Translating Science into Medicine
A future informed by the lessons of COVID

Today's speakers from the University of Washington (UW), Sepsis Center of Research Excellence (SCORE)

Dr. Conrad Liles
Director of SCORE

Dr. Mark Wurfel
Translational Critical Care Research at SCORE

Dr. Pavan Bhatraju
Bioinformatics Research at SCORE

Dr. Grant O'Keefe
Professor of Surgery at UW

Dr. Craig Smith
Co-Director at SCORE

Welcome by
Julie Dunnington
Chief Marketing Officer

Sepsis Center of Research Excellence University of Washington (SCORE–UW)

Dr. W. Conrad Liles

Mission

To improve clinical outcomes in individuals with sepsis
and critical illness (including COVID-19)
through innovative translational research

Sepsis

The patient response of extreme reaction to an infection

Sepsis = a pathogen or infection + patient response

- Infection alone is not sufficient to cause sepsis
- Inflammation alone is not sufficient to cause poor clinical outcomes
- A person's response to inflammation is the key driver of clinical outcomes
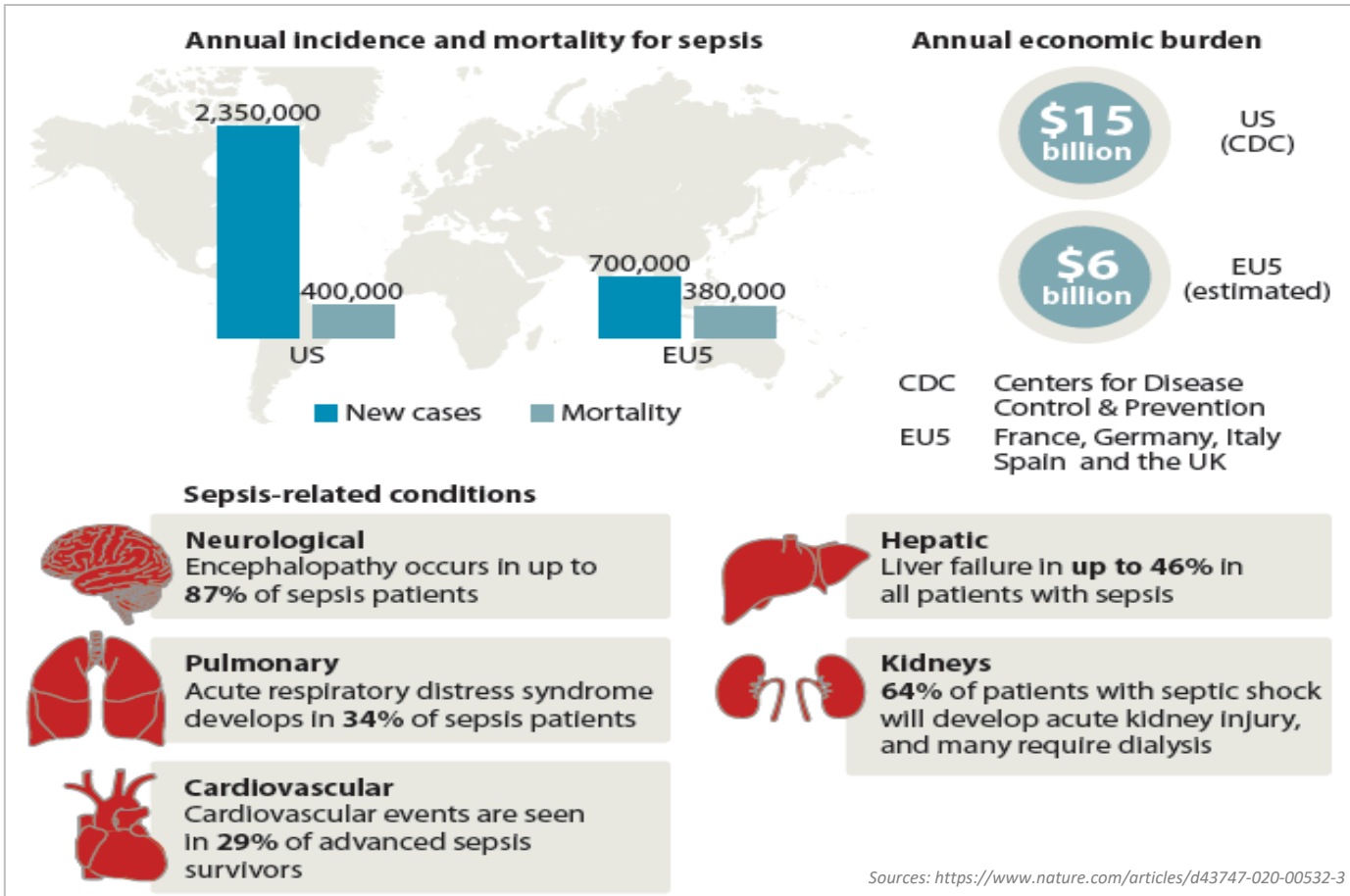
It's a global health problem causing significant medical complications and mortality

- Leading cause of death in ICUs
- Overall incidence increasing worldwide
- Affects all ages
- Organ injury, dysfunction and failure
- No specific treatment exists

Sepsis = SARS-COV-2 + COVID-19 disease

Sepsis

The patient response of extreme reaction to an infection

SCORE–UW

*Innovative and transformative translational research
in sepsis and critical illness*

Unique Focus on the Individual's Response
- Response to inflammation, especially vascular leak and organ failure

Approaches
- New biomarker discovery and validation (Dr. Mark Wurfel)
- Machine learning/artificial intelligence (Dr. Pavan Bhatraju)

Goals
- Identify sub-classifications of patients based on biological pathways of diseases
- Develop new, targeted therapeutic approaches for treatment of different people's responses and related complications (precision medicine)
- Develop a device for multiple biomarker testing and application to improve triage, clinical decision-making, and resource utilization for management of patients with suspected reactions
- Improve survival and decrease death in patients who have an extreme reaction to a disease

SCORE–UW

Innovative and transformative translational research in sepsis and critical illness

Expanding the scope of SCORE-UW research to meet important unmet challenges in medicine

- Trauma – Dr. Grant O'Keefe
- Ophthalmology (eye disease) – Dr. Craig Smith

Sepsis, Critical Illness and Trauma

An up close and personal patient case study

Novel, Clinically Informative Biomarkers in Sepsis and Critical Care

Dr. Mark M. Wurfel

Biomarkers in Medicine: A Primer

Oxford Definition: *"a measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure"*
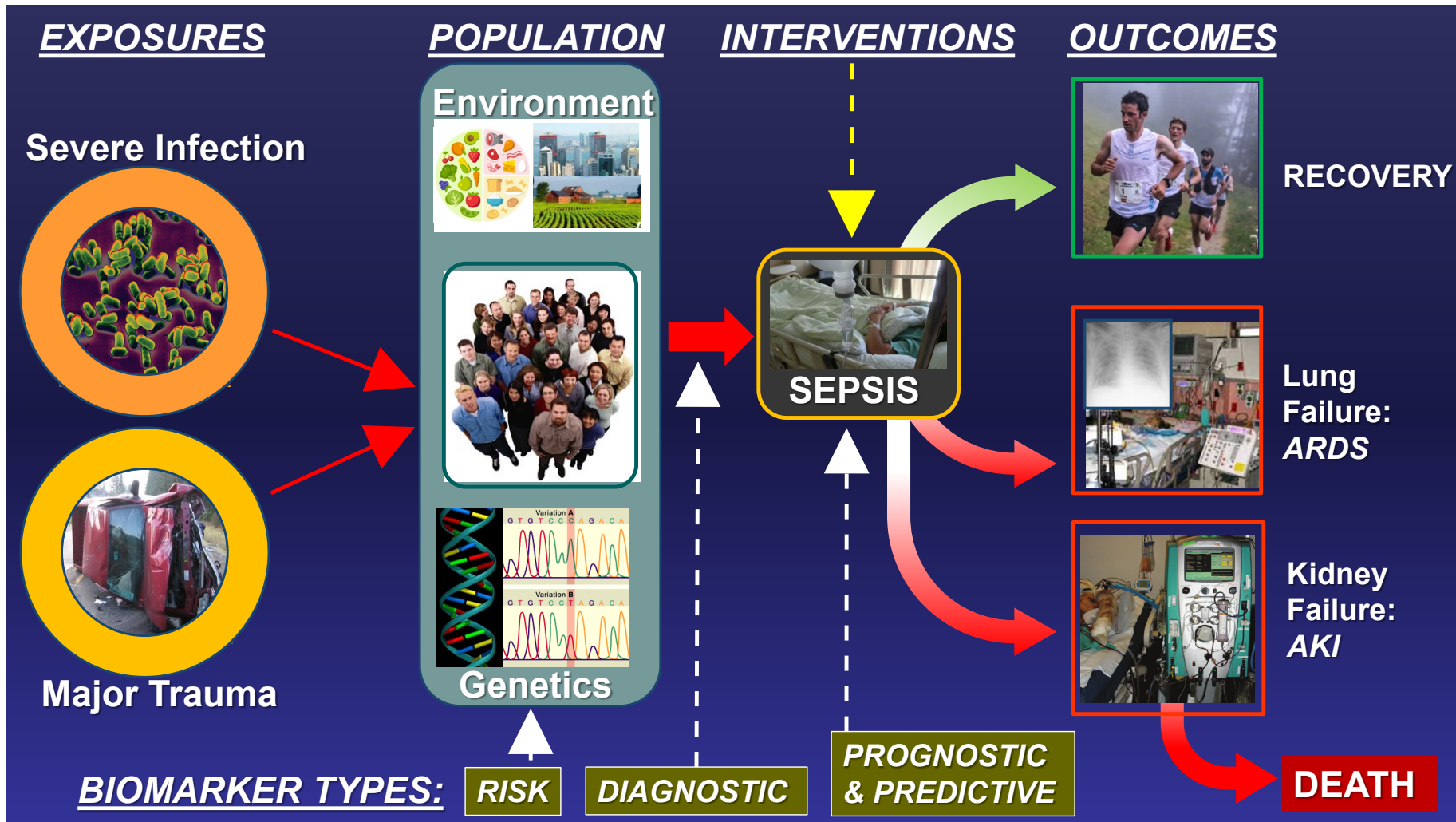
Risk: Quantifies underlying patient factors that increase the chances of developing a disease (e.g. BRCA1/2 genes and breast cancer)

Diagnostic: Indicates likelihood of having a particular disease (e.g. Elevated serum Troponin I levels indicate a heart attack)

Prognostic: Estimates chances a patient will improve or worsen once diagnosed with a disease (e.g. Serum Neuron-specific enolase levels estimate chances of awakening after cardiac arrest)

Predictive: Identifies patients with a particular disease who are most likely to benefit from a particular therapy. (e.g. PD-L1 levels on tumor cells predict benefit from Keytruda (pembrolizumab) treatment)

Biomarkers in Sepsis & Multi-Organ Dysfunction

EXPOSURES

Severe Infection

Major Trauma

POPULATION

Environment

Genetics

INTERVENTIONS

OUTCOMES

SEPSIS

RECOVERY

Lung Failure: *ARDS*

Kidney Failure: *AKI*

DEATH

BIOMARKER TYPES: | RISK | DIAGNOSTIC | *PROGNOSTIC & PREDICTIVE*

SCORE–UW: Prognostic Biomarkers of Death in Sepsis

SEPSIS

- Measured circulating levels of ~10 biomarkers in patients with sepsis at the time of admission to an Intensive Care Unit

- Used statistical modeling to develop simple model with two biomarkers (sTNFR-1 + IL8) that estimated chances of death in 3 groups of critically ill patients with sepsis

- Compared to established clinical severity scores
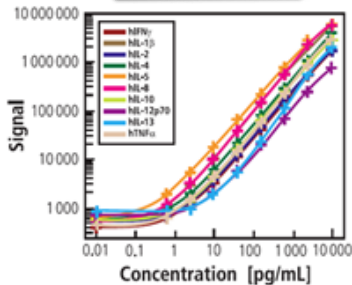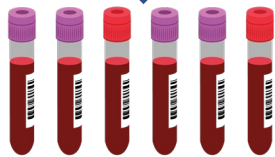
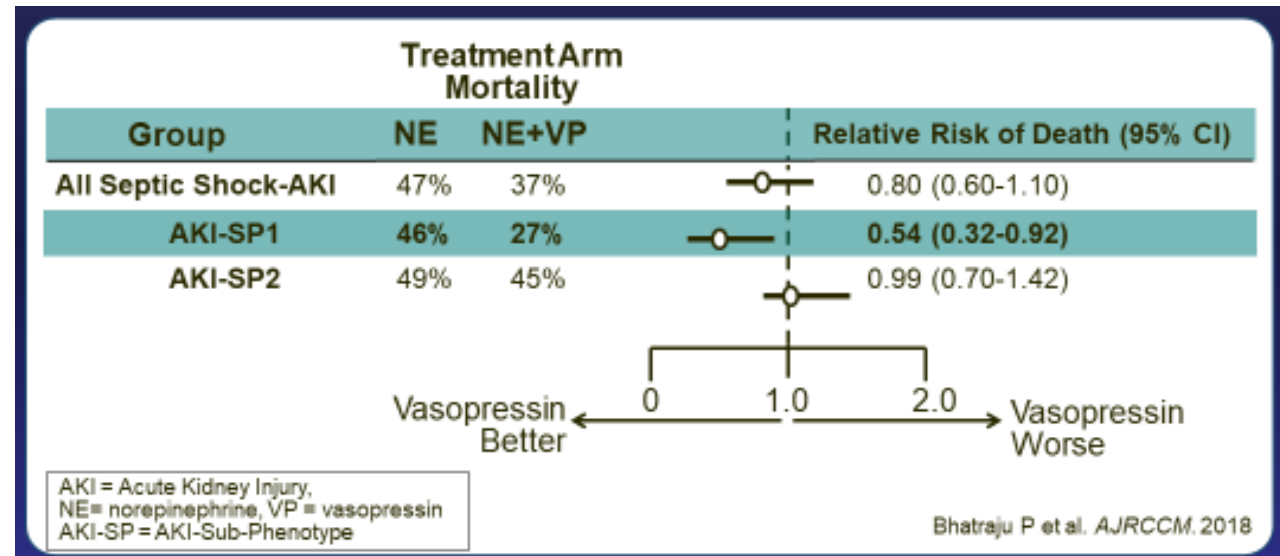| Cohort	Threshold Goal	Model Score Threshold*	Patients above/below Threshold (n)	PPV[†]	NPV[‡]
Derivation	NPV	0.135	642/246	0.29	0.95
	PPV	0.540	868/20	0.60	0.89
Internal test	NPV	0.135	200/78	0.18	0.95
	PPV	0.540	272/6	0.50	0.92
External validation	NPV	0.135	530/229	0.29	0.93
	PPV	0.540	747/12	0.83	0.88

- **High negative predictive value for death (i.e. lack of biomarker signal makes death highly unlikely)**

- **Outperforms severity scores such as APACHE III and SOFA**

Mikacenic C et al. *AJRCCM*. 2017; 196(8)

Signal

Concentration [pg/mL]

SCORE–UW: Predictive Biomarkers of Drug Efficacy in Septic Shock
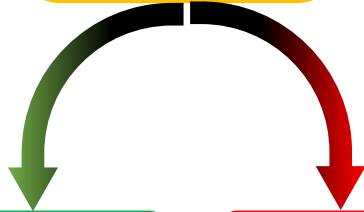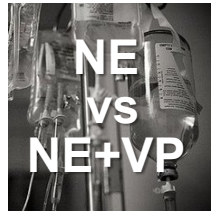
- **Measured circulating levels of two biomarkers in patients with septic shock and kidney failure enrolled in a large randomized controlled trial comparing NE against NE + VP for shock**

- **Compared efficacy between two groups defined by biomarker levels at time of enrollment before receiving drug**

Group	Treatment Arm Mortality		Relative Risk of Death (95% CI)
	NE	NE+VP	
All Septic Shock-AKI	47%	37%	0.80 (0.60-1.10)
AKI-SP1	46%	27%	**0.54 (0.32-0.92)**
AKI-SP2	49%	45%	0.99 (0.70-1.42)

Vasopressin Better ← | 0 | 1.0 | 2.0 → Vasopressin Worse

AKI = Acute Kidney Injury,
NE = norepinephrine, VP = vasopressin
AKI-SP = AKI-Sub-Phenotype

Bhatraju P et al. *AJRCCM*. 2018

- **Pre-intervention biomarker levels identified two groups; one of which (AKI-SP1) had a significant improvement with addition of Vasopressin while the other (AKI-SP2) did not**

SCORE–UW: Mission Goals for Biomarker Development in Sepsis and COVID–19

- Develop robust prognostic biomarkers and test for utility in triage and resource allocation in patients with sepsis and COVID-19

- Develop and validate predictive biomarkers and test utility for guiding initiation of specific drugs or other interventions to treat organ dysfunction and avoid mortality and morbidity in patients with sepsis and COVID-19

- Implement these biomarker-based physician decision support tools within a clinical lab environment linked to the electronic health record

Bioinformatics in Sepsis Artificial Intelligence and Machine Learning

Dr. Pavan K. Bhatraju

Critical Unmet Challenges

- In intensive care units, patients have a rapidly evolving cardiovascular function and clinical picture.

- We lack tools to organize, analyze and **loop it back in real-time to physicians to aid in clinical decision making.**

- Machine learning approaches can identify patients at high risk of organ failure or death as well as sub-groups of patients for therapeutics.

A Critically Ill Patient with COVID–19

Vital signs
Continuous or hourly

Large image datasets
Chest radiographs, ultrasound, CT scans

Laboratory & microbiologic data
Daily or more frequent

Patient documentation
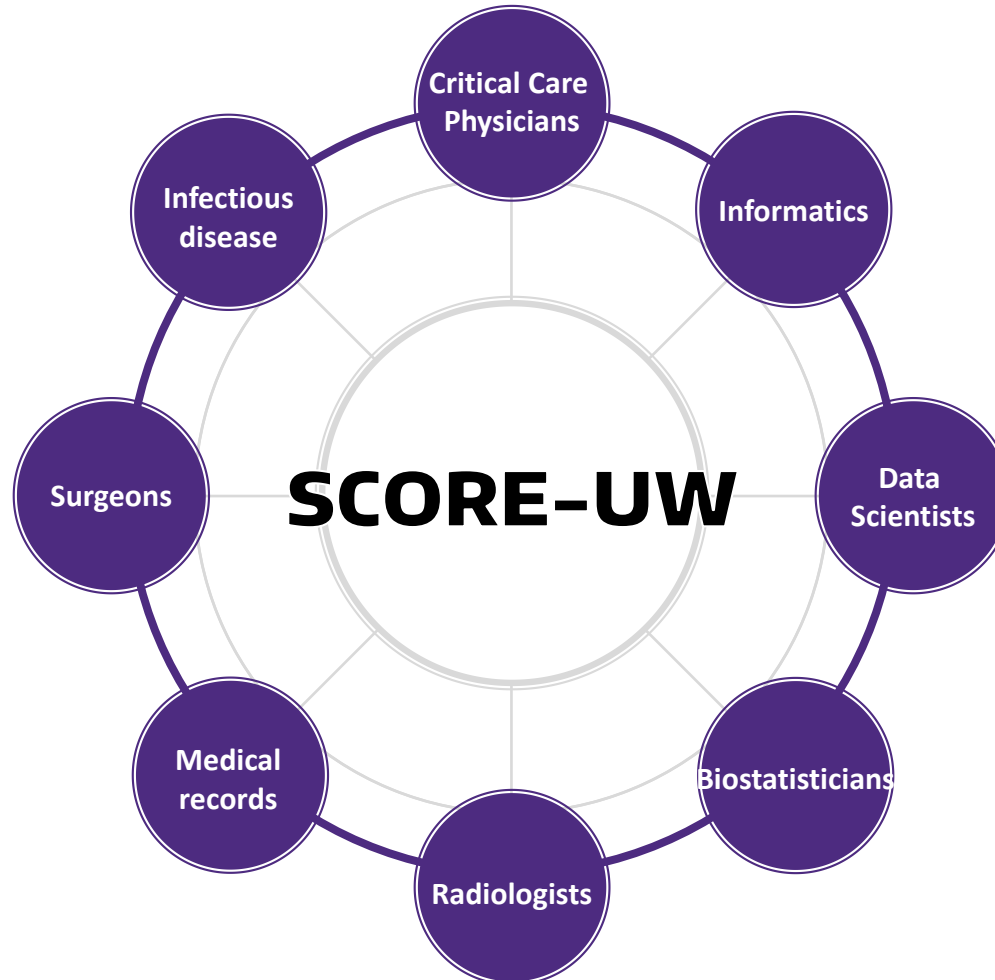*Nurses, physicians, and others*

Pulmonary physiologic data
Every shift

Medications

COVID-19 associated with prolonged hospital course. 14 days on average.[1]

Bhatraju PK. et al. *NEJM*. 2020

Need a Collaborative Research Infrastructure that Brings Together Diverse Fields

SCORE–UW
Machine Learning in Sepsis

Potential Applications

- Continuous blood flow monitoring to identify early organ failure and shock

- Chest CT imaging to identify progression to respiratory failure and intubation

- Identify sub-clinical signs of response to treatment

- Determine patterns in physician behavior that influence patient outcomes

Current Projects with Microsoft AI for Health

- Phase 1: COVID-19 (in progress)

- Phase 2: Sepsis overall

Trivedi A. et al. *Effective Deep Learning Approaches for Predicting COVID-19 Outcomes from Chest Computed Tomography Volumes*. Under review.
Robinson C. et al. *Deep learning models for COVID-19 chest x-ray classification: Preventing shortcut learning using feature disentanglement*. Under review.

Relationship between Trauma and Sepsis

Dr. Grant O'Keefe

Leading Causes of Death

Number of deaths for leading causes of death in the U.S.

- Heart disease: 659,041
- Cancer: 599,601
- Accidents (unintentional injuries): 173,040
- Chronic lower respiratory diseases: 156,979
- Stroke (cerebrovascular diseases): 150,005
- Alzheimer's disease: 121,499
- Diabetes: 87,647
- Nephritis, nephrotic syndrome, and nephrosis: 51,565
- Influenza and pneumonia: 49,783
- Intentional self-harm (suicide): 47,511

Source: Mortality in the United States, 2019, data table for figure 2

Global Burden of Injuries

- More than 16,000 people die per day from injury

- Death is just the tip of the iceberg – Injuries are a leading cause of disability

- Focused development of emergency care and trauma systems has decreased early preventable deaths from hemorrhage

- As a result, trauma care providers globally are now faced with increasing numbers of critically injured patients affected by infection and patient's extreme reactions to infection

Preventing death and disability after trauma

- Injuries are not "accidents" or random events

- Like injury, infection/sepsis after trauma is not random

- Determining risk, developing early identification tools, targeting treatments, and evaluating recovery is the frontier of trauma care research

Understanding Post–Injury Deaths
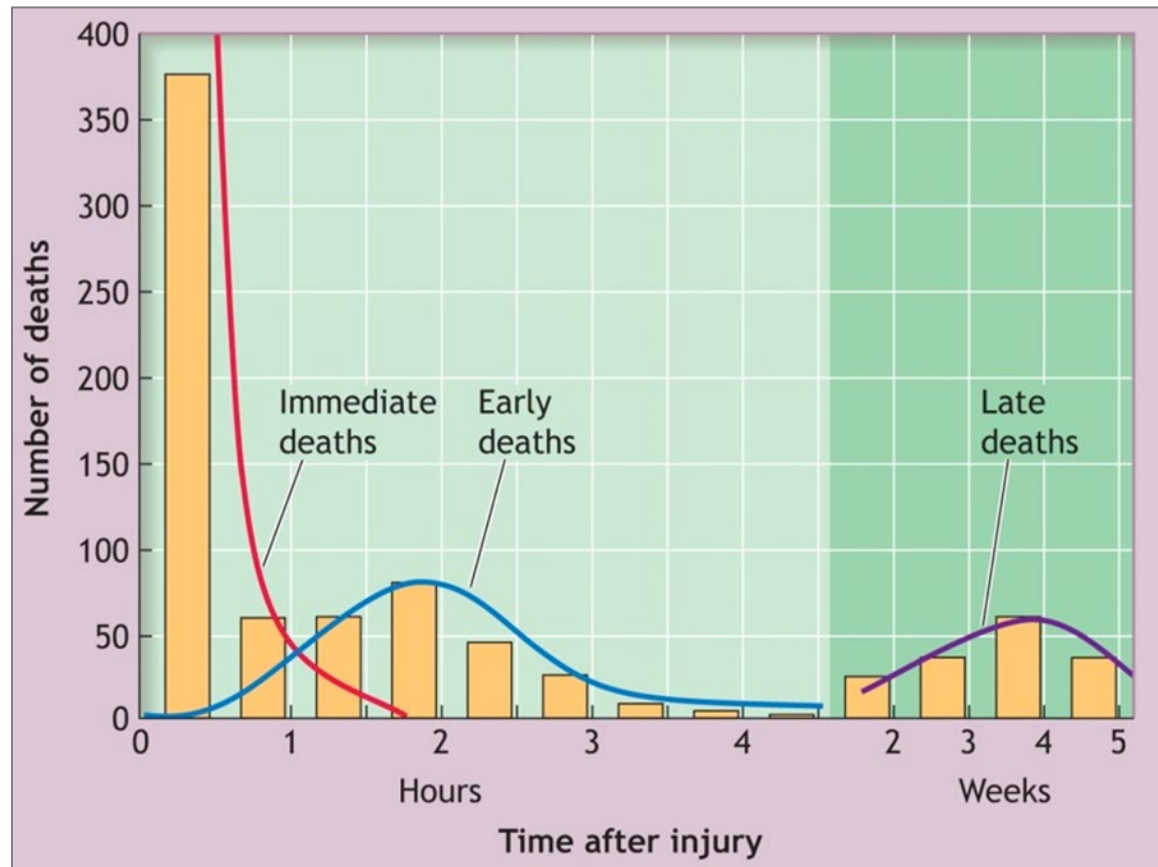
Trunkey DD. Sci Am. 1983 Aug;249(2):28-35.
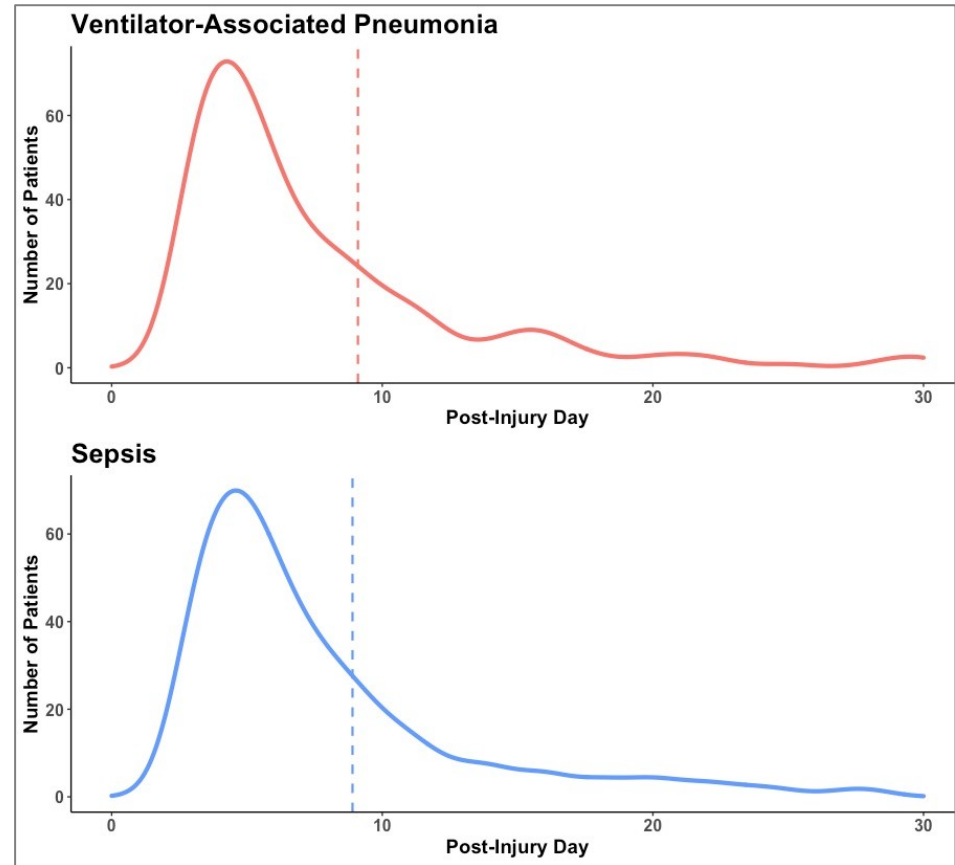
Surviving injury and hemorrhage

Facing infection

Early and accurate diagnosis of infection and sepsis

Present reality:
We "watch and wait" for a patient to develop infection

Future vision:
We use molecular and bioinformatics tools to identify shock and subsequent organ injury earlier

Eye Disease and Other Conditions

Dr. Craig Smith

SCORE–UW

Beyond Sepsis

We think of individual's extreme response and shock as a consequence of infection, but vascular leak and collapse may occur in any body organ:

- Immunologic reaction to COVID ("Long Haulers")
- Trauma of any body part can lead to systemic vascular collapse
  1. General trauma
  2. Brain injury (TBI)
  3. Surgical consequence
  4. Cancer treatment (CAR-T cell therapy)

Applications in Eye Disease

*The eye is the window to the brain*

Vascular dysregulation occurs in the eye

- Age-related macular degeneration
- Diabetic ocular disease
- Ocular trauma
- COVID-19 related eye disease

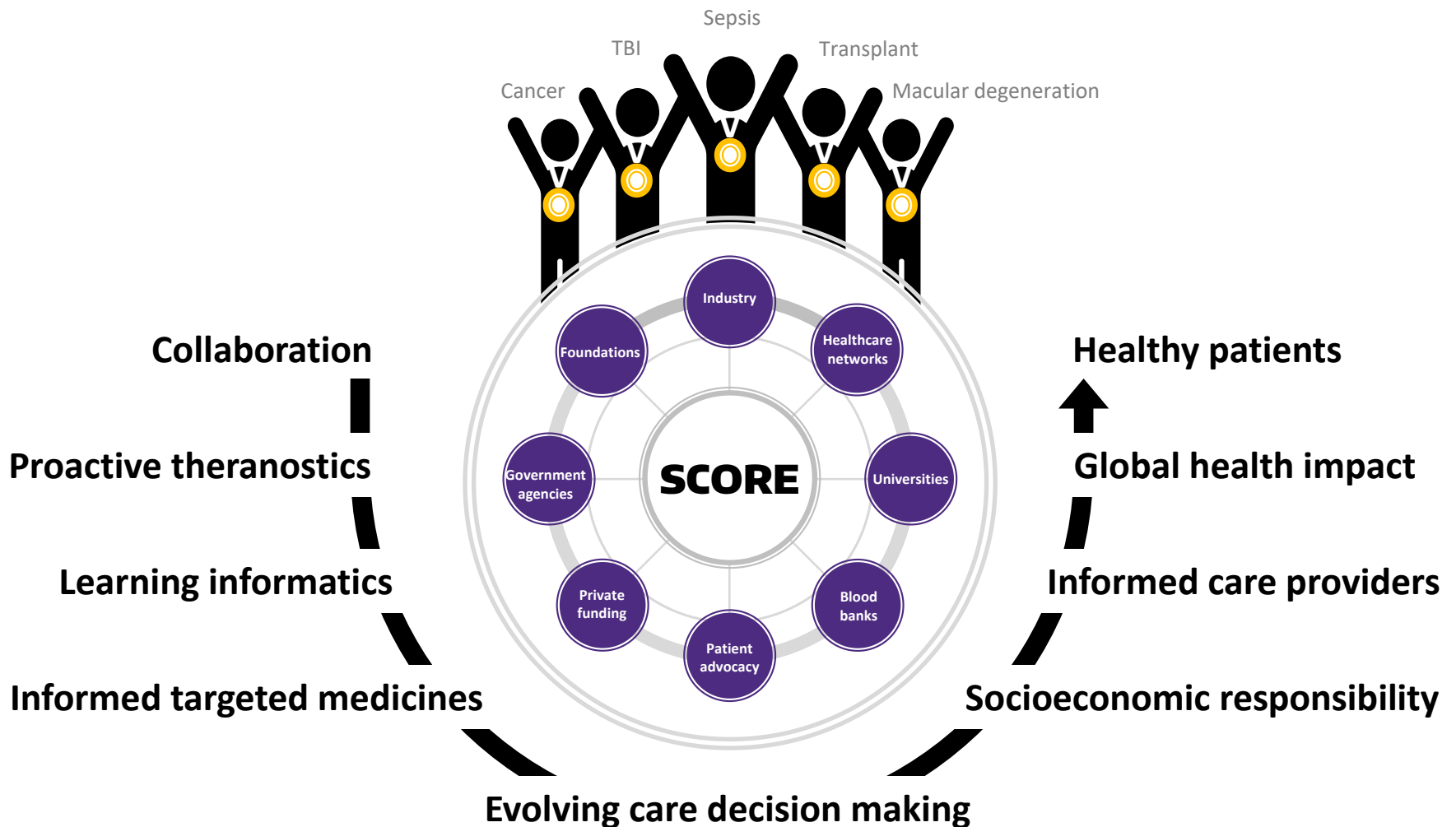**Measuring ocular dysregulation would be pivotal in:**

- Directing when to treat macular degeneration
  - Save both vision and over $1B in misdirected treatments
- Biomarkers are present in eyes
  - Ophthalmologists can access this easily when they diagnose or treat

Machine learning enables innovative predictors of Alzheimer's disease and other systemic diseases
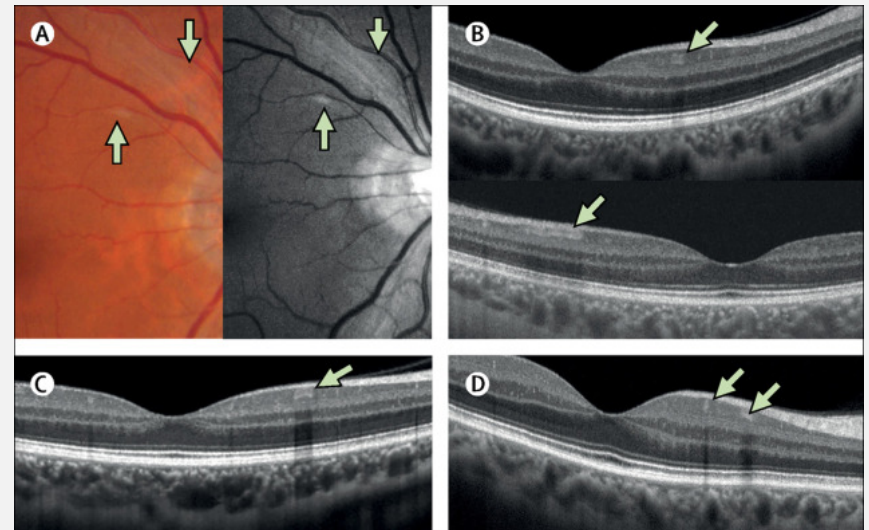
SCORE–UW, Patients Win

A collaborative medical research network focused on sepsis translational science

Questions?

THANK YOU!