - Monitor*: Health, Disease, and Development*

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Human Saliva

- Saliva is a rich source of both human and microbial information
  - Electrolytes, proteins, nucleic acids, drugs, microbes

- Potential to inform caregivers about the oral as well as the systemic health of an individual

- May be collected repeatedly without inflicting harm

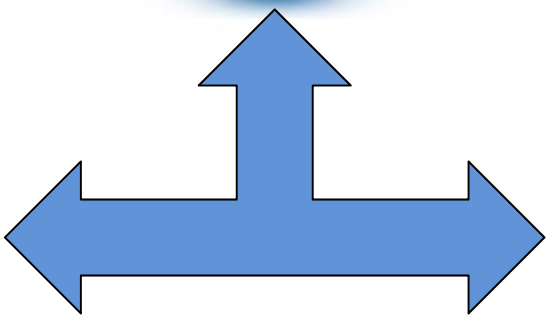
Neonatal Salivary Biomarkers

- **For nearly a decade, my laboratory has explored neonatal saliva at a transcriptomic (gene expression) and proteomic level for biomarker discovery**
  - **Oral feeding readiness**
  - **Speech Emergence**
  - **Development**
  - **Sepsis**

Maron et al., *Clin Chem*, 2010; Maron et al., *PLoS One* 2012; Maron et al., *J Pediatr* 2015; Iyengar et al., Front Pediatr 2014; Zimmerman et al, *Cold Spring Harb Mol Case Stud* 2016

Power of Saliva

One drop of saliva



Gene Expression + Host Response

Microbial Colonization + Function

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Neonatal Saliva

- **Salivary microbial colonization in the newborn is distinct from older children and adults:**

  –Infants are born ‘relatively’ sterile and will colonize rapidly in the first days to weeks to months of life

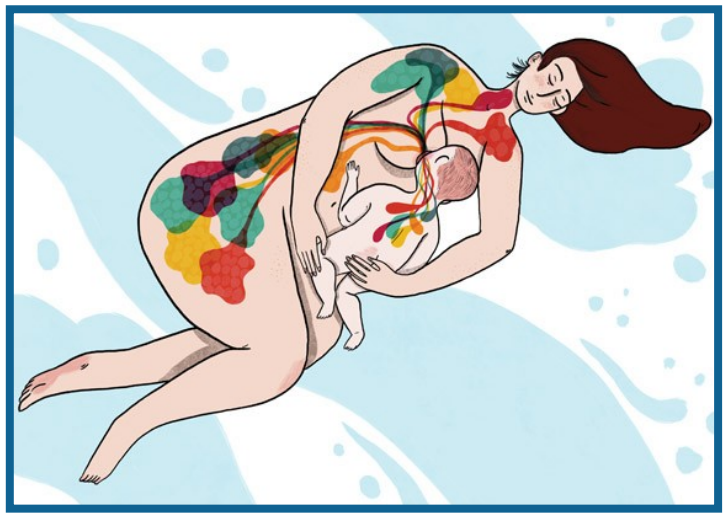
  –Microbial colonization will vary depending upon gestational age, mode of delivery, feeding patterns, and medical complications

  –Infants lack teeth

Neonatal Microbial Colonization

- **Infants develop their initial microbial colonization via swallowing, inhalation and skin-to-skin contact shortly after birth**

- **The oral cavity is an essential conduit to this colonization**



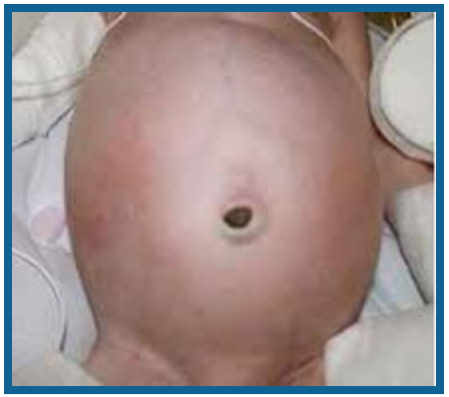
Aims

- **Assess the potential benefit of a metatranscriptomic analysis of neonatal saliva for biomarker discovery**

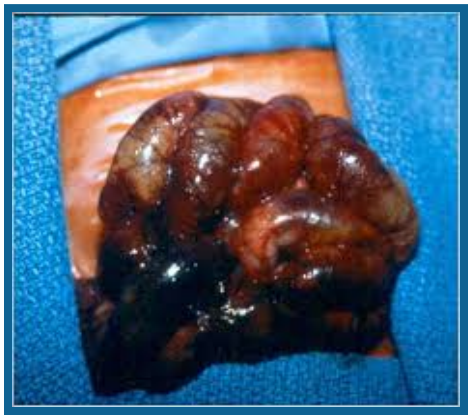
- **Explore both human and microbial gene expression patterns from a single saliva sample in infants who did and did not develop a devastating gastrointestinal disorder—necrotizing enterocolitis (NEC)**

Necrotizing Enterocolitis

- Necrotizing enterocolitis (NEC) presents with acute distension, inflammation and necrosis of the bowel
- It affects between 7-12% of premature newborns born in the United States and Canada
- Inverse correlation between gestational age and NEC



Abdominal Distension



Bowel Necrosis

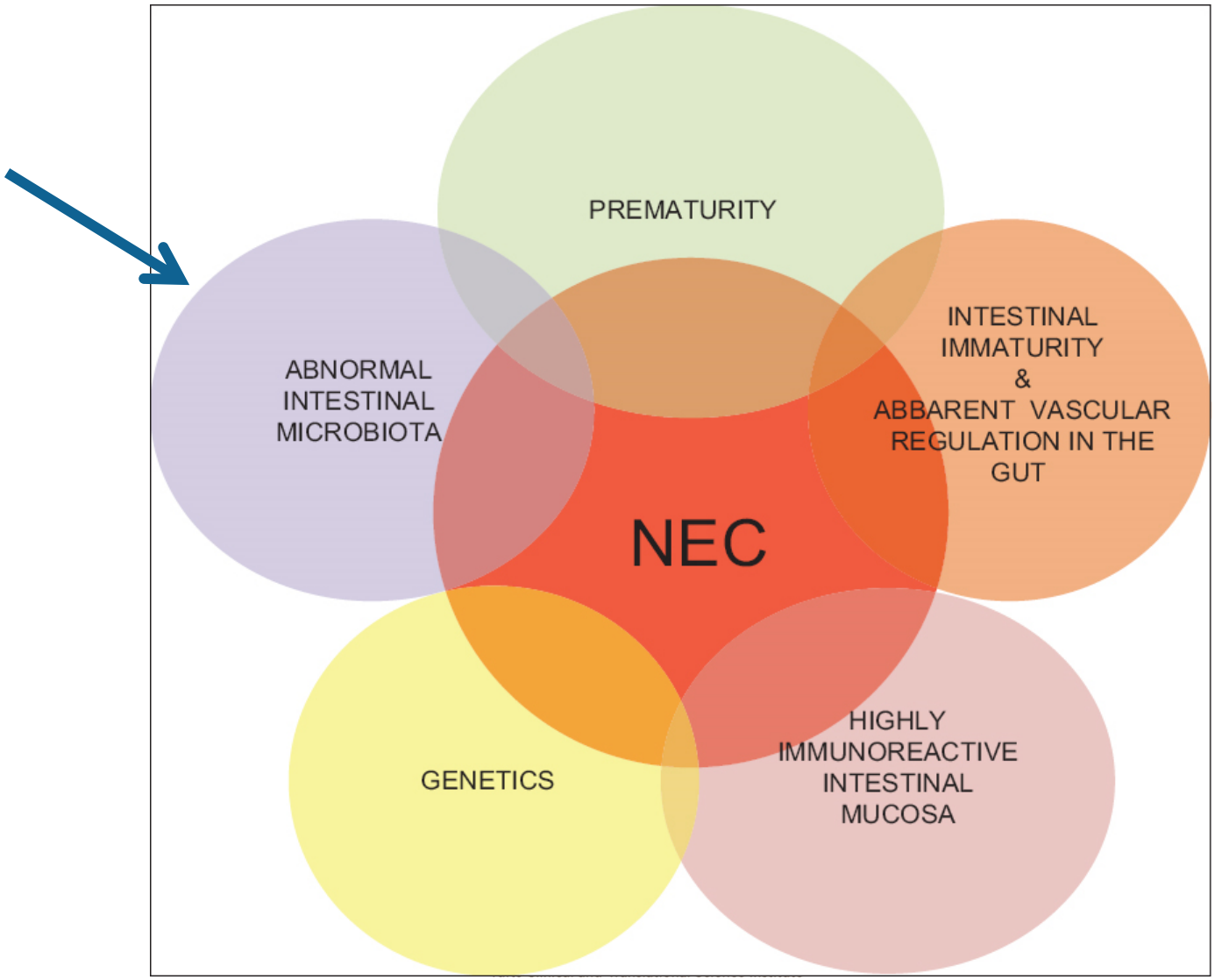
Necrotizing Enterocolitis

- **High rate of associated morbidity and mortality**

- **Survivors of the disease may suffer from:**
  - **Prolonged hospitalization and need for parenteral (IV) nutrition**
  - **Liver failure**
  - **Poor growth**
  - **Short bowel syndrome following resection**
  - **Neurodevelopmental delays**

- ***Etiology of disease remains unknown***

Pathophysiology of NEC



Taken from Haque K. N. *J Clin Neonatal 2016:5:79-90.*

NEC

- Emerging evidence that NEC may be linked to aberrant microbial colonization patterns
- Studies focused on gastrointestinal colonization patterns based upon stool samples
  - Examined the 16s rRNA profiles of serially collected stool samples of infants who developed NEC
  - Lack or loss of microbial diversity has been linked to the disease

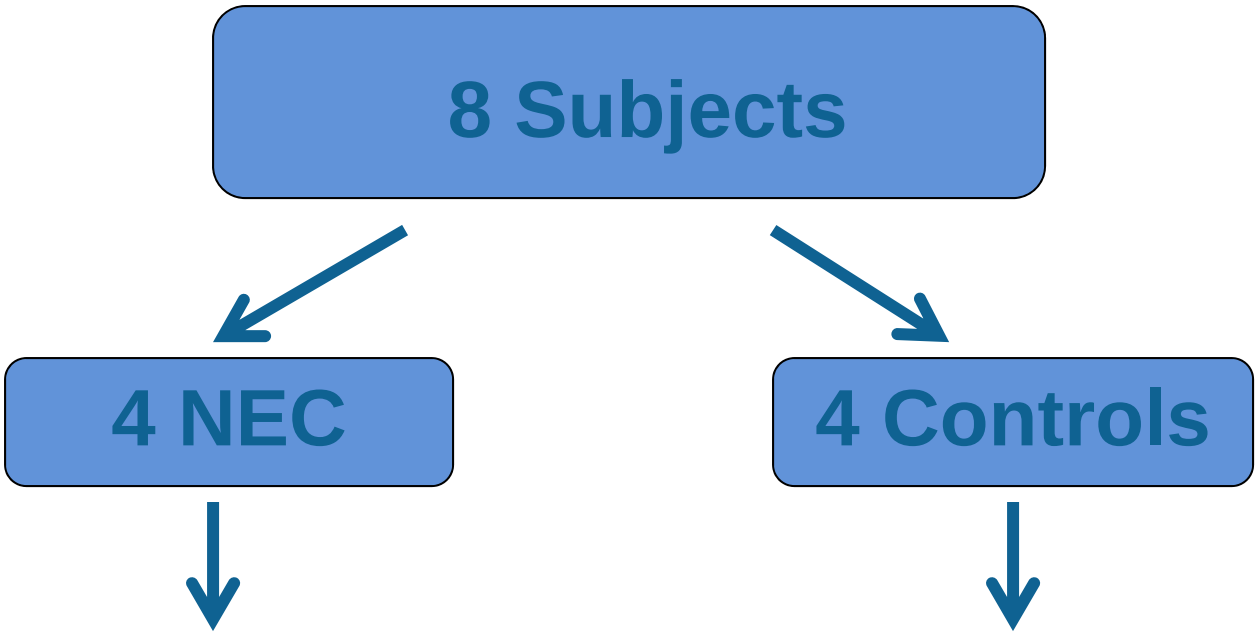
Microbial Profiling

- **While 16s rRNA profiling can identify species and estimate their relative abundance, it cannot explore microbial *function***
- **By limiting analyses to 16s rRNA profiling, we fail to understand human response to microbial colonization patterns**

Study Design

- **Prospective case-control study**
- **With IRB approval, infants born < 34 weeks gestational age (GA) were recruited**
- **Whole saliva samples were collected serially from infants at the bedside**
  - ***1-2 per week associated with enteral feeding advancements***

Patient Demographics



Female: 35 5/7* weeks	⟷	Female: 35 5/7* weeks
Male: 31 5/7 weeks	⟷	Male: 31 4/7 weeks
Male: 31 5/7 weeks	⟷	Male: 32 1/7 week
Male: 29 6/7 weeks	⟷	Male: 29 6/7 weeks

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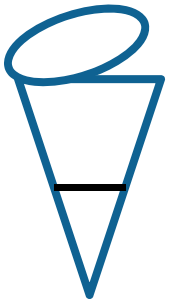
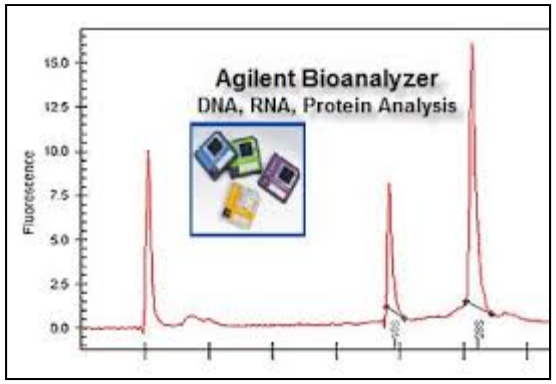
*Twins

RNASeq Methods

Saliva Sample



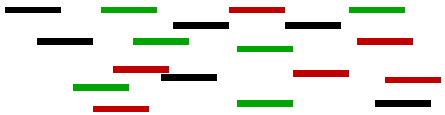
Extracted Total RNA



Quality Assessment

Ribozero

cDNA conversion fragment, ligate, add adaptors, amplify and size select



Illumina HiSeq 2000

Paired end;150 bps per lane

RNASeq Analysis

- Differentially expressed genes underwent systems biology analysis to further explore functions and related networks

- Microbial identification and gene function was determined with MetaTrans
  - An open-source pipeline designed to perform both taxonomic and gene expression analyses of microbes from paired-end RNASeq data

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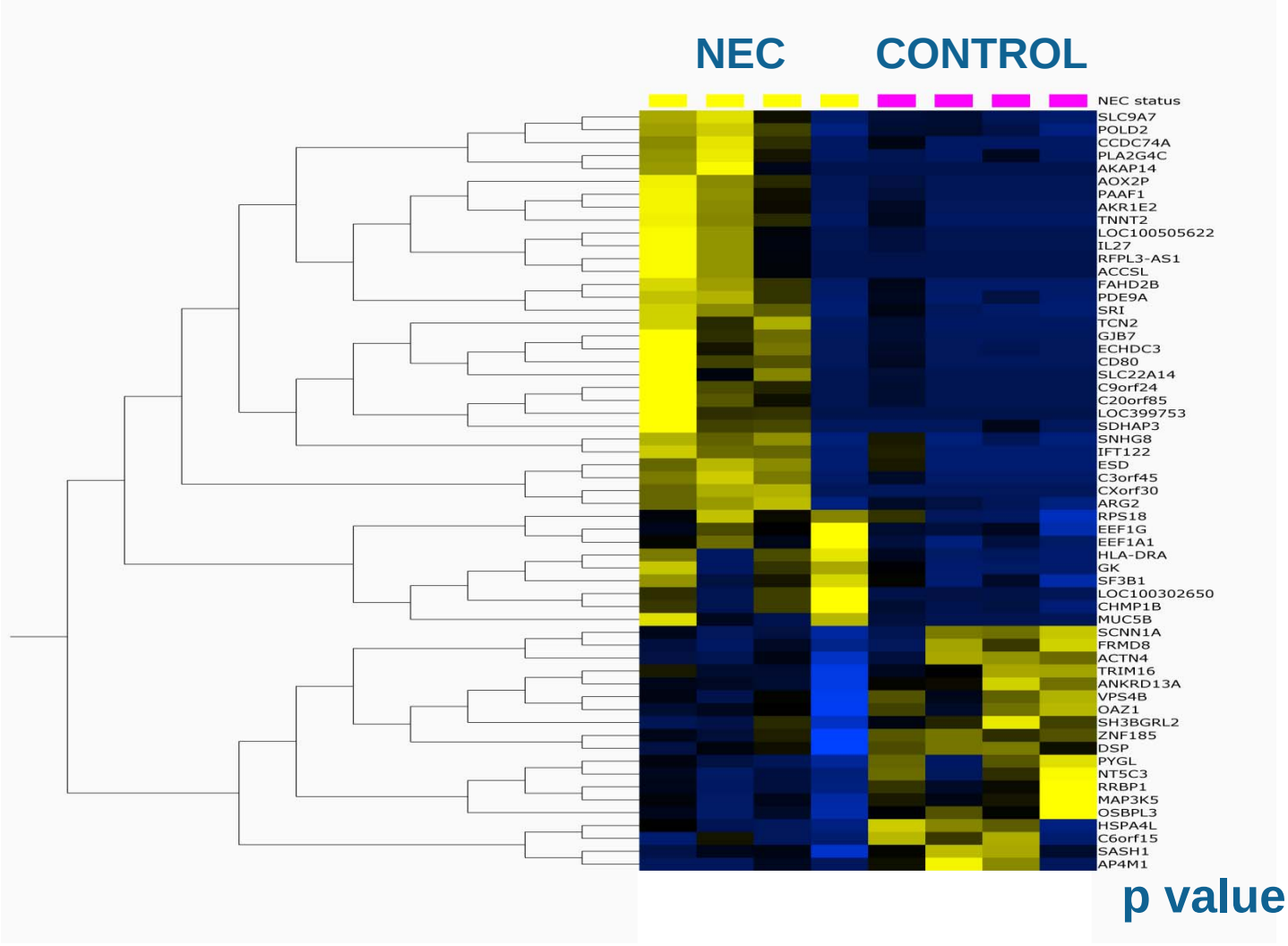
Martinez et al., Nature Scientific

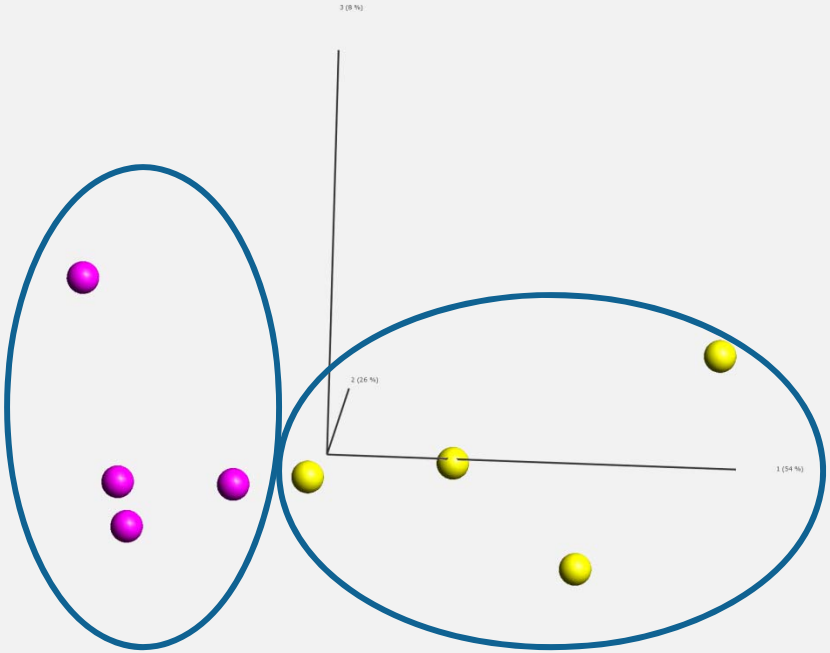
Results (Human)

- **59 candidate biomarker genes were differentially expressed between cases and controls**



p value = 0.1

Principal Component Analysis



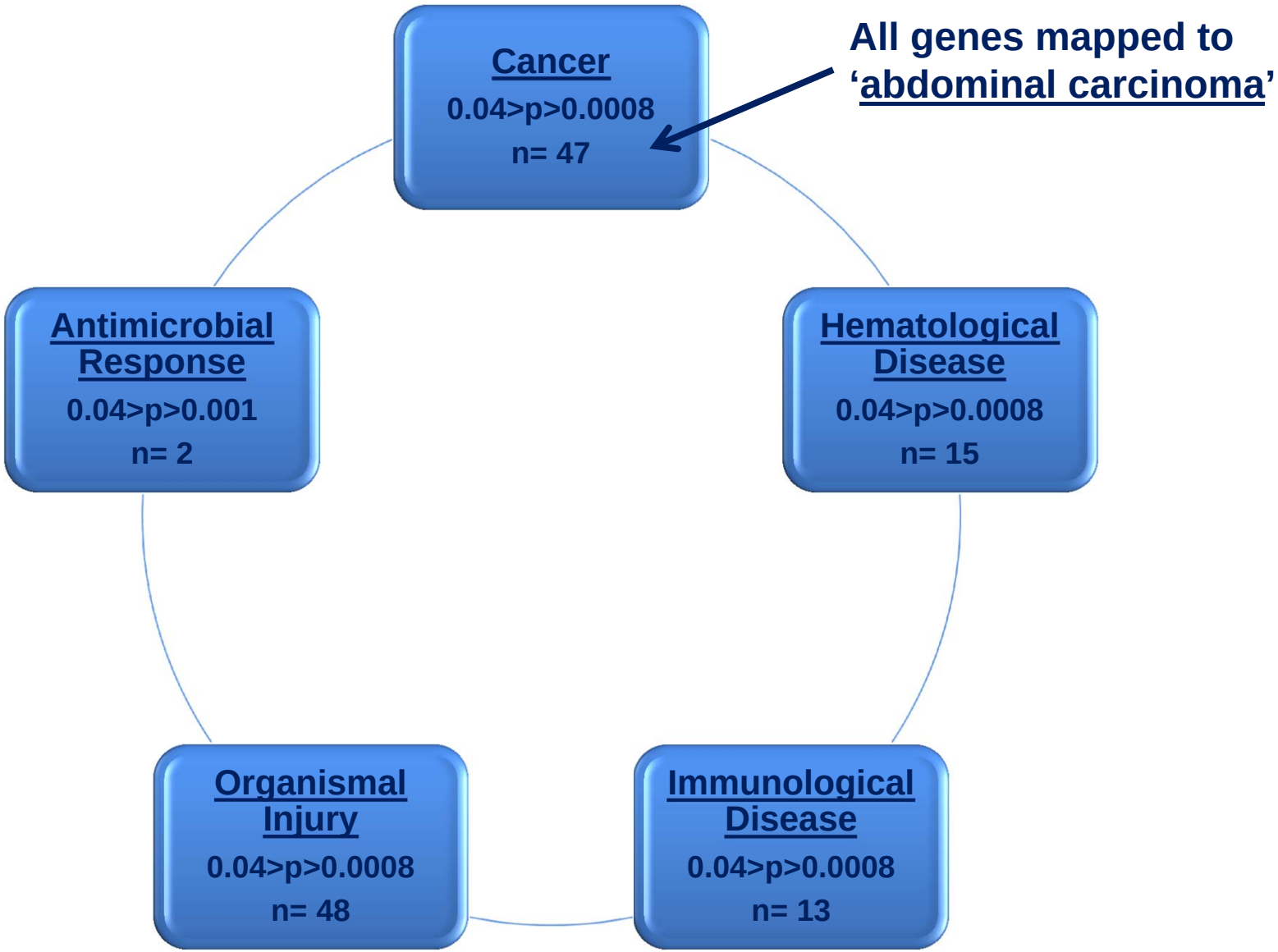
CONTROL

NEC

Distinct clustering profiles *prior to onset of disease*

p value = 0.1

Systems Biology Analysis (IPA)



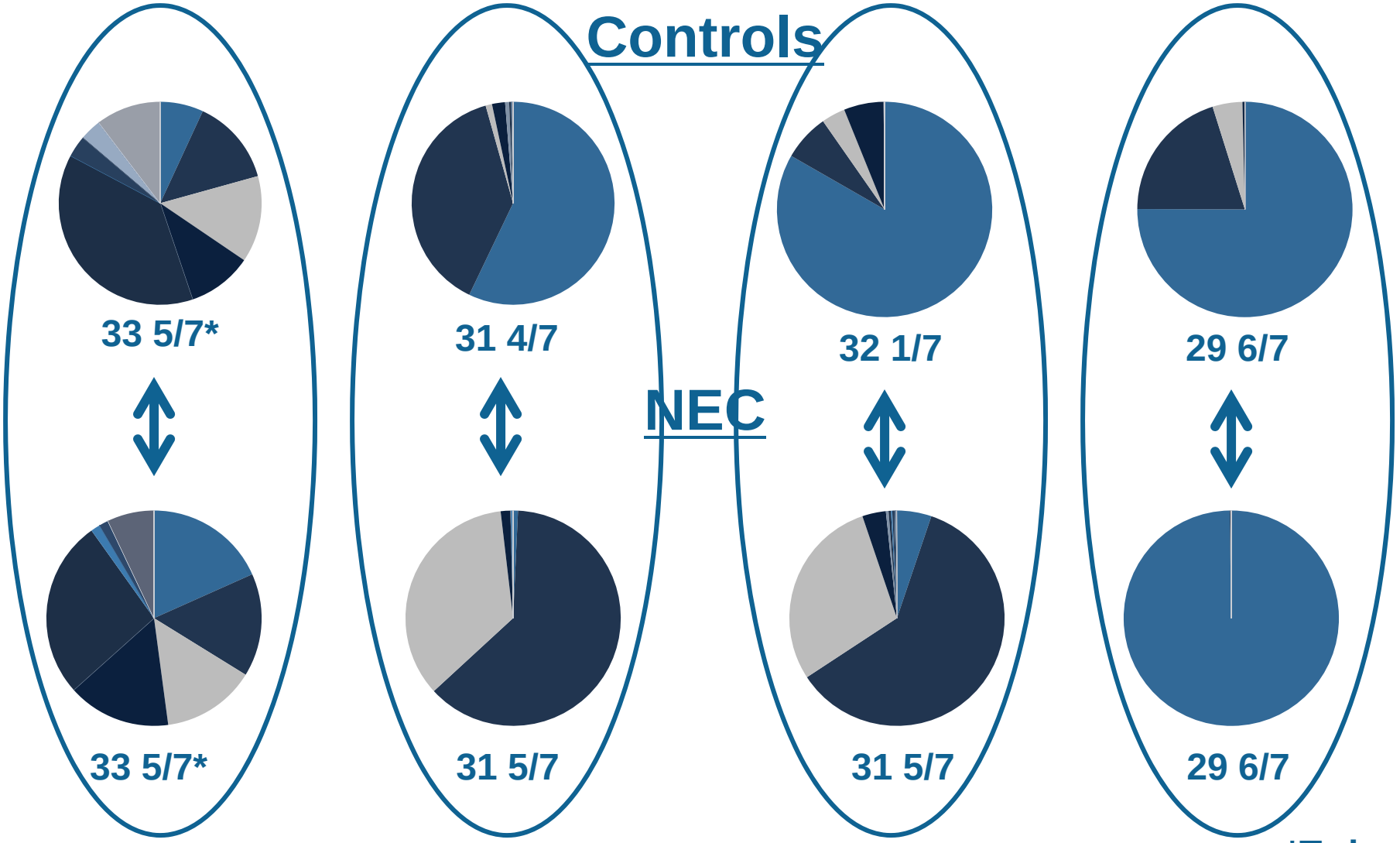
KEGG Analysis

Metabolism

- **Carbon metabolism, glycolysis, gluconeogenesis, biosynthesis of amino acids, fructose and mannose metabolism**

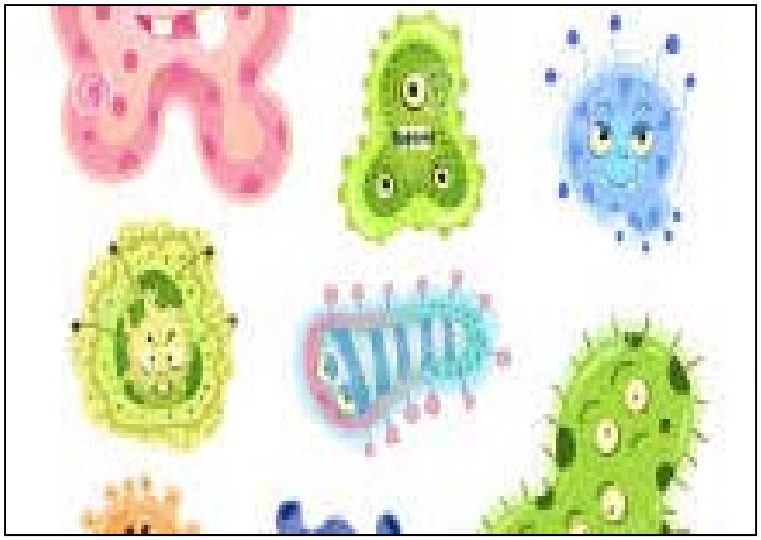
- **Necroptosis**
- **HIF-1 signaling**
- **Intestinal immune network for IgA production**
- **Allograft rejection and Graft-versus-host disease**
- **Tight junctions**

Microbial Diversification



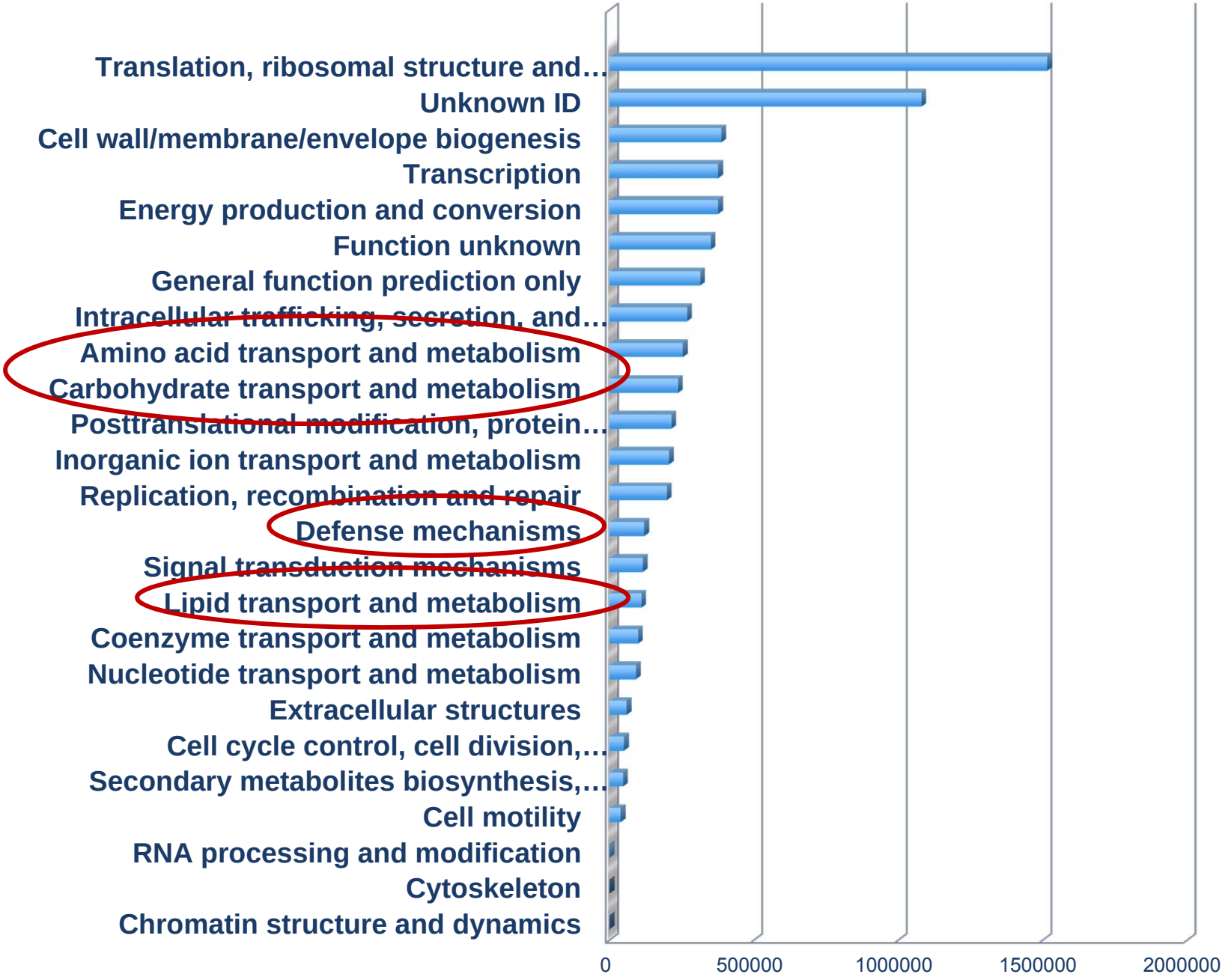
Neonatal Salivary Microbiome

Increasing Age



Increasing microbial diversification

Microbial Function

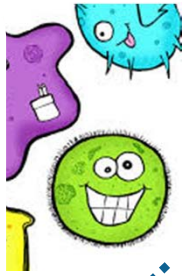


Next Steps

Understanding the Relationship Between Microbial Colonization, Host Response, and Disease

Connect the Dots

?



Conclusions

- **Saliva is a highly informative and valuable biofluid**
  - **Provides a unique, noninvasive opportunity to explore health and disease in the newborn**
  - **Allows Identification of biomarkers and ‘biopathways’ to inform care and improve outcomes**

Conclusions

- **Metatransciptomic analysis of neonatal saliva provides insight into:**
  - **Disruptive pathways and networks associated with disease**
    - **Can be seen prospectively prior to illness**
  - **Timing and patterns of microbial colonization that may be associated with neonatal pathophysiology**
    - **May provide actionable information to improve outcomes**

Acknowledgments

- Members of the Maron Laboratory
  - Prarthana Khanna-PhD Candidate
- Dr. Albert Tai, Tufts University Genomics Core
- Families who graciously participated
- Nurses and Staff in the NICU at Tufts Medical Center
- Current and Recent Funding Sources:
  - NICHD 1R01HD086088 – 02
  - Tufts CTSI Pilot Award
  - NICHD K08 HD05989
  - Charlton Pilot Award
  - Gerber Foundation
  - Charles H. Hood Foundation

Biomarker Development and Application Q&A

Christopher Leptak, MD, PhD
Jill Maron, MD, MPH

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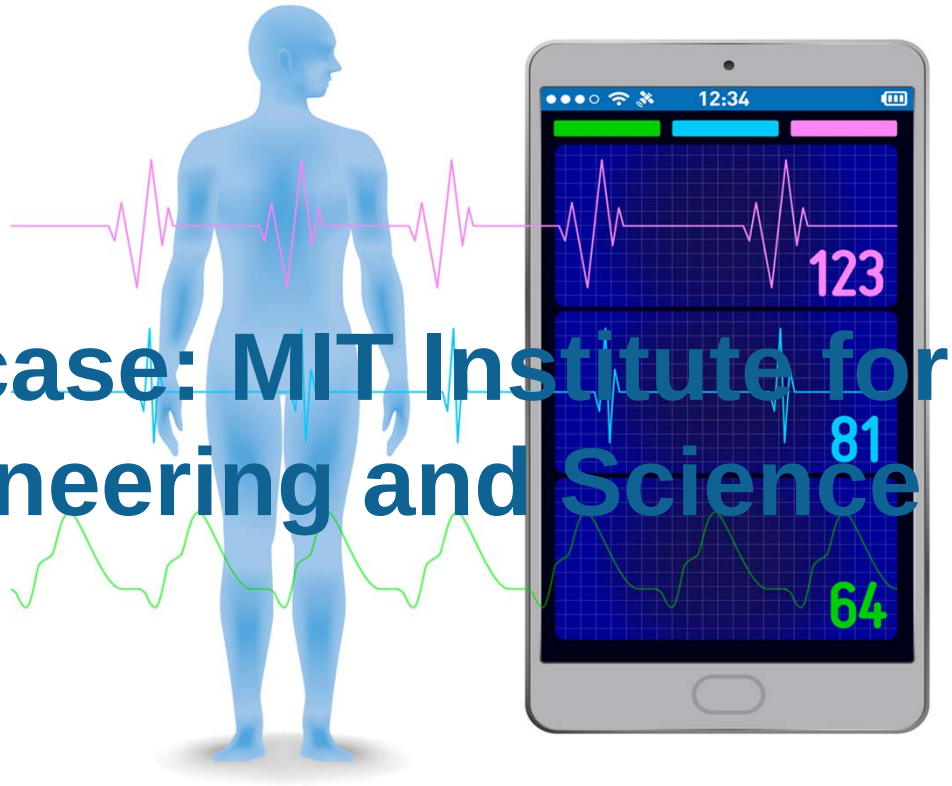

Showcase: MIT Institute for Medical Engineering and Science (IMES)

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Collaborative Data Science in Health Care

Leo Anthony Celi, MPH, MSc, MD

Principle Research Scientist, Massachusetts Institute of Technology (MIT)

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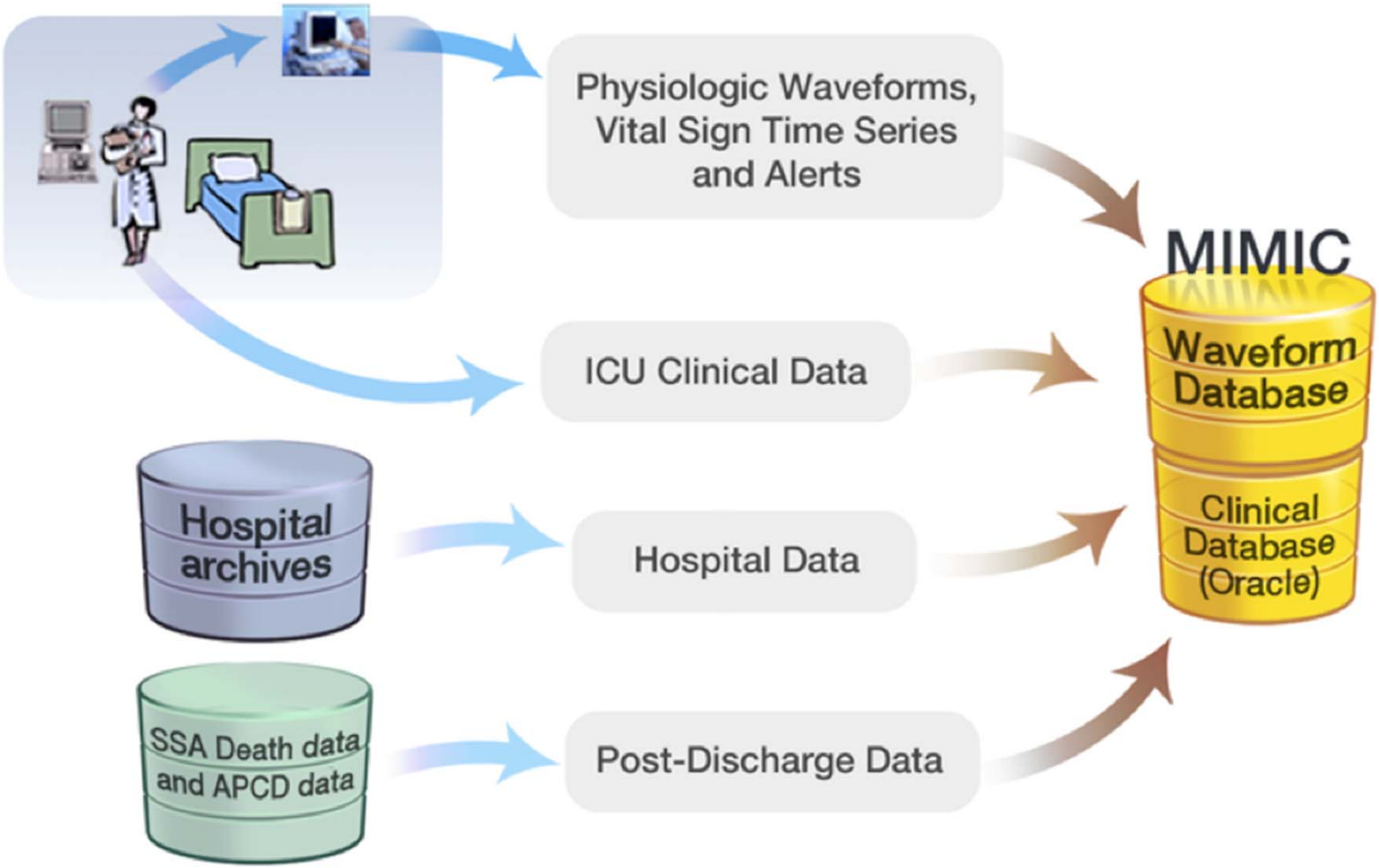
Crowdsourcing Knowledge Discovery

Medical Information Mart for Intensive Care



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NEWS ABOUT PAST EVENTS TEXTBOOK

2017.HST.953: COLLABORATIVE DATA SCIENCE IN MEDICINE

HST.953: Collaborative Data Science in Medicine, focuses on the secondary analysis of clinical data that is routinely collected in the process of care. In this course, students will work with Boston-area clinicians on research projects with the goal of a publication-ready manuscript at the end of the semester. Three of the 15 papers from last fall are already being reviewed by various clinical journals, while the rest are on track for submission over the next few months.

Seating is limited, so please complete the following form to get on the course mailing list and receive priority when enrolling in the course.

Begins **September 8,**
Fridays 9am-12pm
Location: E25-117

Course Directors:
Dr. Leo Anthony Celi
Dr. Alistair Johnson
Dr. Tom Pollard
Dr. Jesse Rafa

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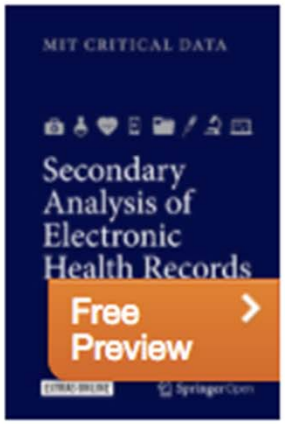

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Secondary Analysis of Electronic Health Records

Authors: **MIT Critical Data**

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About this Textbook | About the authors

This book trains the next generation of scientists representing different disciplines to leverage the data generated during routine patient care. It formulates a more complete lexicon of evidence-based recommendations and support shared, ethical decision making by doctors with their patients.

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CCData LONDON

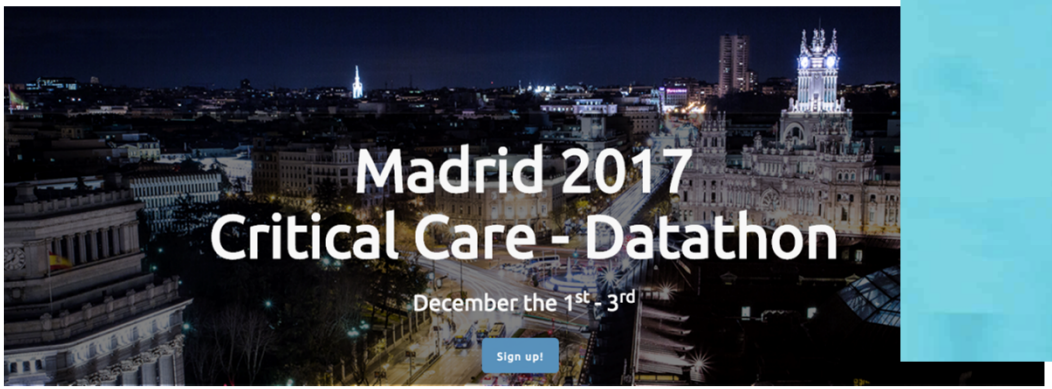
Datathon 2016, 3-4 December 2016

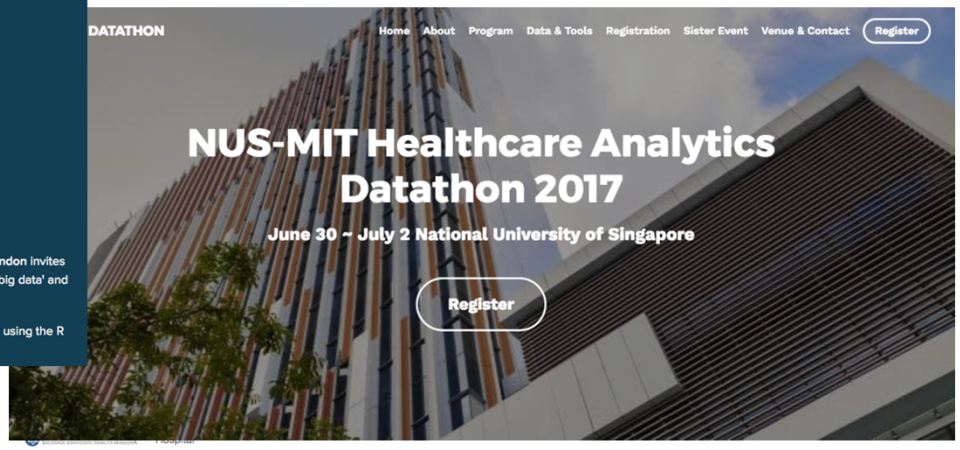
This is the 4th annual Critical Care data weekend, bringing together teams of clinicians and data scientists from London and Boston, USA. **Critical Care Data London** invites clinicians and data scientists, experts and novices to come and explore two iconic clinical data repositories with talks from experts in electronic health records, 'big data' and database design.

Our free *Data Science for Doctors* pre-course workshop on **Friday 2nd December** teaches clinicians practical skills in data wrangling, analysis and visualisation using the R language.

MIT-Chinese PLA Hospital Health Data

Conference and Workshop





中国医疗设备

PLAGH
Chinese PLA General Hospital

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Science Translational Medicine

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SHARE

PERSPECTIVE | REPRODUCIBILITY

A "datathon" model to support cross-disciplinary collaboration

Jerôme Aboab[1,*], Leo Anthony Celi[1], Peter Charlton[1], Mengling Feng[1], Mohammad Ghassemi[1], Dominic C. Marshall[1,†], ...

+ See all authors and affiliations

Science Translational Medicine 06 Apr 2016:
Vol. 8, Issue 333, pp. 333ps8
DOI: 10.1126/scitranslmed.aad9072

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sana.mit.edu

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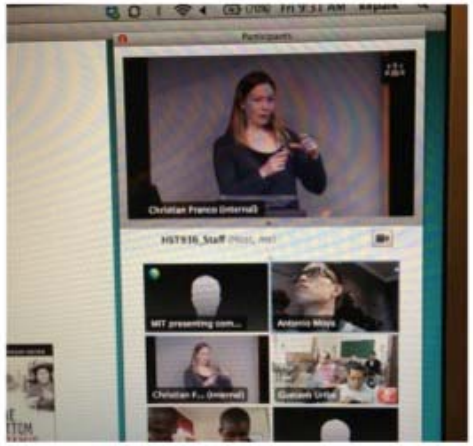
HST.936: Global Health Informatics to Improve Quality of Care



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Global Health Informatics to Improve Quality of Care

Learn how to design health information and communication technology (ICT) solutions for the developing world.

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About this course

4 Reviews 4/5

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What you'll learn

- Global health burden
- Design thinking
- Health informatics
- Software development process
- Evaluation and monitoring

Meet the instructors

Leo Anthony Celi MD SM MPH
Course Co-director
MIT

Alon Dagan MD
Course Instructor
MIT

Rodrigo Deliberato MD PhD
Course Instructor
MIT

Length:	10 weeks
Effort:	2-3 hours per week
Price:	FREE Verified Certificate option closed
Institution:	MITx
Subject:	Medicine
Level:	Advanced
Languages:	English
Video Transcripts:	English

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Prerequisites
None

Global Health Informatics

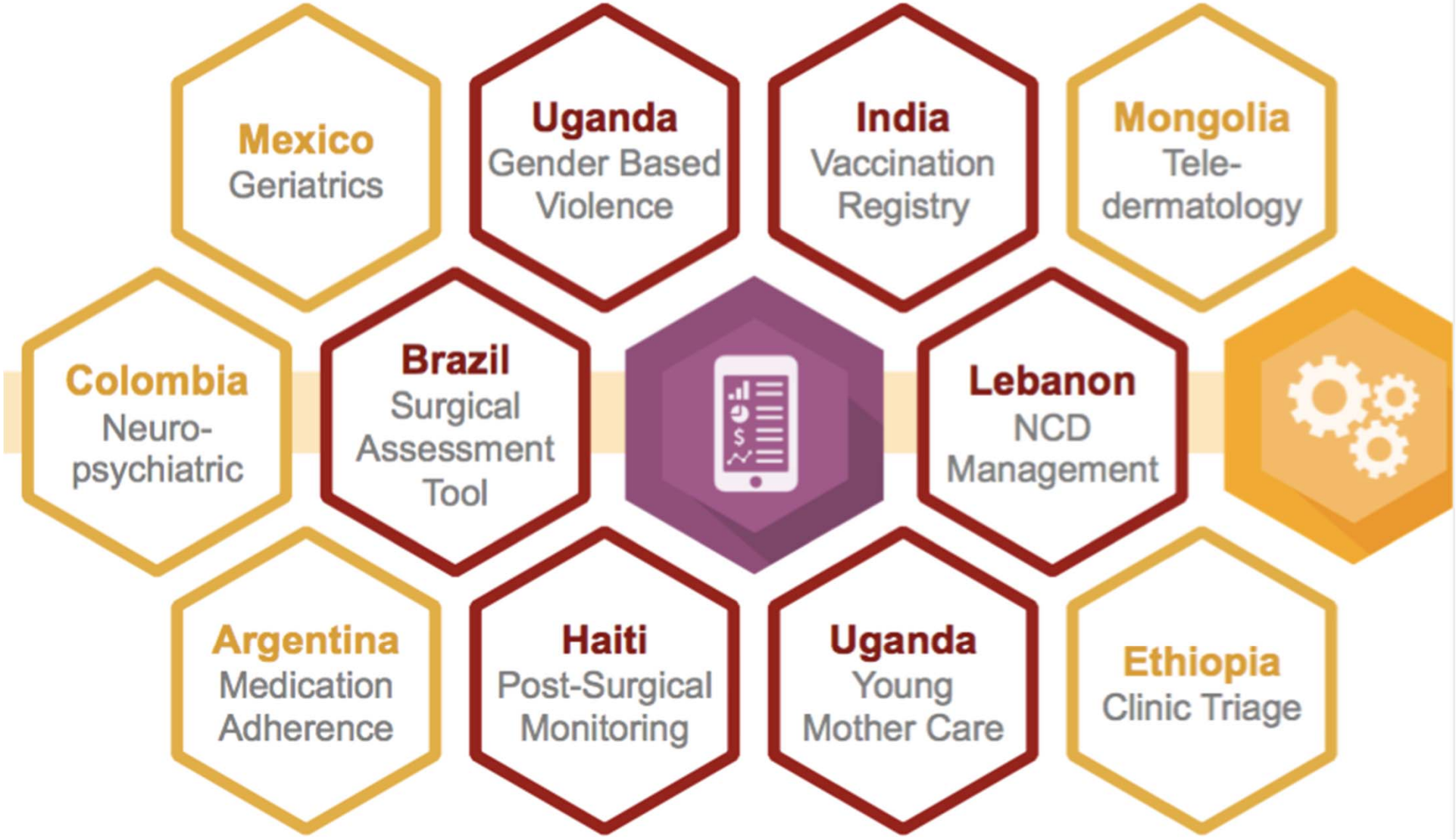
Principles of eHealth and mHealth to Improve Quality of Care

Edited by Leo Anthony G. Celi, Hamish S. F. Fraser, Vipan Nikore, Juan Sebastián Osorio and Kenneth Paik

Overview

The widespread usage of mobile phones that bring computational power and data to our fingertips has enabled new models for tracking and battling disease. The developing world in particular has become a proving ground for innovation in eHealth (using communication and technology tools in healthcare) and mHealth (using the affordances of mobile technology in eHealth systems). In this book, experts from a variety of disciplines--among them computer science, medicine, public health, policy, and business--discuss key concepts, frameworks, examples, and lessons learned in designing and implementing digital health systems in the developing world.

PROJECTS


Mexico
Geriatrics
Uganda
Gender Based Violence
India
Vaccination Registry
Mongolia
Tele-dermatology
Colombia
Neuro-psychiatric
Brazil
Surgical Assessment Tool
Lebanon
NCD Management
Argentina
Medication Adherence
Haiti
Post-Surgical Monitoring
Uganda
Young Mother Care
Ethiopia
Clinic Triage

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Evidence for Health Decision Making — Beyond Randomized, Controlled Trials

Thomas R. Frieden, M.D., M.P.H.

"For much, and perhaps most of medical practice, RCT-based data are lacking and no RCT is being planned or is likely to be completed to provide evidence for action. It leaves practitioners with large information gaps for most conditions and increases reliance on clinical lore."

Key Messages

- The breakthroughs in AI are a result of dumping Big Data into decades-old machine learning methods, and not from advances in algorithms.
- Adoption of AI in healthcare will depend NOT on performance metrics (e.g. AUC) but on its impact on relevant clinical outcomes, along with satisfaction of both patients and providers.

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The Landscape in the ICU

- <50% of clinical decisions in the ICU supported by data-substantiated evidence
- Last 15 years: majority of RCTs in critical care had negative results; only ~10% demonstrating benefit of an intervention
- Far too many questions in the ICU that can be addressed by a relatively small group of researchers

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Clinical Practice Guidelines We Can Trust

ISBN
978-0-309-16422-1

300 pages
6 x 9
PAPERBACK (2011)

Robin Graham, Michelle Mancher, Dianne Miller Wolman, Sheldon Greenfield, and Earl Steinberg, Editors; Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Institute of Medicine

- For many clinical domains, high-quality evidence is lacking, or even non-existent
- Often rely on low-quality evidence or expert opinion

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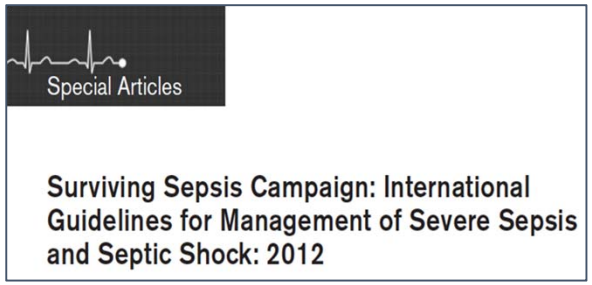
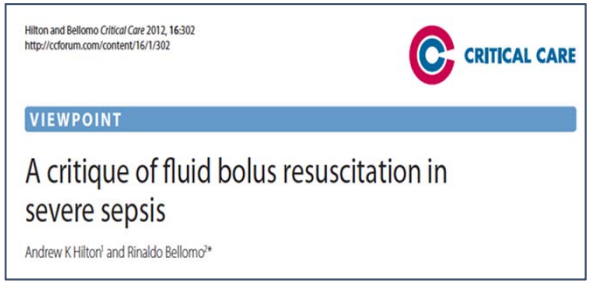
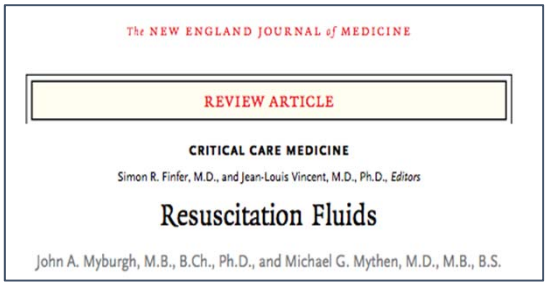
Fluids and Sepsis







- Fluid resuscitation is considered cornerstone intervention in sepsis
- *SSC* recommends 30 ml/Kg

"Based on expert opinion and lack of adequate experimental and control human evidence"

Surviving Sepsis Campaign

TABLE 5. Recommendations: Initial Resuscitation and Infection Issues

A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Published observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥ 65 mm Hg as well as $Scvo_2$ ≥ 70% (measured in the superior vena cava, either intermittently or continuously [18]). Many studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced

Intensive Care Medicine
August 2005, Volume 31, Issue 8, pp 1066–1071

Hemodynamic variables related to outcome in septic shock

Authors | Authors and affiliations

Marjut Varpula, Minna Tallgren, Katri Saukkonen, Liisa-Maria Voipio-Pulkki, Ville Pettilä

Objective

To assess the impact of hemodynamic variables on the outcome of critically ill patients in septic shock and to identify the optimal threshold values related to outcome with special reference to continuously monitored mean arterial pressure (MAP) and mixed venous oxygen saturation (SvO_2).

Design and setting

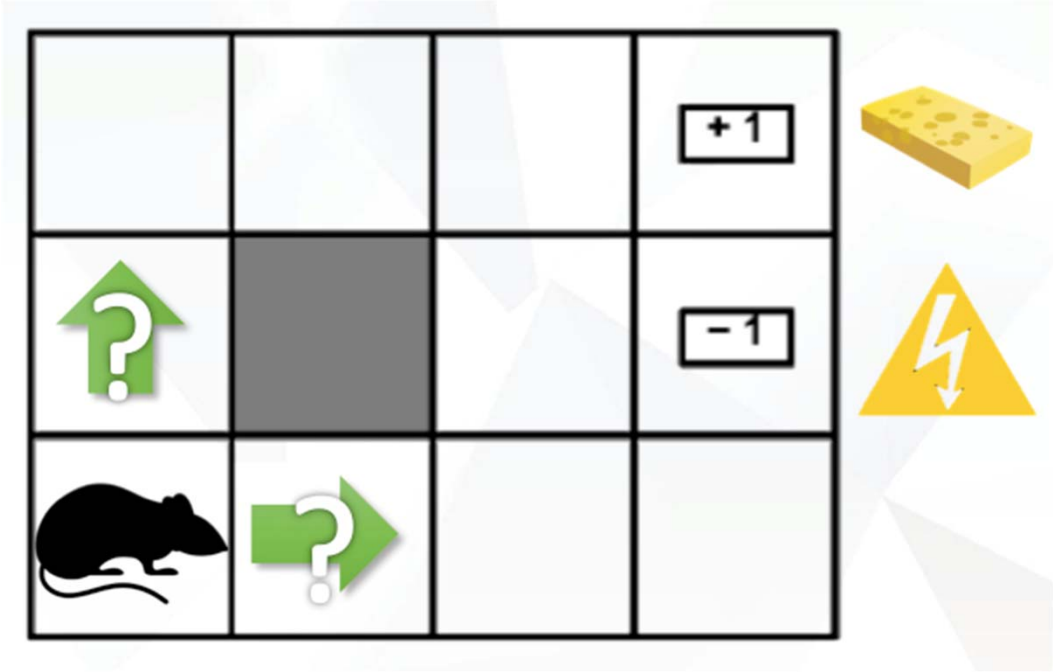
Retrospective cohort study in a university hospital intensive care unit (ICU).

Patients

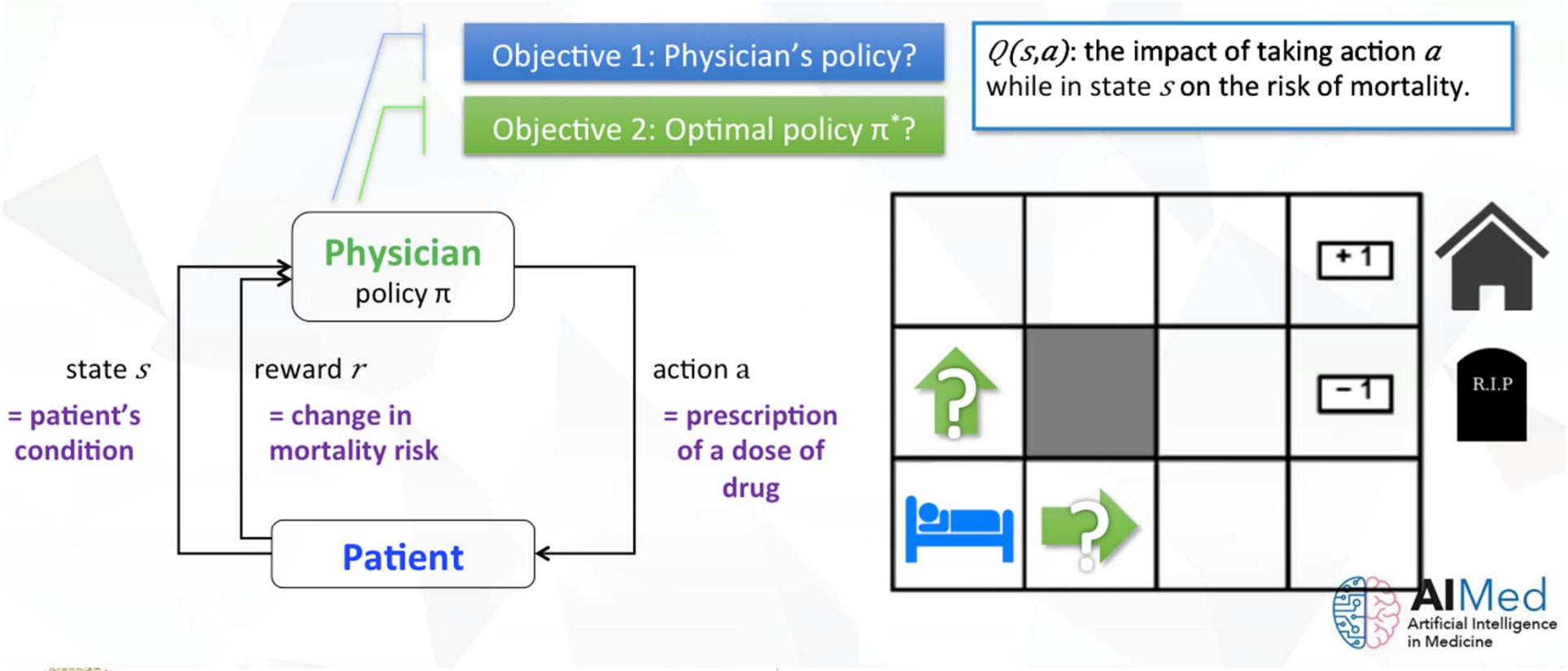
All consecutive 111 patients with septic shock treated in our ICU between 1 Jan. 1999 and 30 Jan. 2002.

Optimizing resuscitation strategy in sepsis with reinforcement learning

Matthieu Komorowski, Leo Anthony Celi,
Omar Badawi, Anthony C. Gordon, A. Aldo Faisal



Medical Decision as a Reinforcement Learning Problem



AIMed
Artificial Intelligence in Medicine

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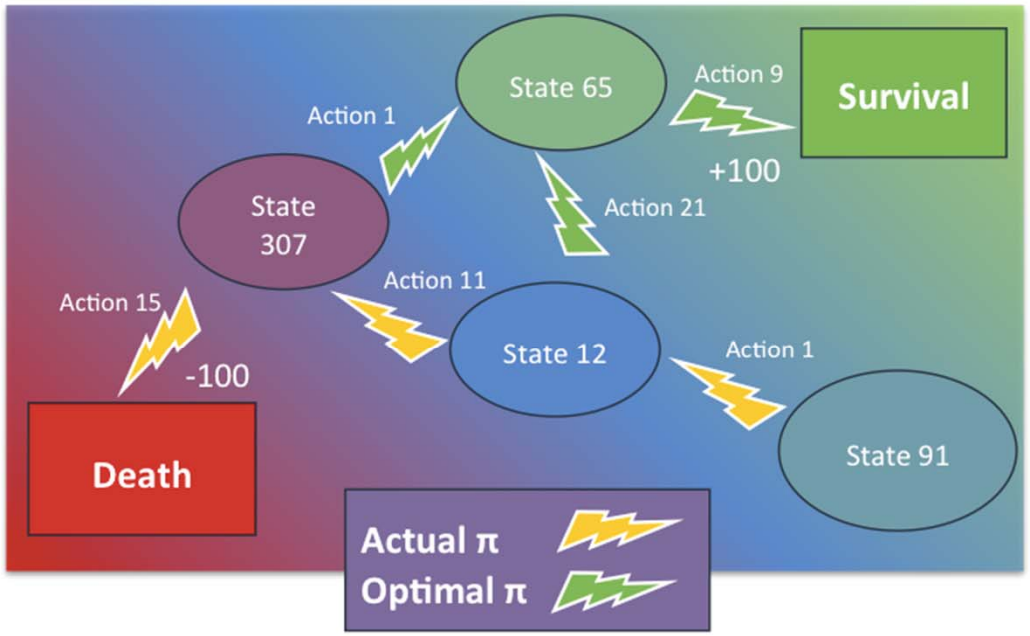
Markov Decision Process

- A general framework used for modelling sequential decision making.
- Most useful in problems involving **complex, stochastic and dynamic decisions**, for which they can find optimal solutions.

- Defined by $\{S, A, T, R\}$
  - S: a finite set of states
  - A: a finite set of actions
  - $T(s_{t+1}, s_t, a_t)$: the transition matrix
  - R: the immediate reward



[Schaefer 2005]

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Tasks at Hand

- Model the prescription of intravenous fluids and vasopressors using a Markov decision process
- 750 states defined by k-means clustering of time series of 52 variables, up to 72 hrs of data per patient
- Identify optimal decisions from one state to another based on 90-day survival

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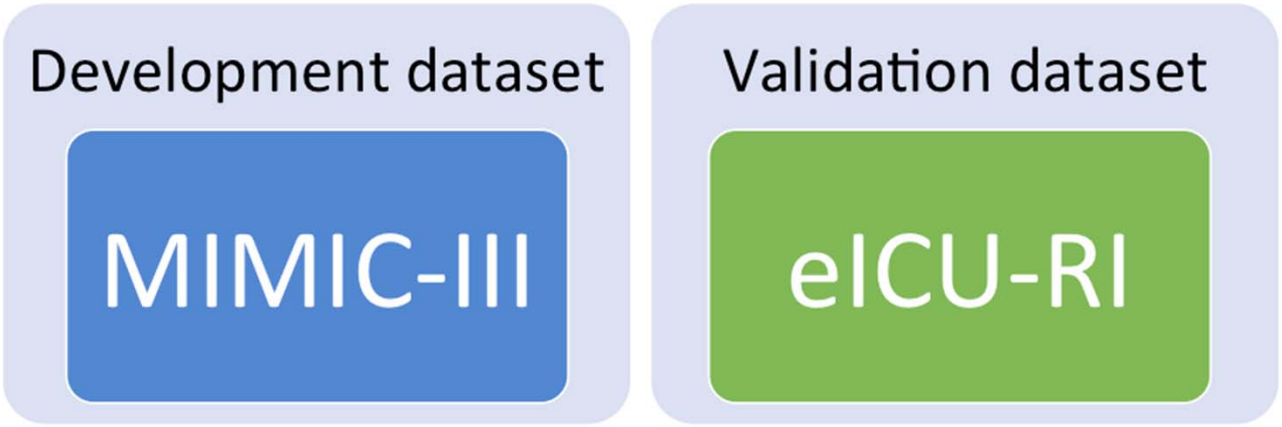
The datasets



- Inclusion: adults with sepsis [sepsis-3 definition]
- Exclusion: excessive missingness, patients coming from hospitals with low data quality in eICU-RI

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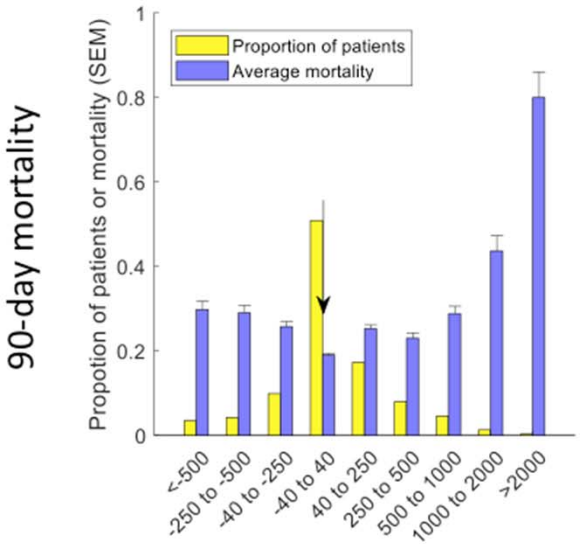
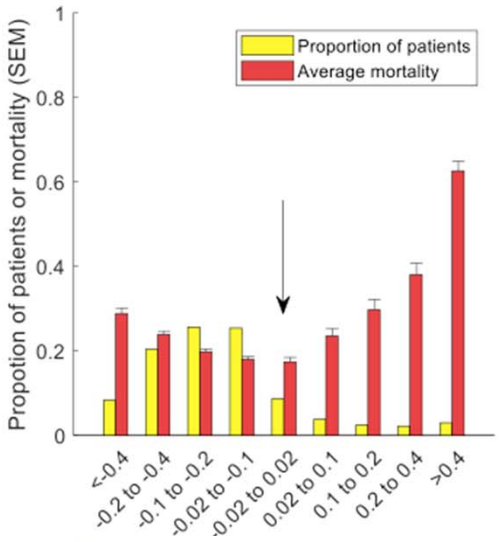
	Development dataset	Validation dataset
Source	MIMIC-III	Philips eICU-RI
# ICU admissions	17,898	80,257
# ICUs	5	128
Primary ICD code		
• Sepsis	34%	52%
• Cardiovascular	31%	14%
• Other resp.	10%	11%
• Neurological	9%	9%
• Other	15%	13%
Mean age, years	65	65
Gender	56% male	52% male
Initial SOFA (0-24)	7.3 (3.3)	7.0 (3.5)
Initial OASIS (0-70)	33.5 (8.8)	34.8 (12.4)
Procedures:		
• Mech. vent.	55%	50%
• Vasopressors	35%	30%
• Dialysis	9%	8%
Hospital mortality	13.7%	17.7%
90-day mortality	22.5%	Not available

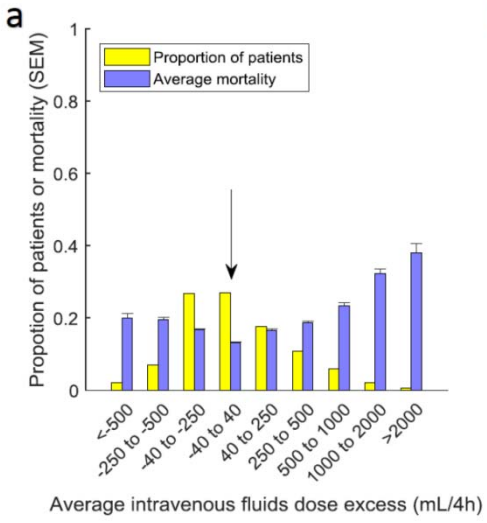
Is the optimal strategy associated with the best outcome?

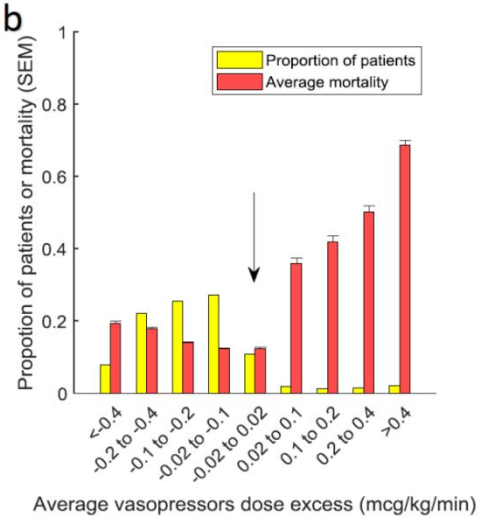




MIMIC Test Set

eICU Validation Set





Results

- On average, patients were given more intravenous fluid and less vasopressor vs optimal strategy.
- Median dose excess of fluids was 76 ml/h (IQ=40-133 ml/h), median dose deficit of norepinephrine-equivalent was 0.14 mcg/kg/min (IQ=0.05-0.30 mcg/kg/min).

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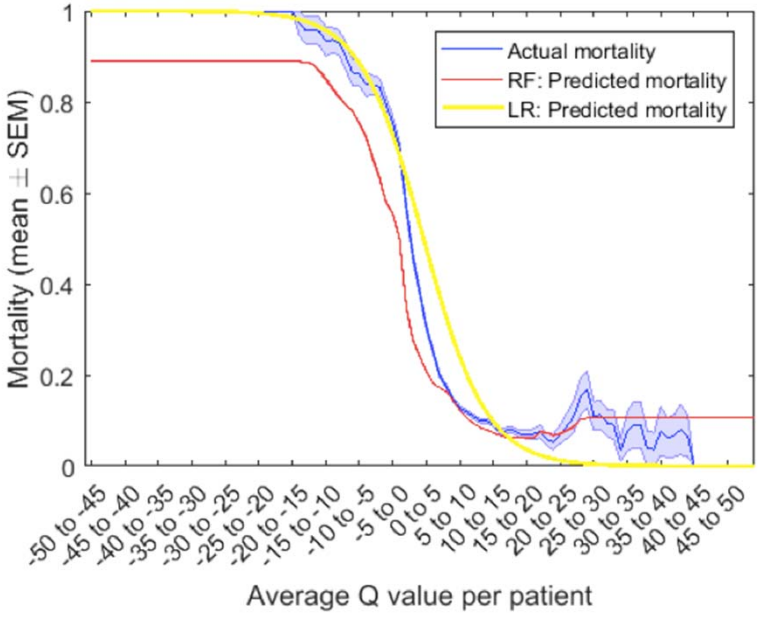
Mortality Benefit from Optimal Strategy



- Random forest and regression models were built that map fluid and vasopressor dose in each state with hospital mortality
- Predicted mortality when optimal action is followed: 9.6% (vs. 17.7% actual); 8.2% absolute reduction (95% CI: 7.8% - 8.5%)

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Leo Anthony Celi
Intensivist and Principal Research Scientist
Massachusetts Institute of Technology
Cambridge, USA

Beth Israel Deaconess Medical Center
Boston, USA

lceli@mit.edu

"For a true health data revolution to occur in healthcare, we must become better at sharing and integrating data. Greater emphasis on collaboration—outside the traditional 'multidisciplinary' realm and into the engineering, mathematical, and computer sciences—will help us to achieve this."

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Leo Anthony Celi

lceli@mit.edu

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Summary Remarks

Elazer Edelman, MD, PhD

Director of the MIT/IMES Clinical Research Center (CRC)
Thomas D. and Virginia W. Cabot Professor of
Health Sciences and Technology at MIT
Professor of Medicine at Harvard Medical School
Senior Attending Physician in Coronary Care at
Brigham and Women's Hospital

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Showcase: MIT Institute for Medical Engineering and Science (IMES)

Q&A

Leo Anthony Celi, MPH, MSc, MD
Elazer Edelman, MD, PhD

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Tufts CTSI Opportunities for Funded Research

Graham Jones, PhD

Associate Director and Director of Research Collaborations
Tufts CTSI

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Pilot Studies Program

Resource & Service

Funds innovative, high impact, translational science projects, with a focus on interdisciplinary research teams.

- Seed grants up to $60,000 for full spectrum of translational research
- Program prioritizes methods development and Tufts CTSI signature program research areas
- Pilot Project teams must consist of interdisciplinary researchers (two or more disciplines) in which the PI has a full-time appointment or position at a Tufts CTSI academic, medical, or nonprofit partner institution.
- **Annual applications - cycle begins in fall**
  http://www.tuftsctsi.org/funding-opportunities/tufts-ctsi-pilot-studies-program/

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Pilot Studies Information Sessions

- Wednesday, November 15, 2017 at 8:30AM
- Thursday, November 16, 2017 at 4:30PM.

Register and email any inquiries at
pilots@tuftsctsi.org.

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Clinical & Translational Science (CTS) Graduate Program

Resource & Service

Graduate Courses are available through the Clinical and Translational Science program at the Sackler School of Graduate Biomedical Sciences: *http://www.tuftsctsi.org/education/clinical-and-translational-science-graduate-program/*

- Summer Institute, & Certificate, Master's, PhD programs
- TL1 Fellowships – now recruiting

Leadership:

- Director: David Kent, MD, MSc
- Associate Director: Jessica Paulus, ScD
- Manager: Elizabeth Wiltrout, PhD

Lunch Poster Session & Networking and Introduction to Afternoon Program

Graham Jones, PhD

Associate Director and Director of Research Collaborations
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Lunch Poster Session & Networking

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Case Studies

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Introduction

Graham Jones, PhD

Associate Director and Director of Research Collaborations
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The Challenge of Making Things Work Well: An Academic Perspective

Kumaran Kolandaivelu, MD, PhD

Medical Director of the MIT/IMES Clinical Research Center (CRC)
Associate Director, Harvard Catalyst/MIT Bridge
Instructor of Medicine, Harvard Medical School

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Massachusetts Institute of Technology

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Translational Research Day

Sensors, devices and biomarkers in medicine

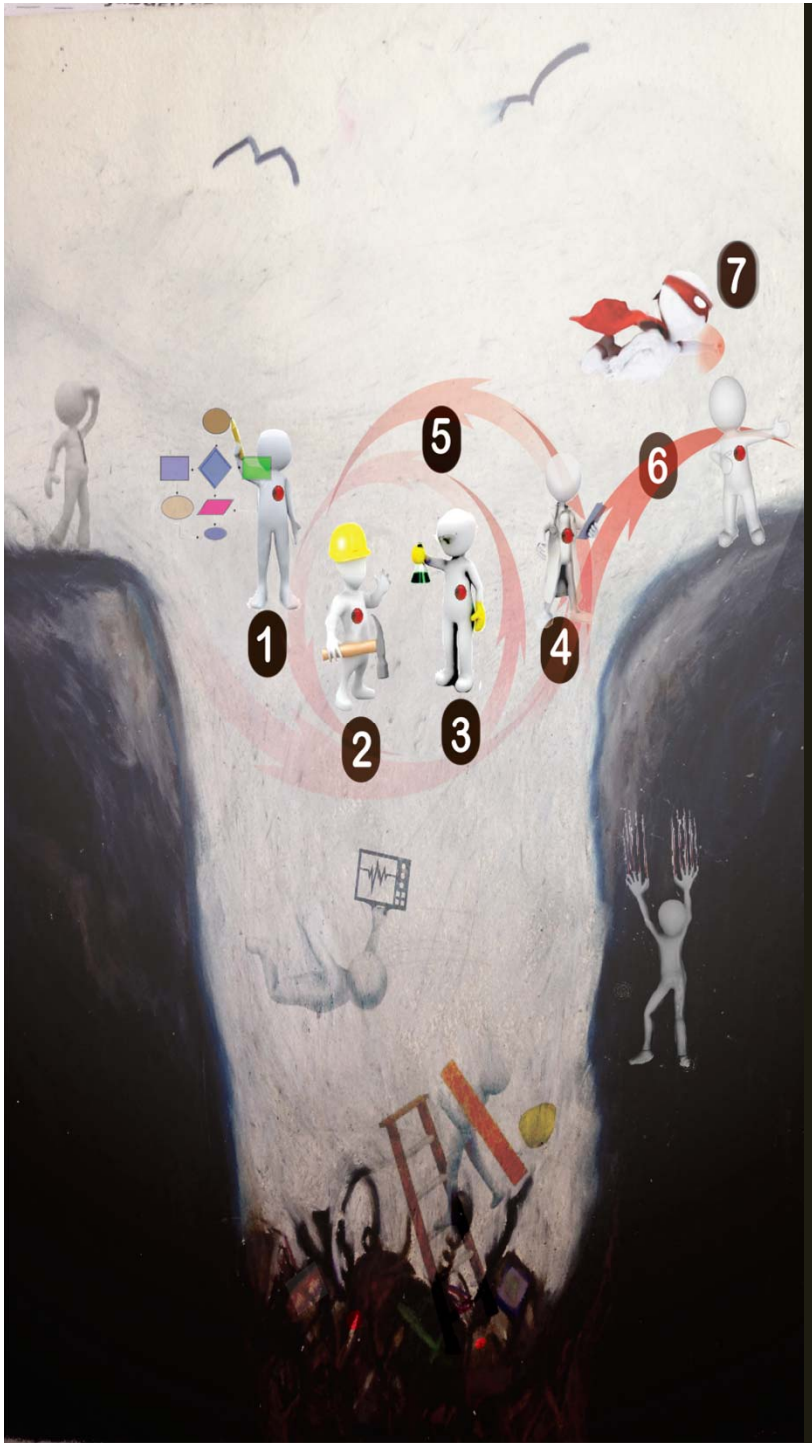
11/14/2017

The challenge of making things work well

(An Academic Perspective)

Kumaran Kolandaivelu, MD PhD

Assistant Professor, Cardiovascular Division, Brigham and Women's Hospital
Co-Director MIT Clinical Research Center, Massachusetts Institute of Technology



1. Clinical Use Constraints
2. Testable Prototyping
3. Stage Appropriate Models
4. First-in-Human
5. Iterative R&D
6. T.5 to T1 Transfer
7. Failure Analyses

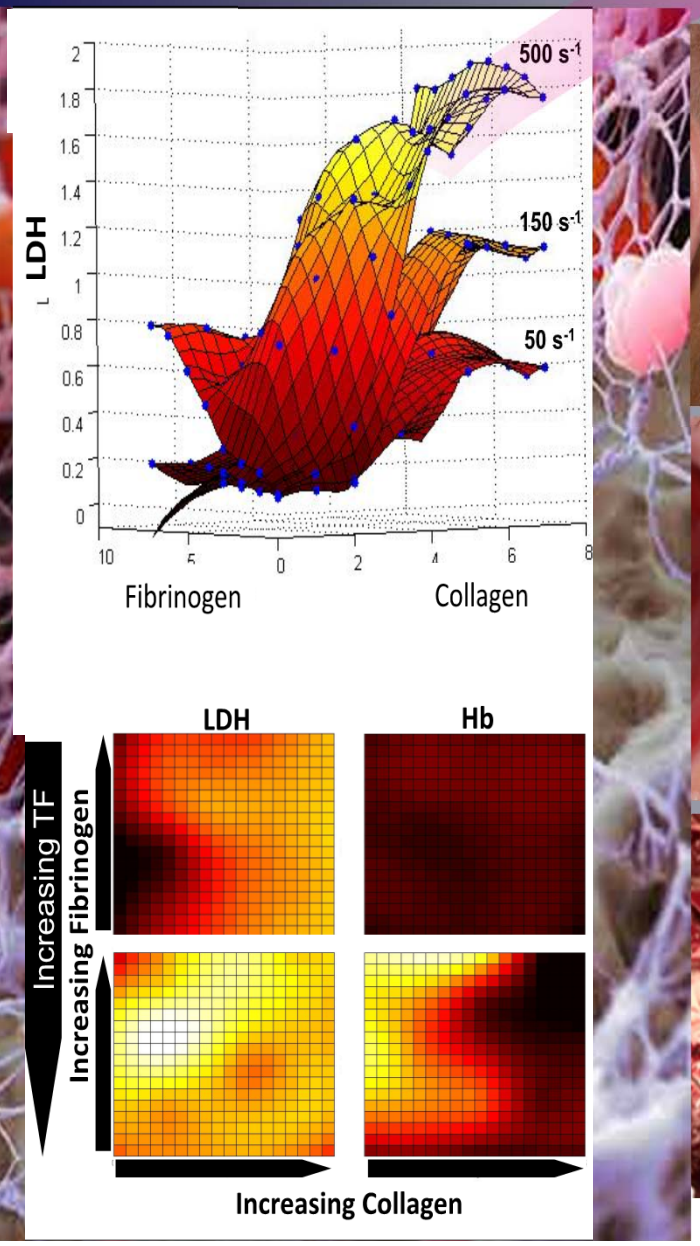
T.5

BRIDGE

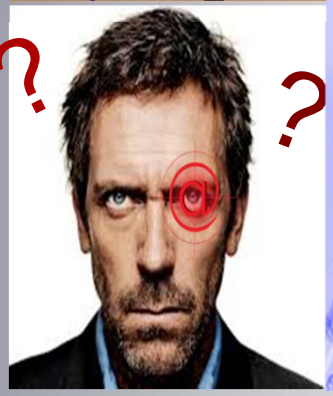
(Devices & Diagnostics)

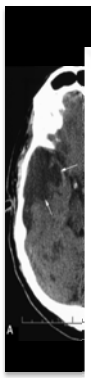
Example: The Clinical Pain Point

and my



Precision Hemostatic Management





$30M – 90M
(Industry)

$1M
(Academic)

CIMIT PILOT AWARD : 25K

CIMIT INNOVATION GRANT – 100K

SBIR : 165K

SBIR : 225K

AHA – 500K

YR7
PRODUCT
LAUNCH

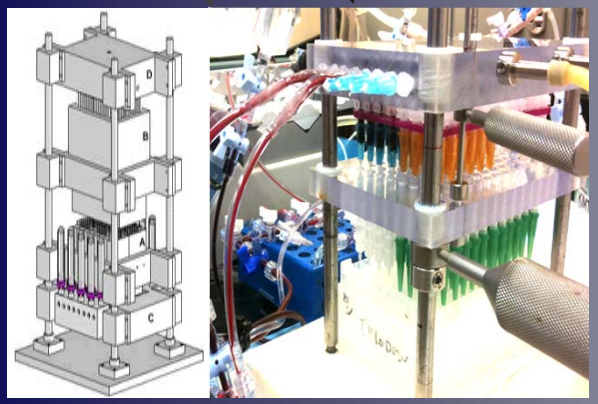
Minimal Validation

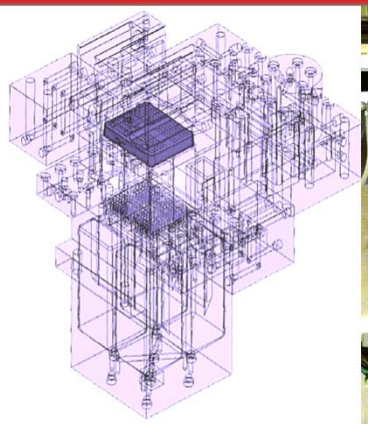
Preclinical Testing

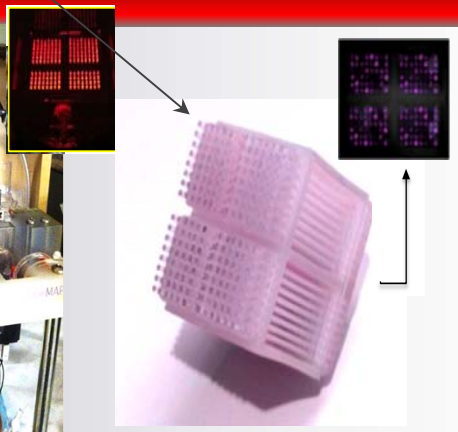
First-In-Man Studies

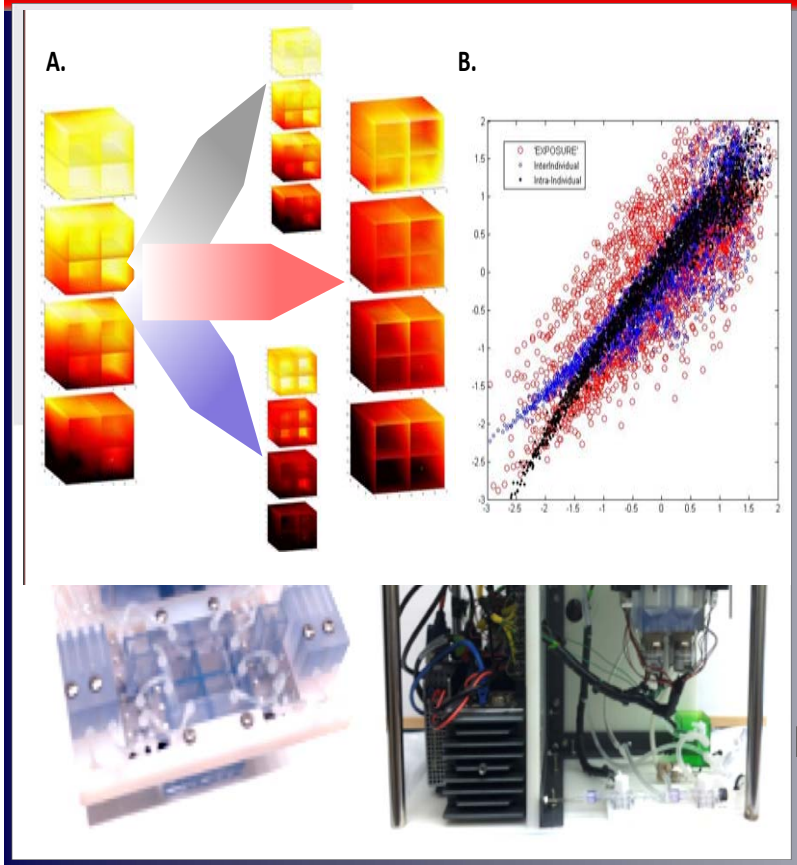
Equivalence Testing & 510K

RESEARCH









ACADEMIC CHALLENGES

- Trans-domain expertise:

  (Microfluidics, optics, electrical, applied math, industrial designers, system designers, reagent chemists, clinical experts)
- Incomplete design specifications (scientific, not user)
- Limited management expertise
- Diagnostic sensors for precision medicine
  - Excess sensor variability pre-optimization
  - Limited ability to validation pre-optimization

NDUSTRY REALITIES PUSH RAPID PRODUCTIZATION

Novel precision diagnostics require new pathways for creating and evaluating testable, clinical-grade prototypes.

How CTSI is poised to help

- Trans-domain expertise
- Limited management expertise
- Incomplete design specifications (scientific, not user)
- Excess sensor variability pre-optimization
- Limited ability to validation pre-optimization

Expert / Stakeholder T.5
Project Committees

\User Need Definition

Shift ability to produce optimized, clinically grade prototypes from academic settings

Interconnected networks for cohort discovery will facilitate patient identification and precision validation

THANK YOU

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Lessons Learned from the Front Lines

Michael Naimark, MS
Director of Business Development
CBSET, Inc.

Rami Tzafriri, PhD
Director of Research and Innovation
CBSET, Inc.

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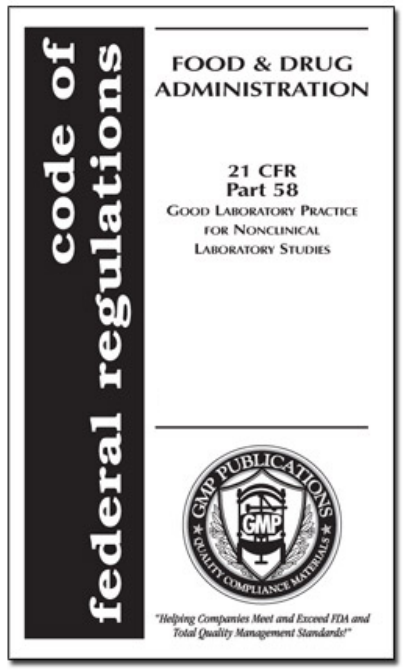
The CRO in Biomedical Research

- **Many types of CRO offering services, but when most people think of the term, they think of preclinical CROs.**



CBSET, a novel CRO model for addressing the service gap…

BRIGHAM AND WOMEN'S HOSPITAL

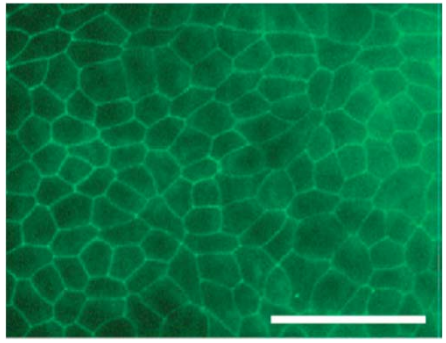
- Fuse Cutting Edge Research with Operational Expertise

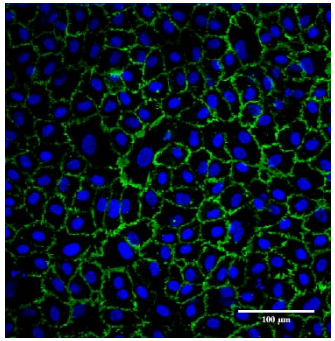
- **Address Service Gap**: Translational Research
  - Complex pre-clinical & surgical research in GLP-compliant facility with participation of thought leaders/clinical experts / KOLs to advance novel therapies through early efficacy trials and GLP safety assessment

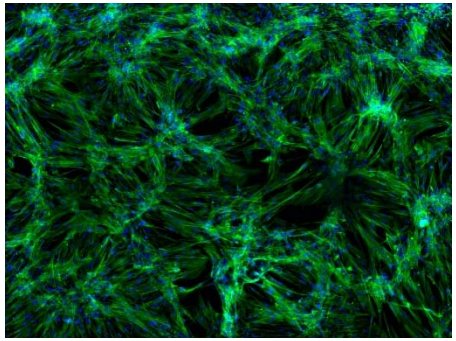
Regulatory process for frontier areas: cell therapy as an example

Regulatory Challenges of Cell Therapies:

"As if the science wasn't hard enough."







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Cell therapy regulation, the same but different...

- Just another test article!
  - Same paperwork, same FDA approach to data, same clinical indications.

- But it's alive!
  - New manufacturing challenges
  - New storage & shipping challenges
  - New preparation challenges
  - New studies required by FDA

Cell therapy is the same, but different.

- "Talk to us early.
- "Manufacture for the future."
- "Make your case – we're listening."

A successful program is a team effort!

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Teaming Up For Regulatory Review

	CRO	CMO	You
Preclinical	X		X
Regulatory	X	X	
Scientific justifications			X
CMC		X	

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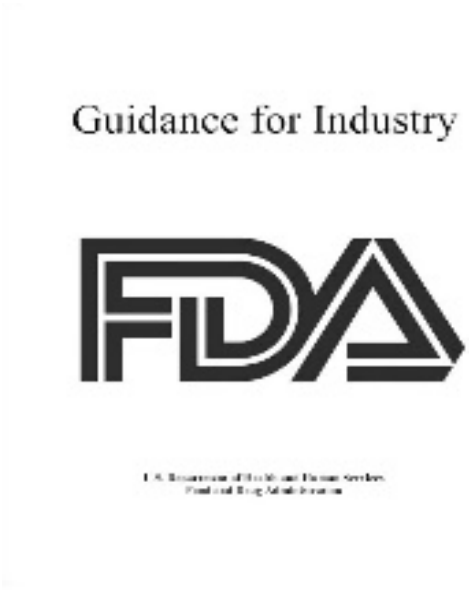
“Talk to us early.”

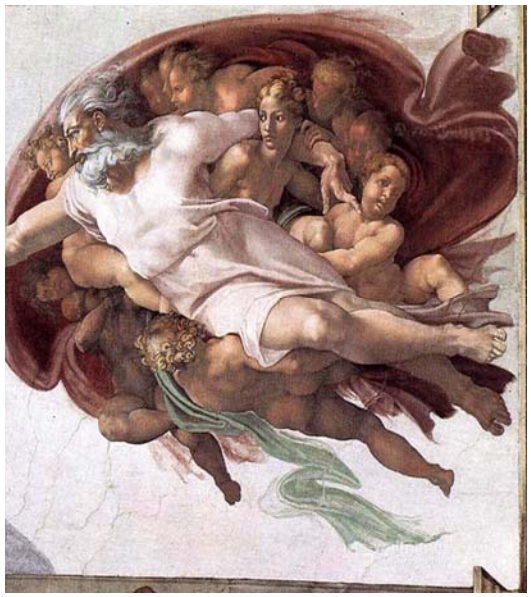
- The pre-pre-IND meeting is unique.
- Generates no official minutes.
- The goal: early input from reviewers.
  - Safety designs
  - Efficacy designs
  - Cell-specific studies

“Manufacture for the future.”

- Everything that touches a cell is suspect!
- Anything animal-derived is doubly-suspect!
- Have you considered alternatives?
- CMC (“Chemistry, Manufacturing, and Controls”) are especially difficult with cell-based therapies.

“Make your case, we’re listening.”





- Use the lack of historical studies to your advantage
- Good science makes the difference in design
- CBER wants to learn from the experts – you!

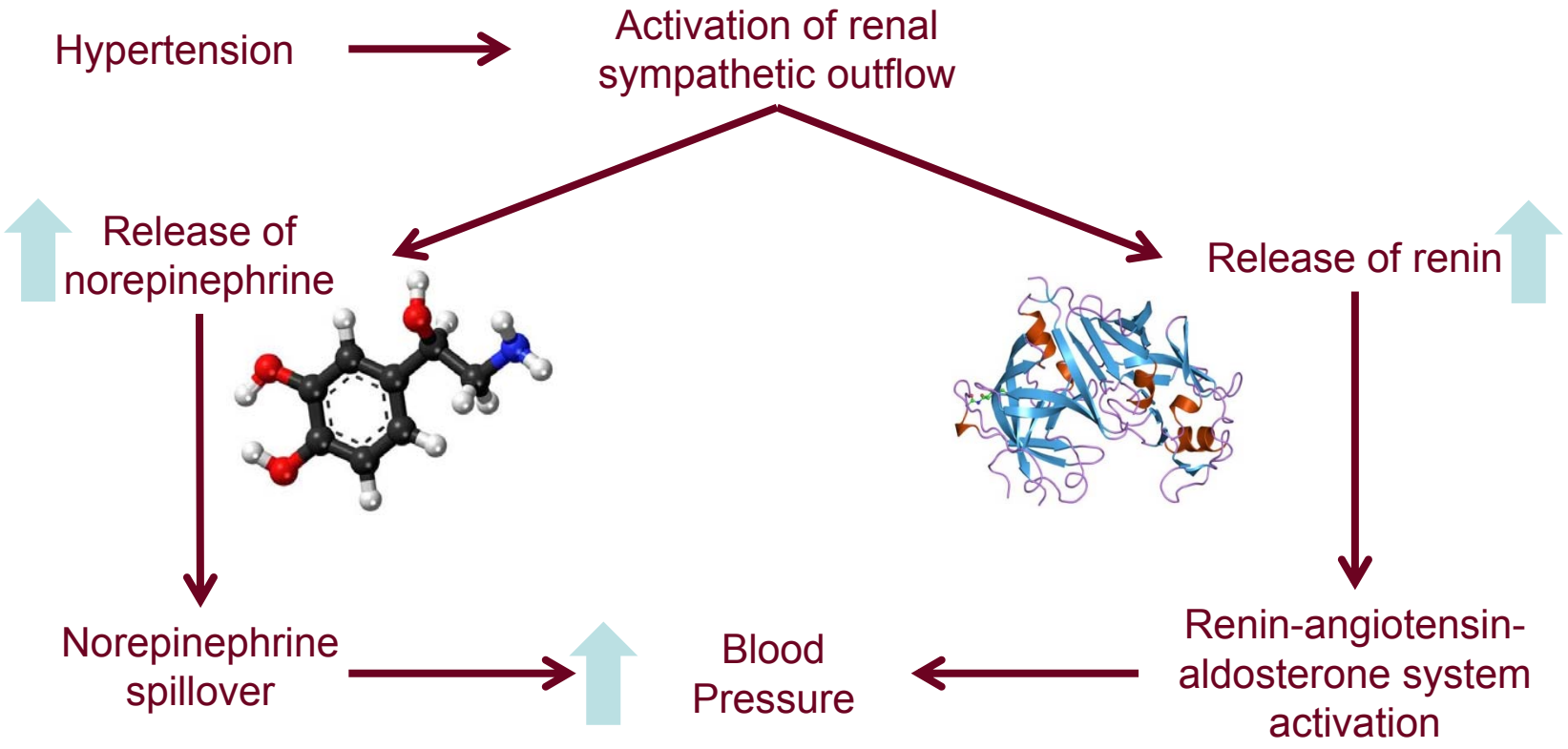
Getting novel therapies to market is a collective, collaborative effort.

The science behind Catheter Based Neuroablation Therapies

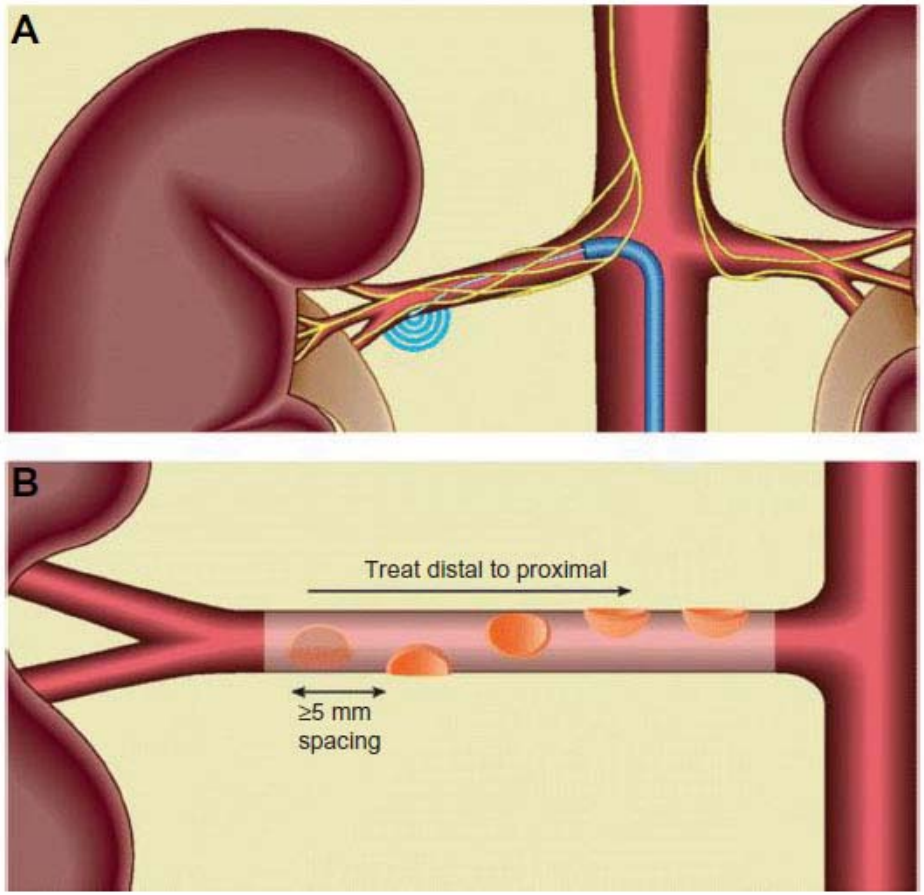
Rami Tzafriri, PhD

Role of sympathetic nerves in hypertension

- Sympathetic nerve activity (SNA) regulates blood pressure

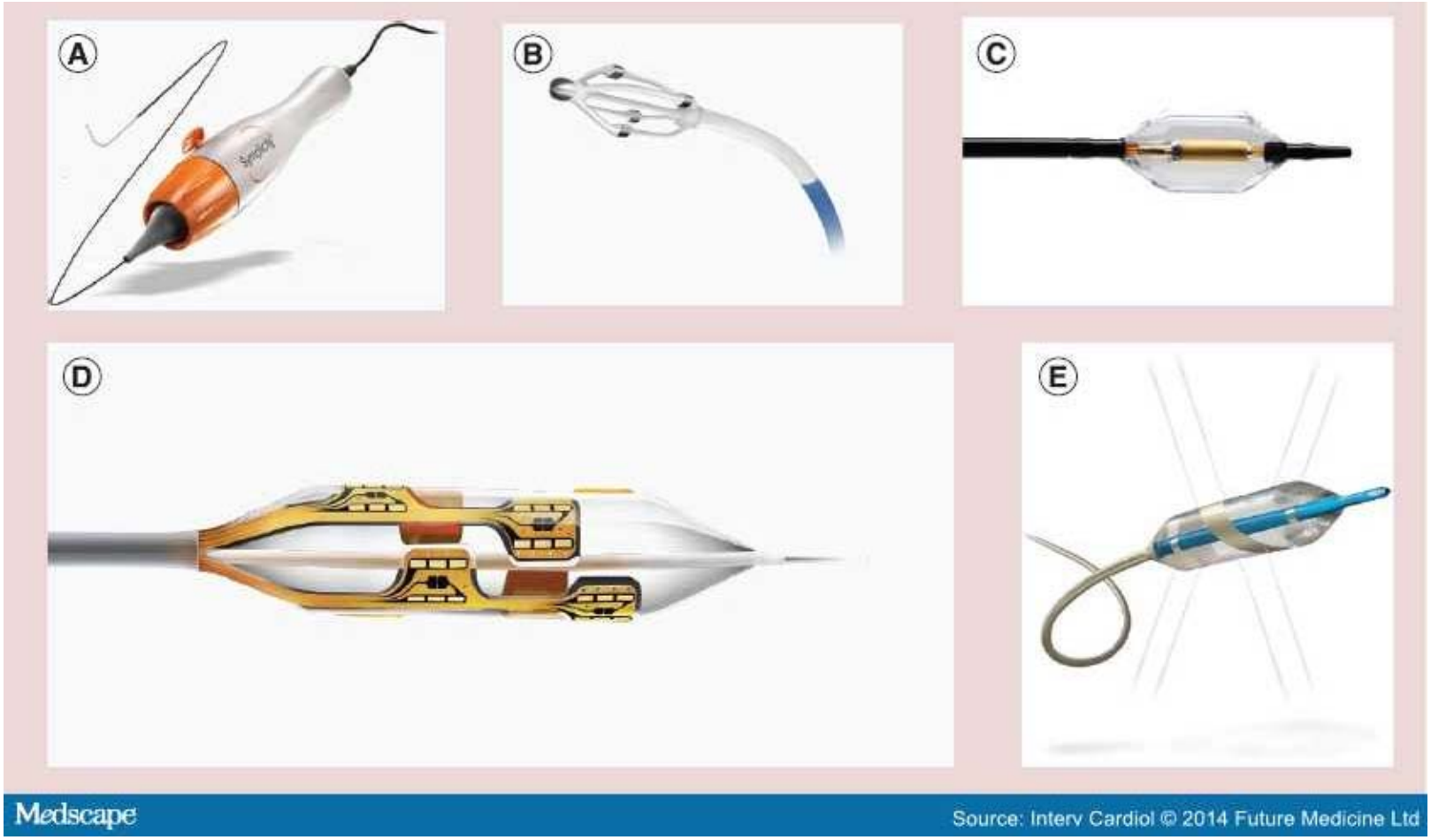


Catheter based Renal denervation (RDN) therapy for MDR hypertension



- Ardian: First generation RDN catheter with single RF electrode promising 1st in man result - 2010
- Medtronic acquires Ardian, Jan 2011 for $1.6B!

Why just one electrode?



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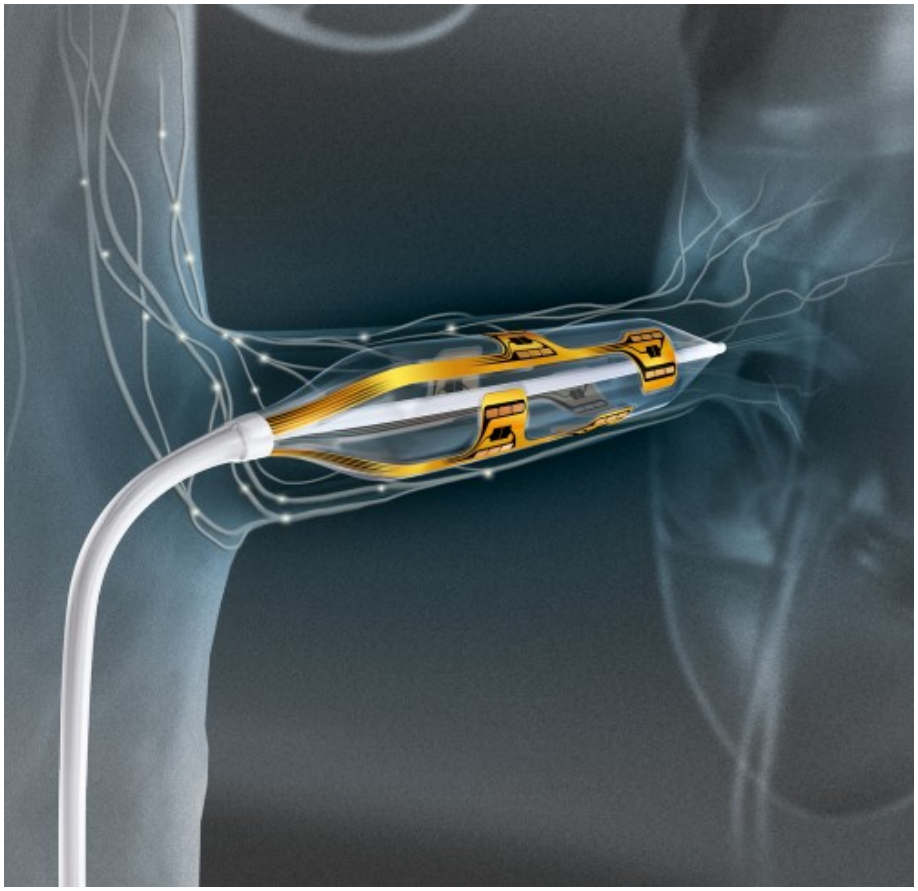
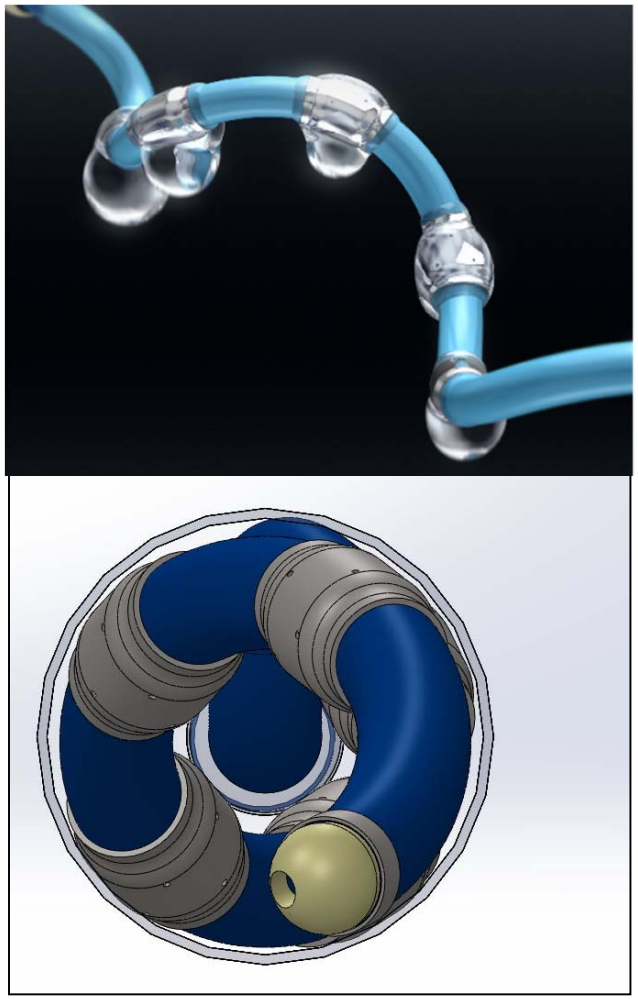
Minnow Medical
Fast Follower Project Goals



First follower, 2011

- Multi-electrode design for faster treatment
- Balloon for better wall apposition
- Simple procedure
- Bipolar vs unipolar (lower temp, less pain?)

Biosense Webster
Fast Follower Project Goals



Fast follower, 2011

- Multi-electrode design for faster treatment
- Simple procedure
- Electrode irrigation to improve safety and efficacy

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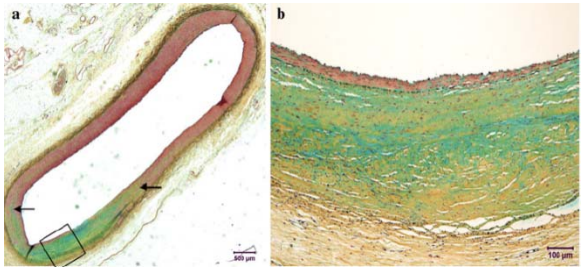
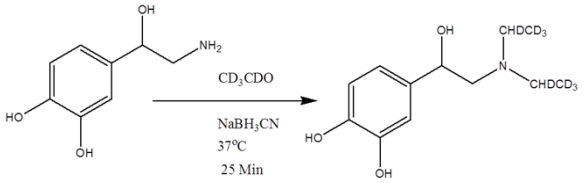
What fast followers wanted from their CRO partner, May 2011

- **Large animal model**
  - safety/histopathology
  - efficacy/biomarker
- **Product differentiation**



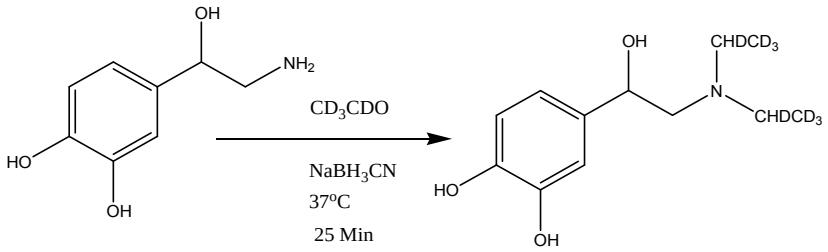



Original Article

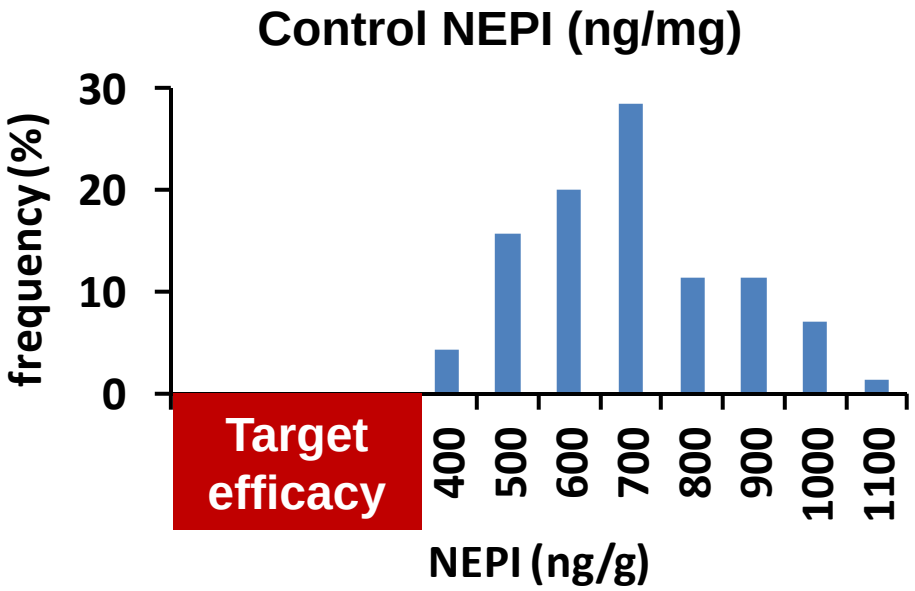
Evaluation of renal nerve morphological changes and norepinephrine levels following treatment with novel bipolar radiofrequency delivery systems in a porcine model

Predicative markers of effect

LC/MS/MS method for Quantifying Norepinephrine in kidney tissue



Variable baseline levels



N = 70 arteries
Mean = 649
SD = 161

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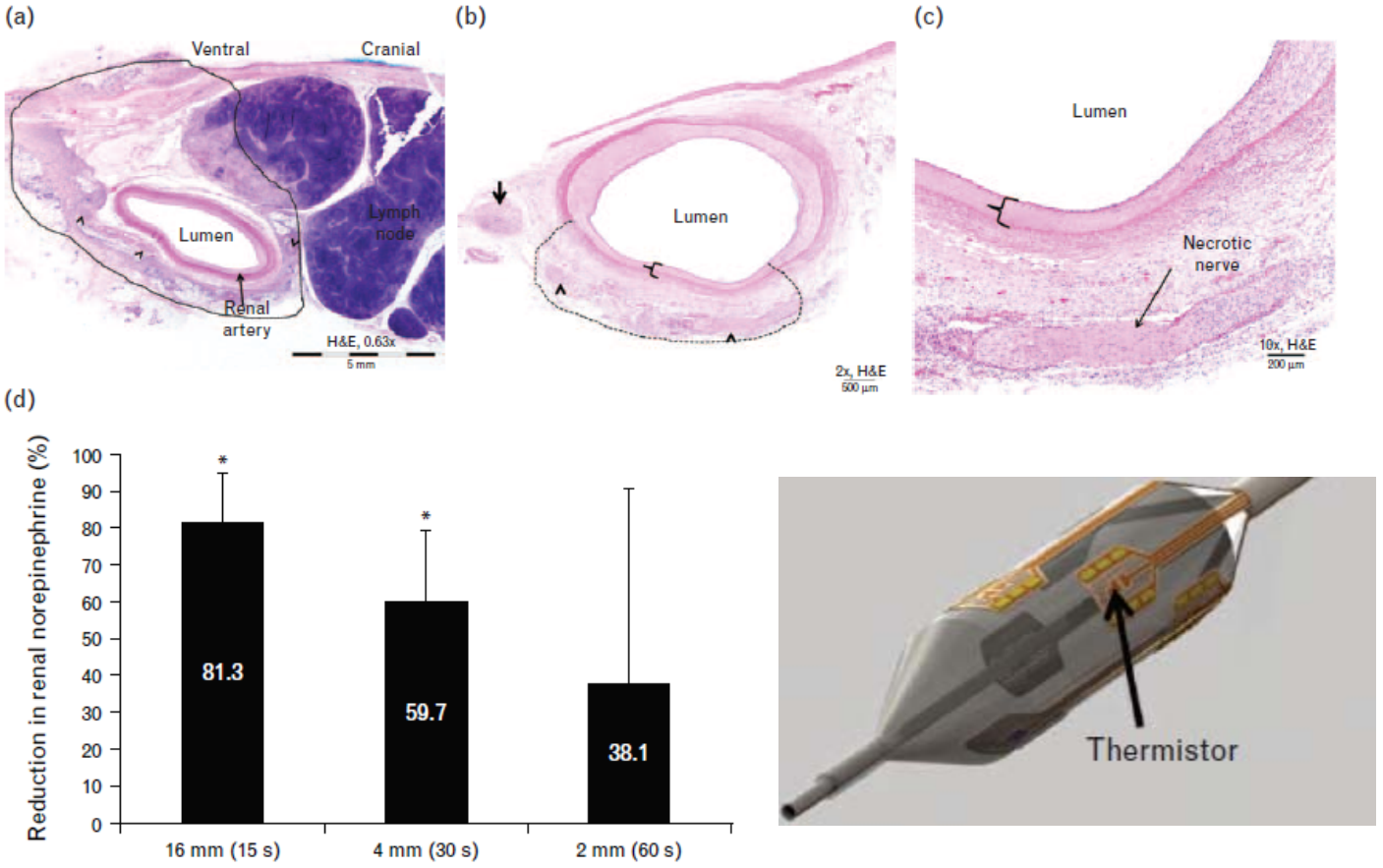
Porcine safety & efficacy model



Cohen-Mazor et al, J Hypertension 2014

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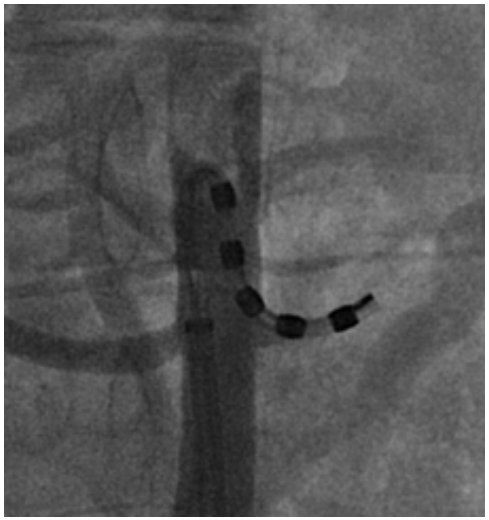
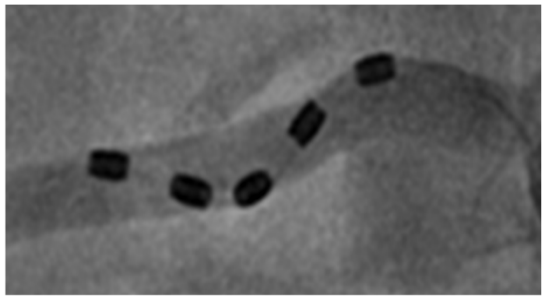
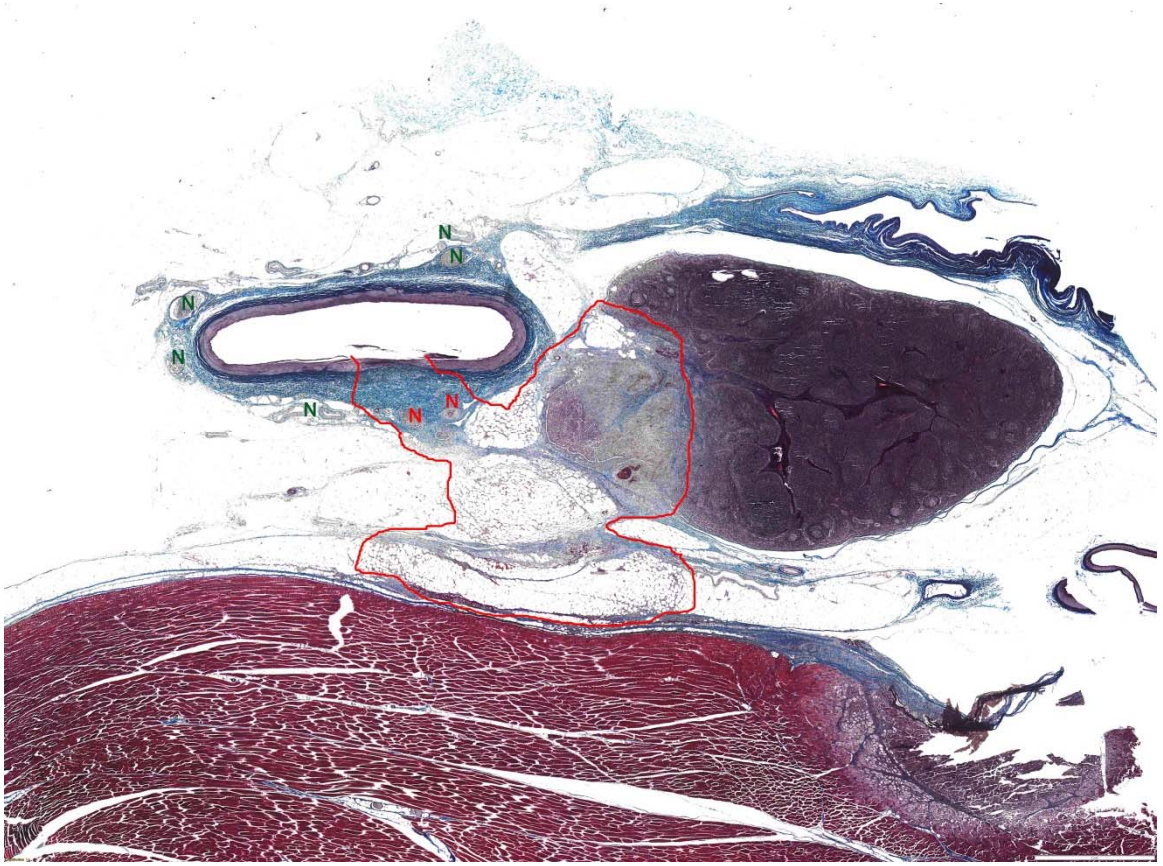
Porcine safety & efficacy model



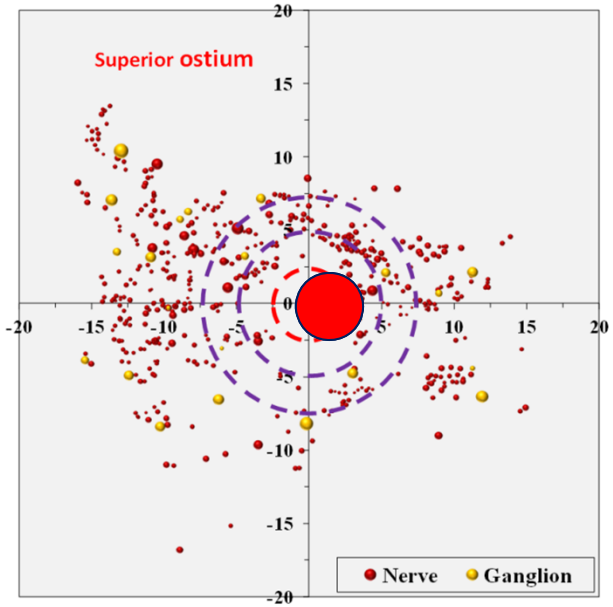


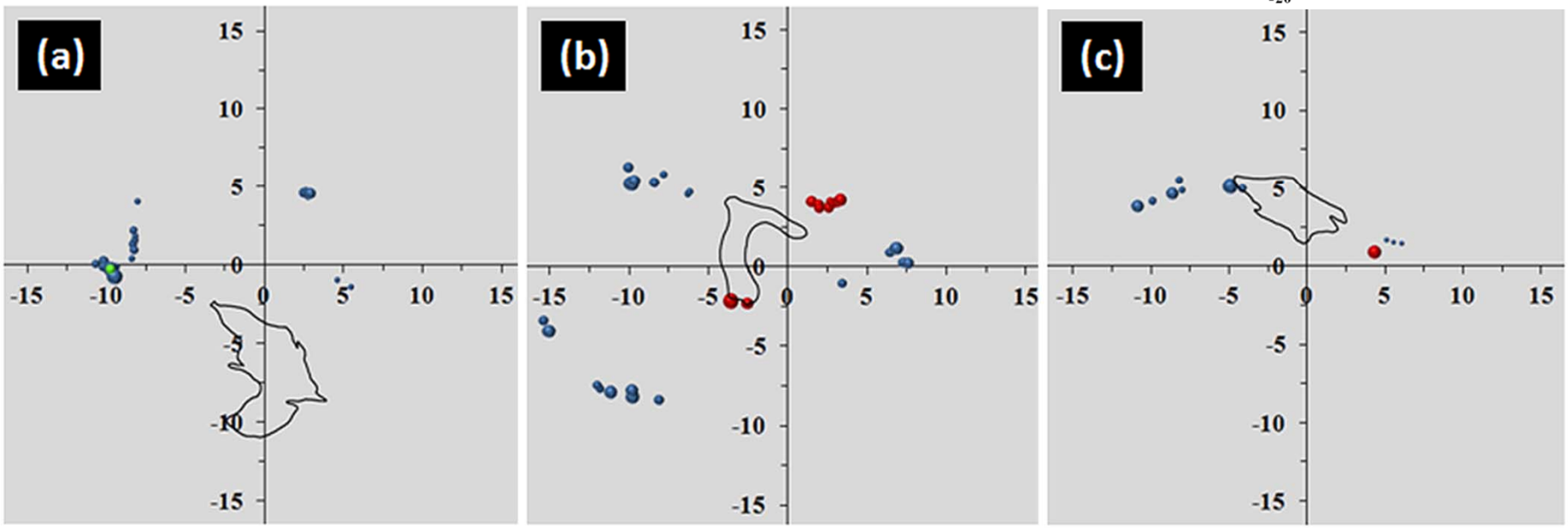


Efficacy:

Requires convergence of variable & asymmetric

* innervation
* ablation geometry





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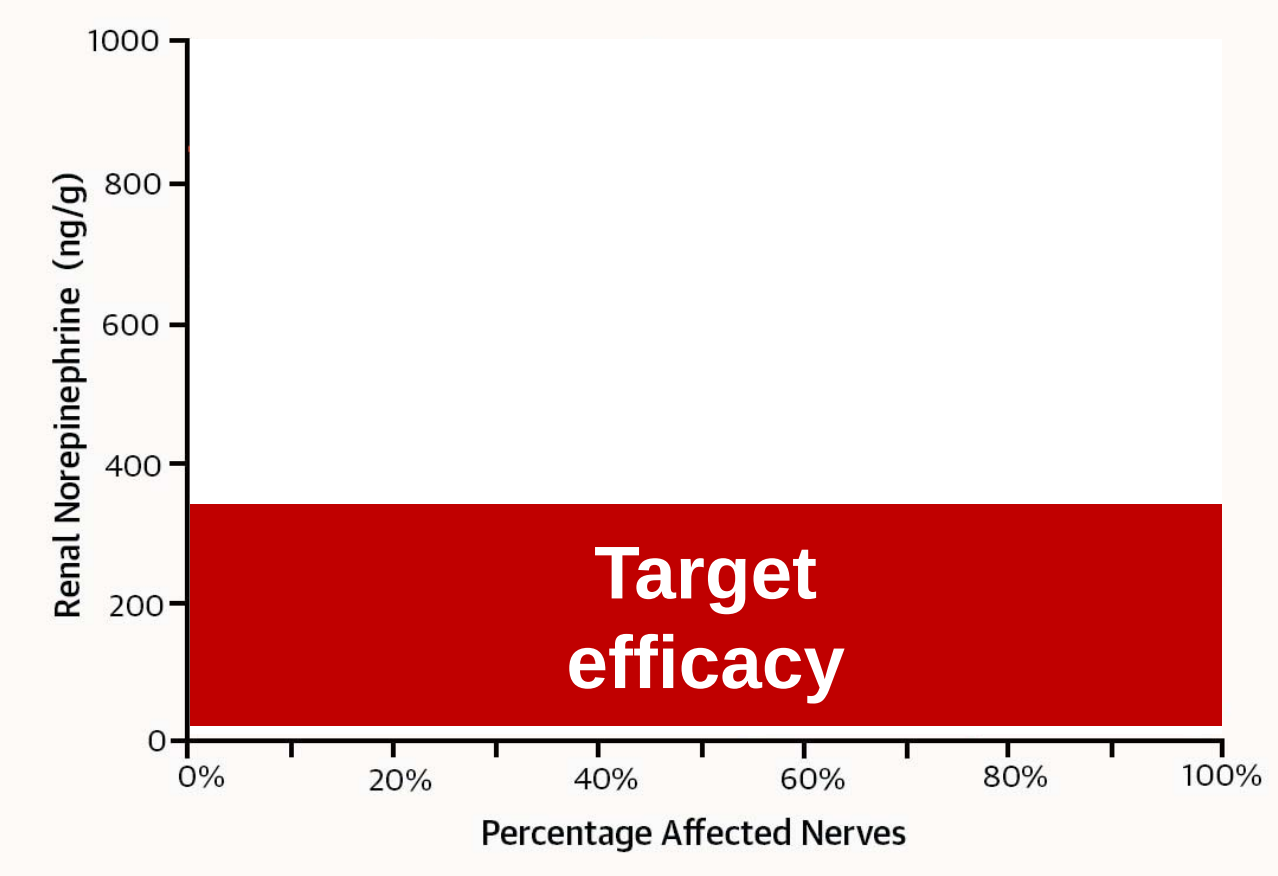
Tzafriri et al., JACC 2014

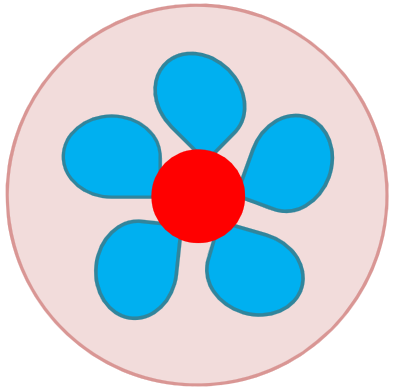
NEPI reduction correlates with nerve effects: single electrode treatments



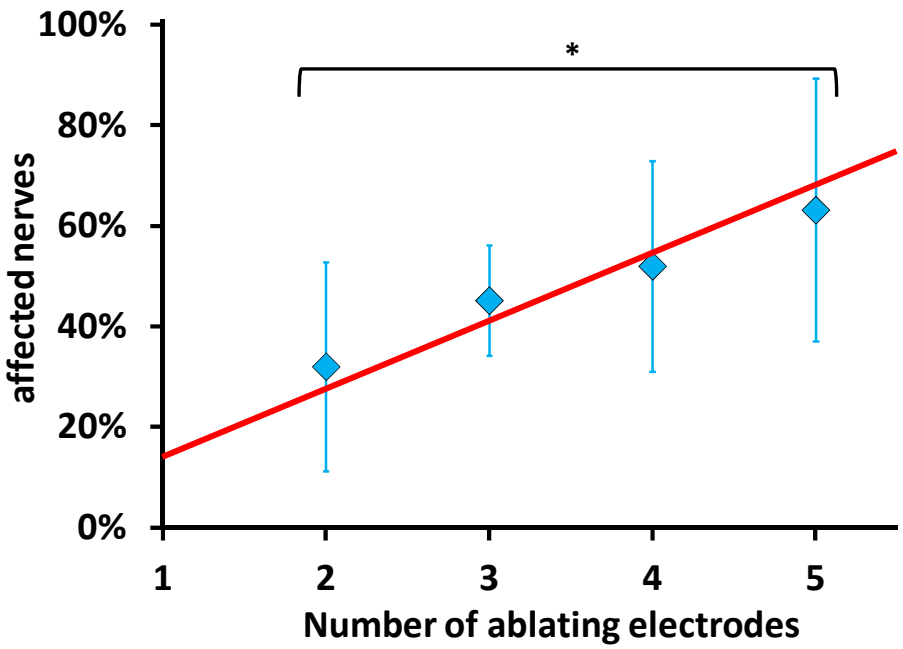
N=8 Ostial treatments

Tzafriri et al., JACC 2014

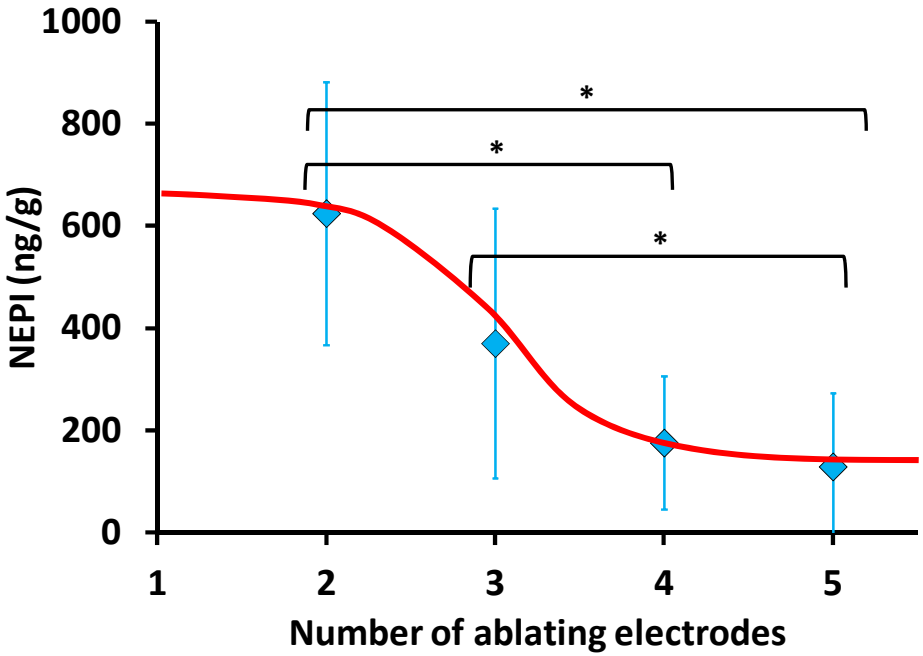
Biomarker effects vs number of helically staggered RF treatments



% Denervation



NEPI Reduction



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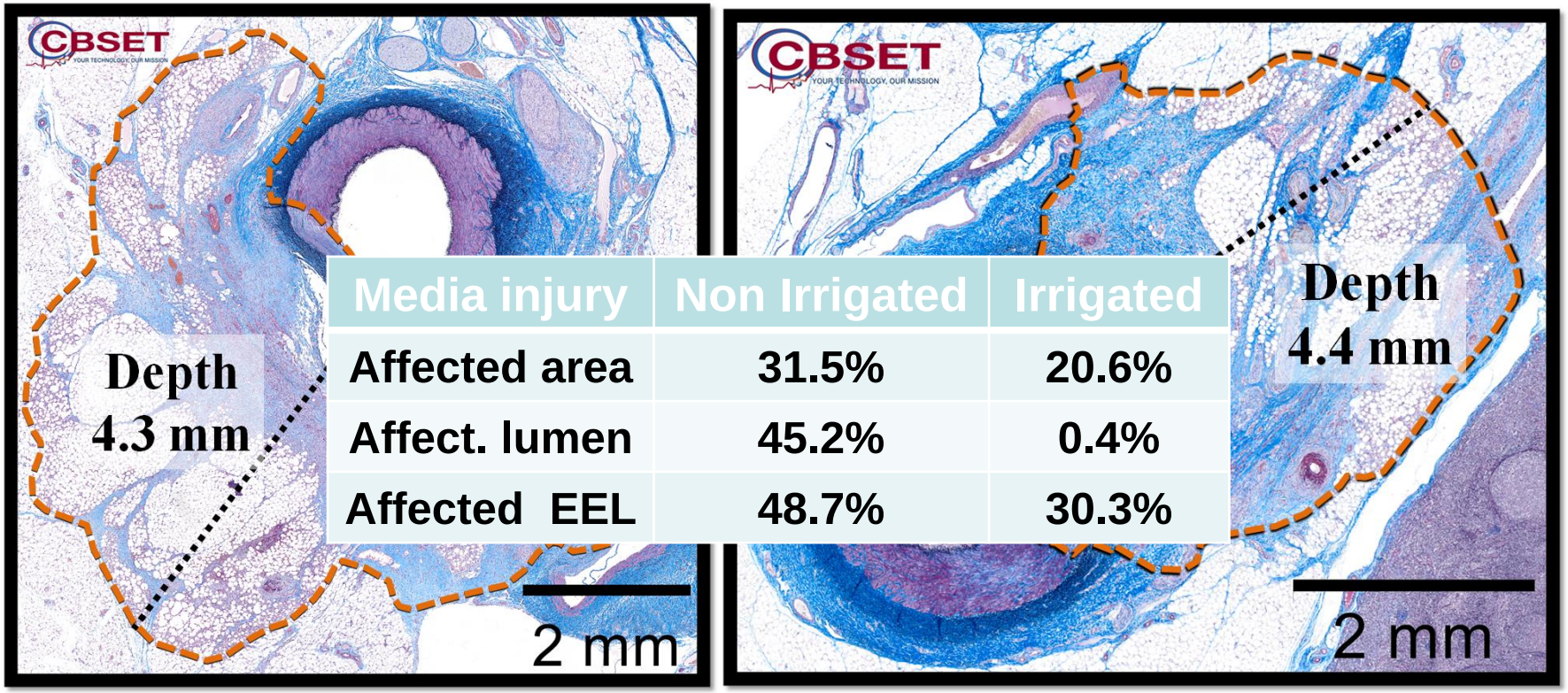
Irrigation protects the media Adjacent to the ablating electrode

Non Irrigated **Irrigated**



Media injury	Non Irrigated	Irrigated
Affected area	31.5%	20.6%
Affect. lumen	45.2%	0.4%
Affected EEL	48.7%	30.3%

Tzafriri et al Sci Transl Med 2015

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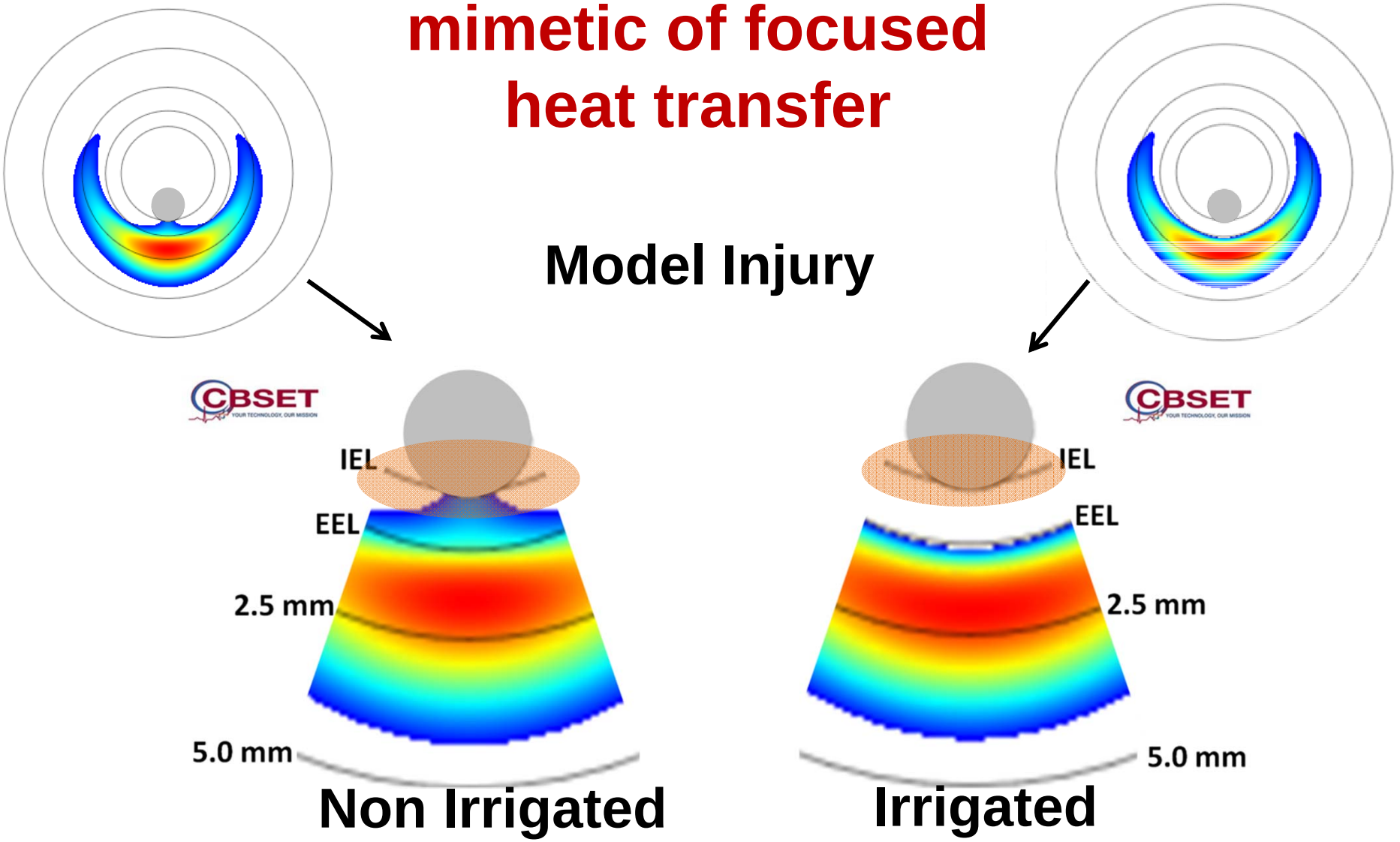
Electrode irrigation as a bio-mimetic of focused heat transfer



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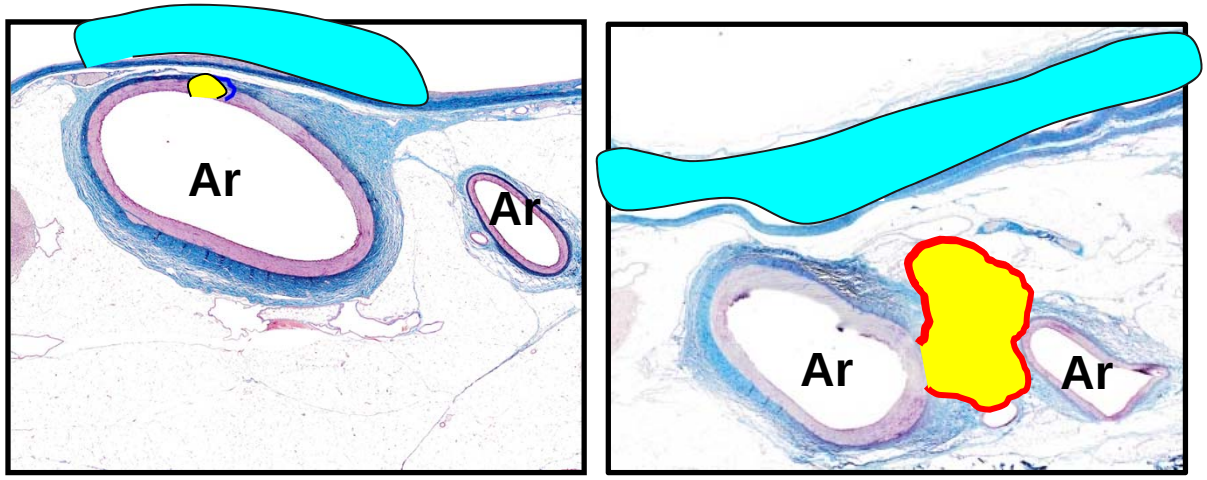
Variability in efficacy VS heat sinks

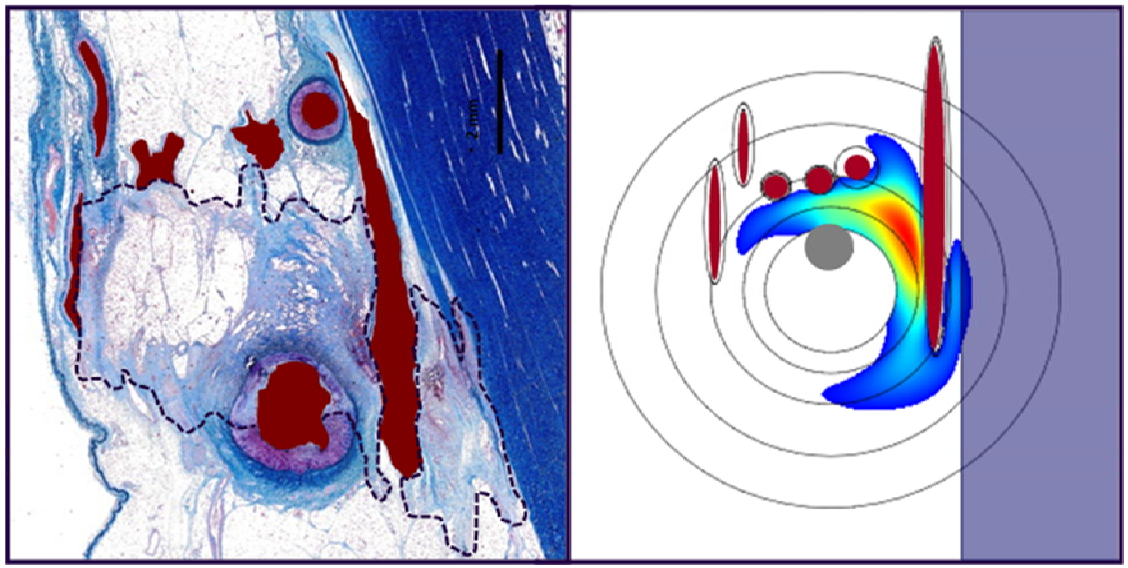


RESEARCH ARTICLE

HYPERTENSION

Arterial microanatomy determines the success of energy-based renal denervation in controlling hypertension

Abraham R. Tzafriri,[1]* John H. Keating,[1] Peter M. Markham,[1] Anna-Maria Spognardi,[1] James R. L. Stanley,[1] Gee Wong,[1] Brett G. Zani,[1] Debby Highsmith,[2] Patrick O'Fallon,[2] Kristine Fuimaono,[2] Felix Mahfoud,[3] Elazer R. Edelman[4,5]



FOCUS

HYPERTENSION

Renal denervation: Not as easy as it looks

Murray Esler

Renal sympathetic denervation with intravascular radiofrequency catheters in hypertensive patients is less effective than anticipated, owing to radio frequency energy being applied to a part of the renal artery where the nerves are at the greatest distance from the aortic lumen and to distortion of energy distribution and temperature gradients by regional tissue anatomical variations (Tzafriri *et al.*, this issue).

Lessons from the frontline

- **Getting novel therapies to market is a collective, collaborative effort**
- **First follower – Don't just follow first generation testing paradigm. Speed and differentiation are most important**
- **New product in a crowded field – Find a partner that can help you differentiate your technology via key publications and presentations**

Case Studies

Panel Discussion

Kumaran Kolandaivelu, MD, PhD

Rami Tzafriri, PhD

Michael Naimark, MS

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Funding Opportunities:

Tufts CTSI Symposium Plus

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Introduction

Graham Jones, PhD

Associate Director and Director of Research Collaborations
Tufts CTSI

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Tufts CTSI Symposium Plus Model

- **Stage 1: Solicitation of Nascent Projects (RFP)**
  A request for research abstracts is issued.
- **Stage 2: Project Pitch at a Launch Symposium**
  4-5 selected research teams pitch project ideas and receive feedback from the audience and topic-specific experts.
- **Stage 3: Proposal Development**
  The research teams prepare a proposal for ~6-8 months with expert consultations from assigned mentoring teams.
- **Stage 4: Project Follow-up**
  Project & mentoring teams assemble for a second meeting to share additional feedback.

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Participant Experience

Alysse Wurcel, MD, MS
Attending Physician, Tufts Medical Center
Assistant Professor, Tufts University School of Medicine

John Leong, MD, PhD
Edith Rieva and Hyman S. Trilling Professor of
Molecular Biology & Microbiology,
Tufts University Sackler School of Graduate Biomedical Sciences

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2018 Symposium Plus:
Sensors, Devices, and Biomarkers in Medicine

- **Request for Proposals DUE - January 5, 2018**
- **Symposium Date - April 24, 2018**

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Refreshments & Networking (*Lobby*)

Or

Tufts Analytics Platform (TAP): Enhancing Research with Integrated Analytics (*Sackler 114*)

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Tufts Analytics Platform (TAP)
Enhancing Research with Integrated Analytics

William Harvey, MD, MSc, FACR
Medical Director Clinical Informatics
Tufts Medical Center

Joseph Gormley
Senior Systems Project Director
Tufts CTSI

Svetlana Rojevsky, MSC
Program Manager
Tufts CTSI

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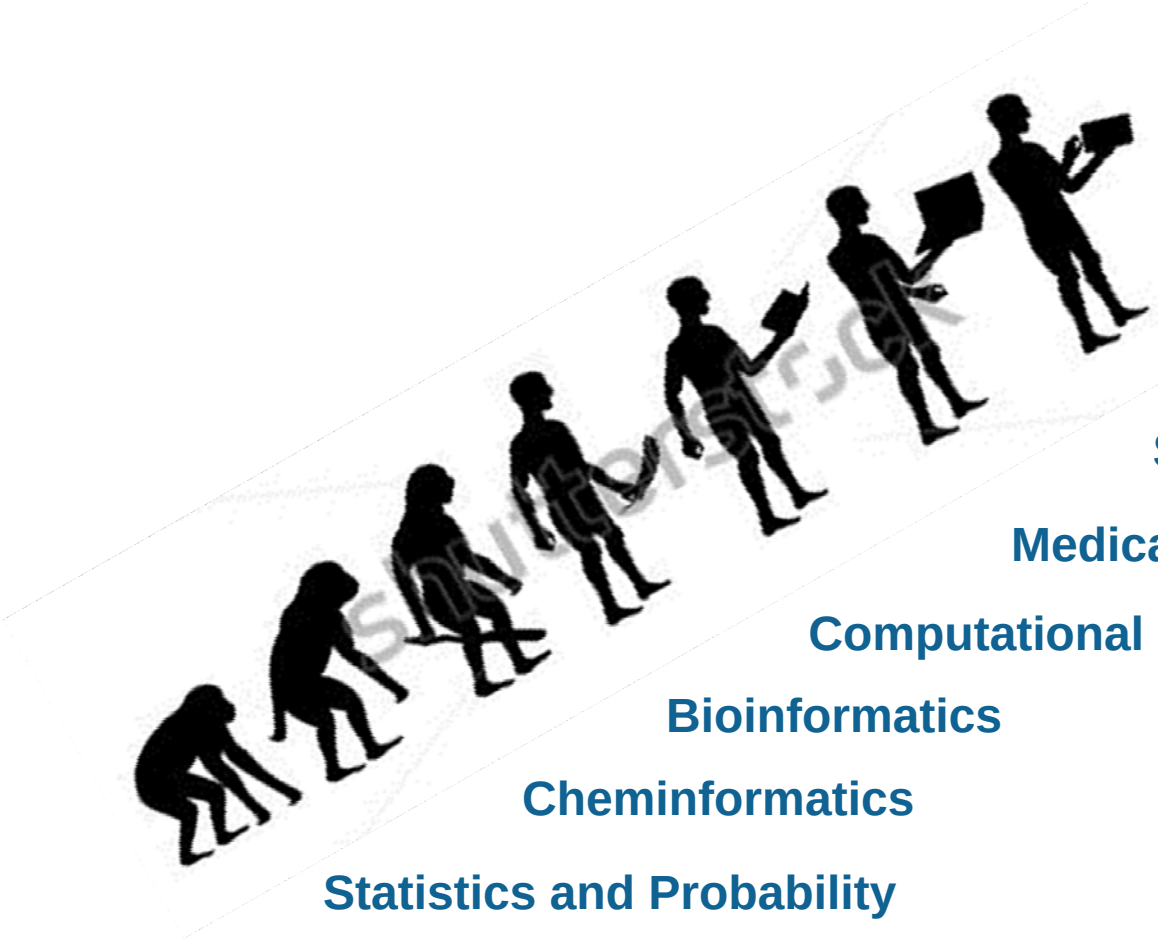
Research Paradigms

- Descriptive Science
- Hypothesis-Driven Science
- ***Discovery Science***
- Engineering Science

The Evolution of Discovery



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Network Medicine

Systems Biology

Medical Informatics

Computational Biology

Bioinformatics

Cheminformatics

Statistics and Probability

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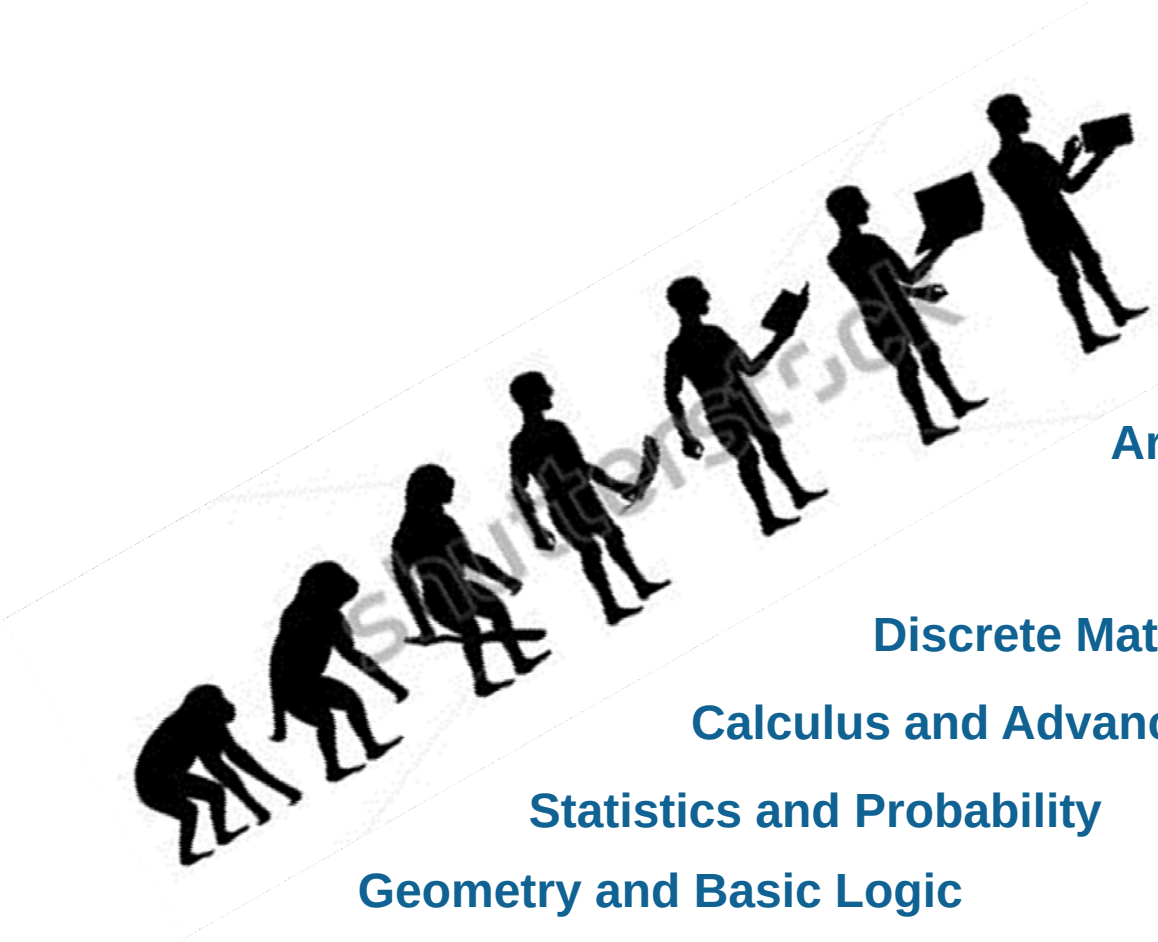
The Evolution of Techniques



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Explainable AI

Artificial Intelligence

Machine Learning

Deep Learning

Discrete Mathematics

Calculus and Advanced Logic

Statistics and Probability

Geometry and Basic Logic

Basic Arithmetic

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State of Biomedical Sciences

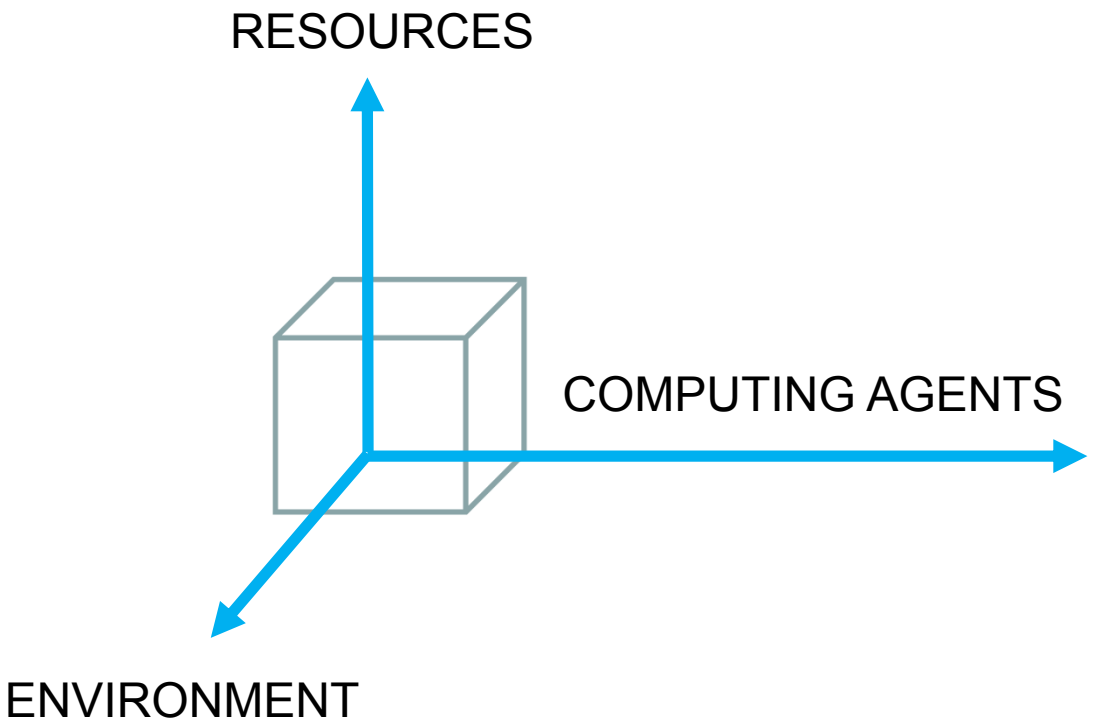
- Ever expanding data capturing modalities
- Lack of same-data integration (i.e., silo problem)
- Failure to employ multiscale and heterogeneous data sets
- Current analytics techniques are often underutilized
- Suboptimal use of emerging analytics techniques
- Lack of adequate method and/or tool training in the lab
- Questions continue to increase in complexity

….The Discovery Process Remains Inefficient

Adaptive Workflows

- Specification or GOAL DRIVEN
- Dynamic sequencing of tasks
- Focus on solutions versus individual tasks
- Opportunity to maximize resource use
- Continuous quality improvement

AWS Dimensions



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Why TAP...Why Now?

- Adaptive workflows are now viable as automation frameworks
- Diverse range of computing resources for multiscale analysis
- Tools now available that permit cost-effective data engineering
- Methods now available that permit robust machine learning
- Automating solution steps will reduce process errors
- Potential to increase quality, throughput and reproducibility

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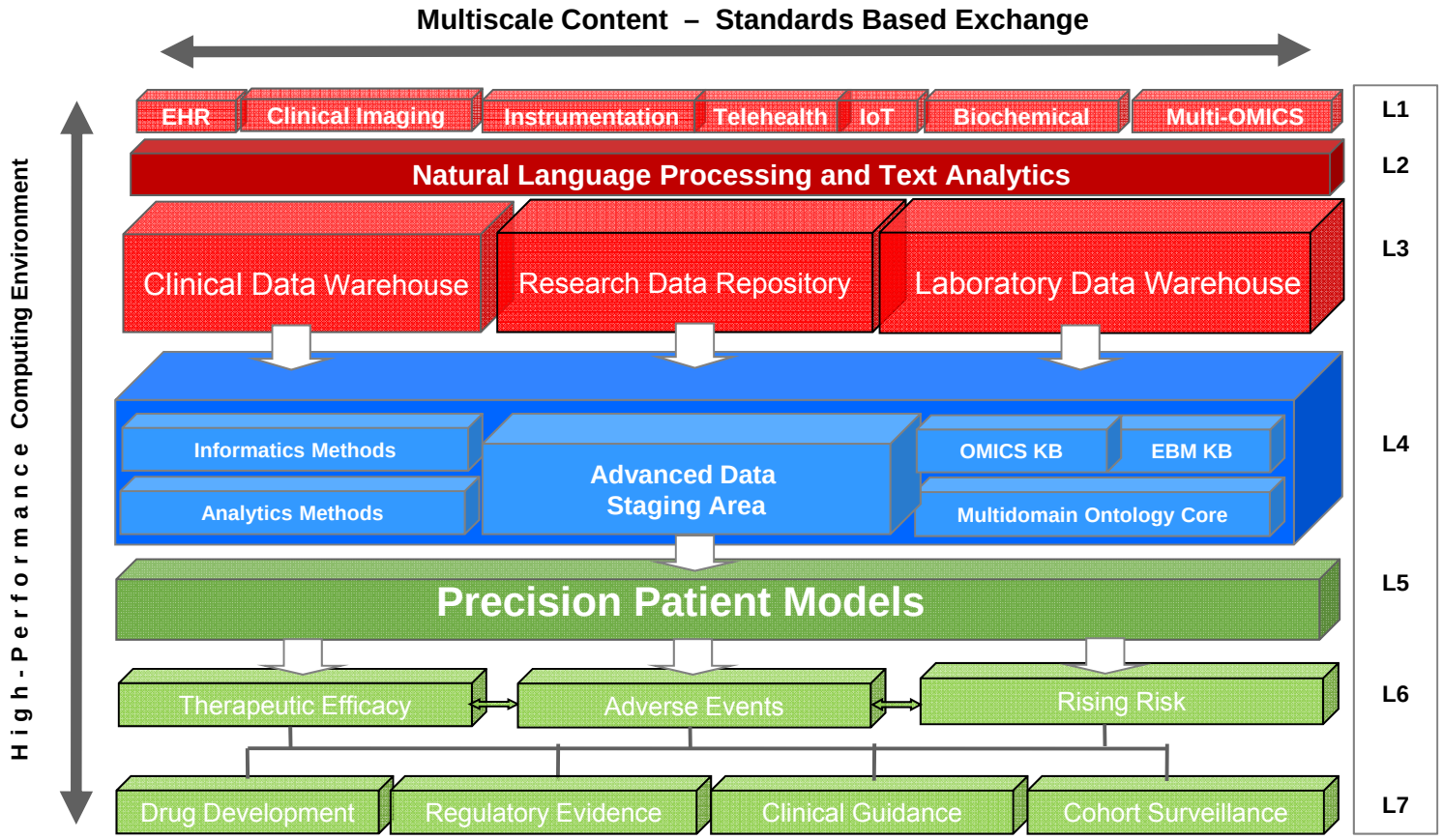
TAP Architecture



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L4 Support Methods

- Cheminformatics
- Bioinformatics
- Medical Informatics
- Machine Learning
- Dynamic Network Analysis
- Ontology-based Representation/Reasoning

Engineering Challenges

- Integrating NLP effectively
- Integrating ontologies effectively
- Avoiding ill-posed workflows
- Avoiding data gaps during computation
- Obtaining acceptable QoS from external resources

TAP Goals

- Capture Heterogeneous Data
- Harmonize Multiscale Data
- Compute Actionable Information
- Seamless *In Situ* Deployment

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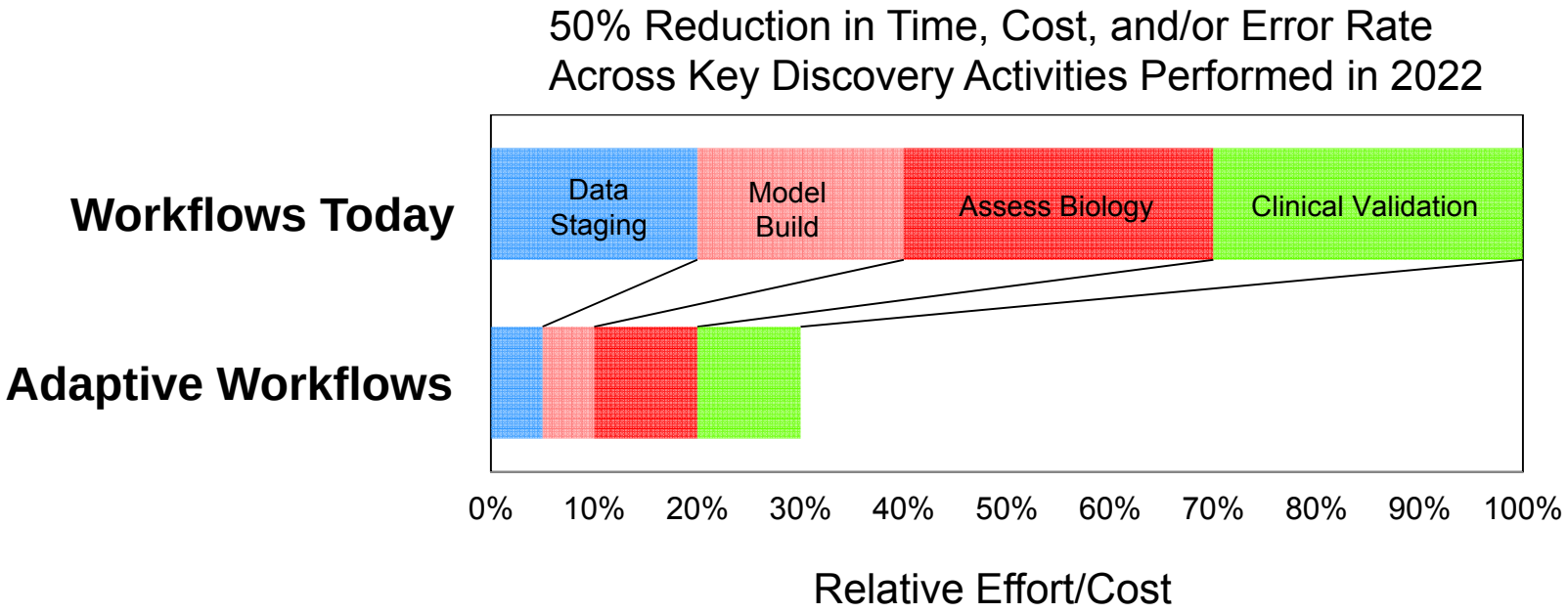
Human vs Machine



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Success Criteria

- Generate new methodologies
- Increased grant funding
- Increased publication rate
- Increased Institutional IP
- Unique staging area for institutional collaborations

…. New Science, Better Science, Different Science

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QUESTIONS?

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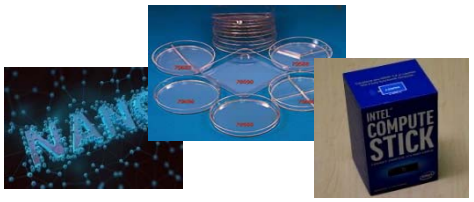
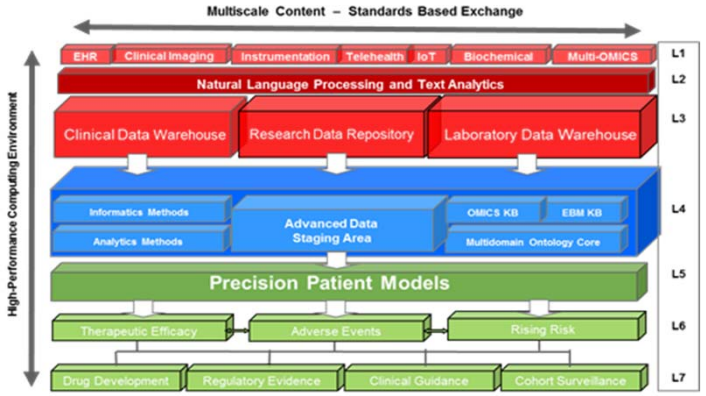
UC 1: Sensoring Our Cells

- Nanomaterials
- Nanoparticles
- Nanofibers

- Research Models





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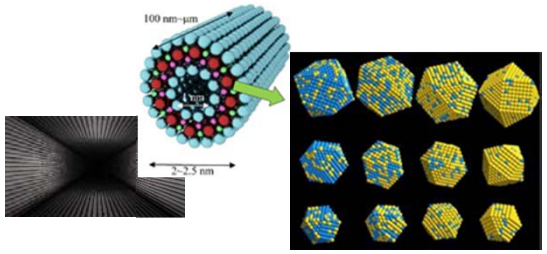
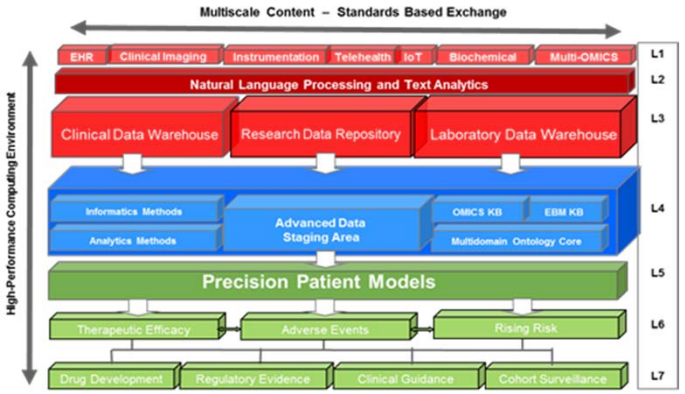
UC 2: Sensoring Tissue

- Nanoelectronics
- Nanocomposites
- Nanomaterials

- Research Models
- Drug Delivery
- Smart CDSS





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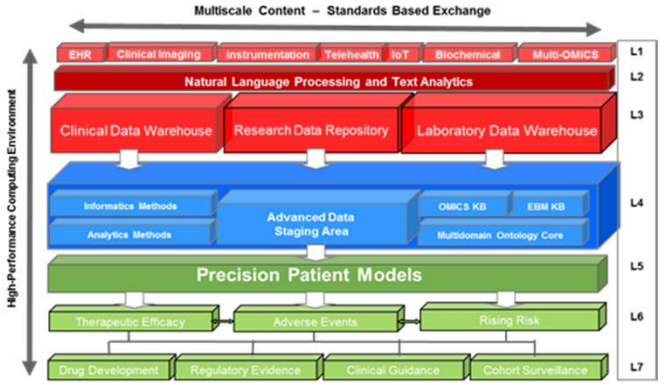
UC 3: Sensoring Behavior

- Smart Phone Technology
- Edge Computing
- *In Situ* Monitoring

- Research Models
- Smart CDSS



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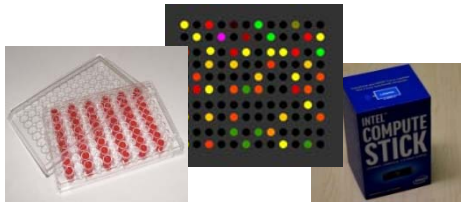
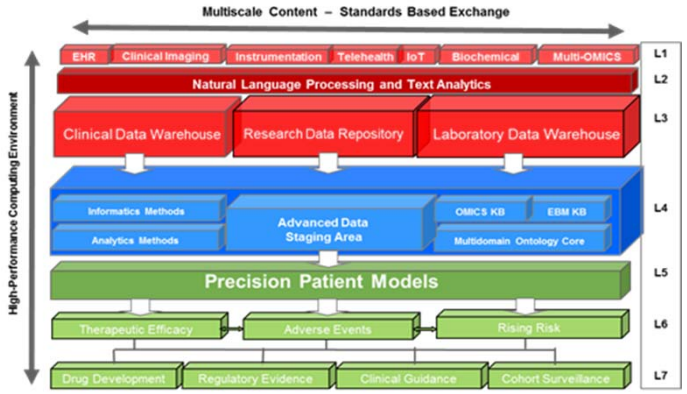
UC 4: Sensors in the Clinic

- Biochemical Assay
- Whole Genome Assays
- High Complexity Assays

- Research Models
- Smart CDSS





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Thank you very much!

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Translational Research Day 2017:
Sensors, Devices, and Biomarkers in Medicine

November 14, 2017

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