Artificial Intelligence and Disruptive Technologies in POC

UC DAVIS MEDICAL CENTER

Acknowledgements: AI/ML modeling by Dr. Hooman Rashidi, MD, UC Davis

Nam K. Tran, PhD, HCLD (ABB), FACB,
Director of Chemistry, Special Chemistry/Toxicology, POCT, and SARC
Dept. of Pathology and Lab Medicine

Learning Objectives

At the end of this presentation, you will be able to:

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- Identify areas where AI/ML could be used in laboratory medicine and its potential impact in point-of-care settings.

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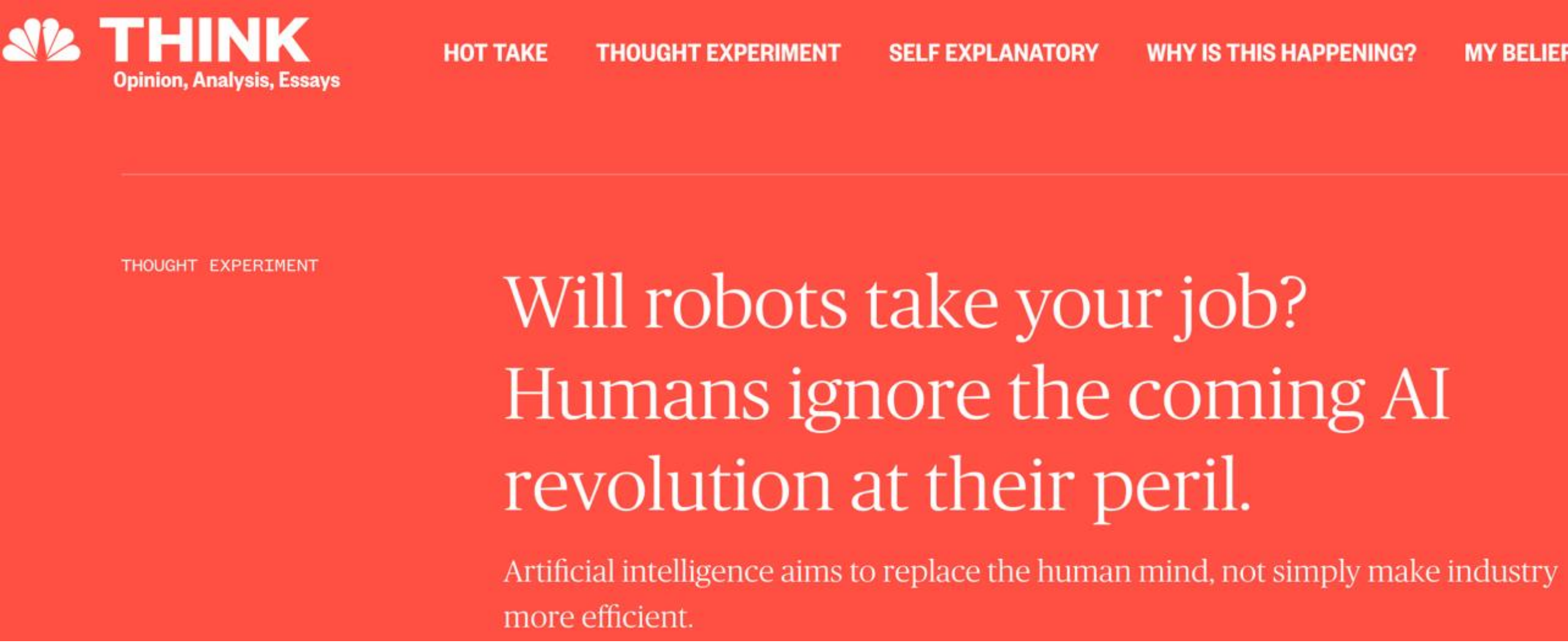
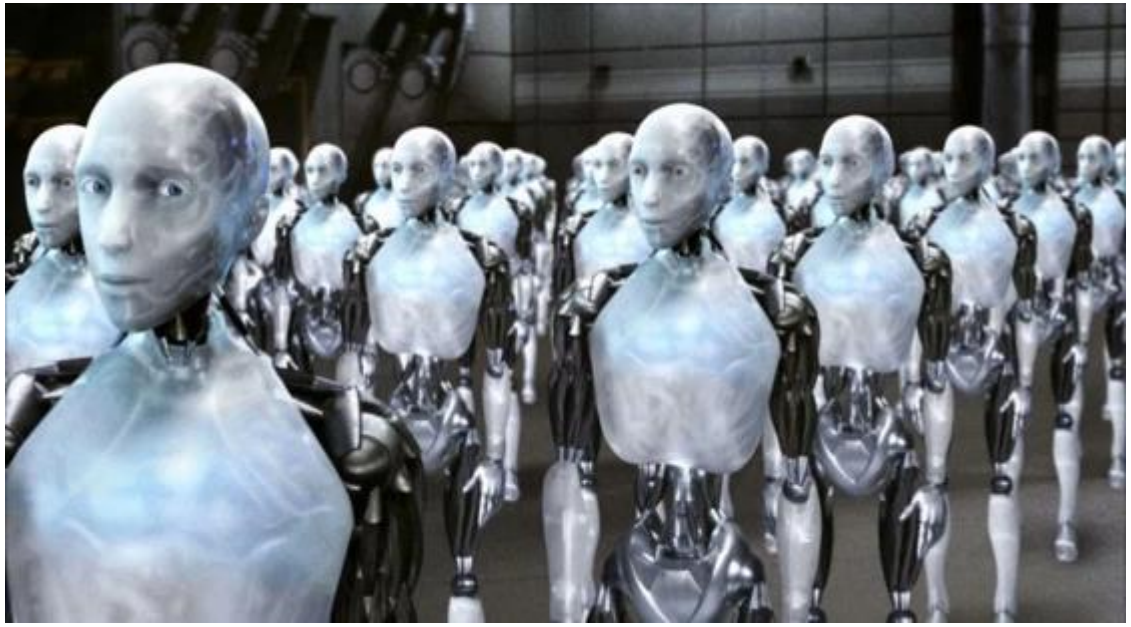
- Identify areas where AI/ML could be used in laboratory medicine and its potential impact in point-of-care settings.
- Discuss the future of AI/ML in POC testing and how it impacts healthcare.



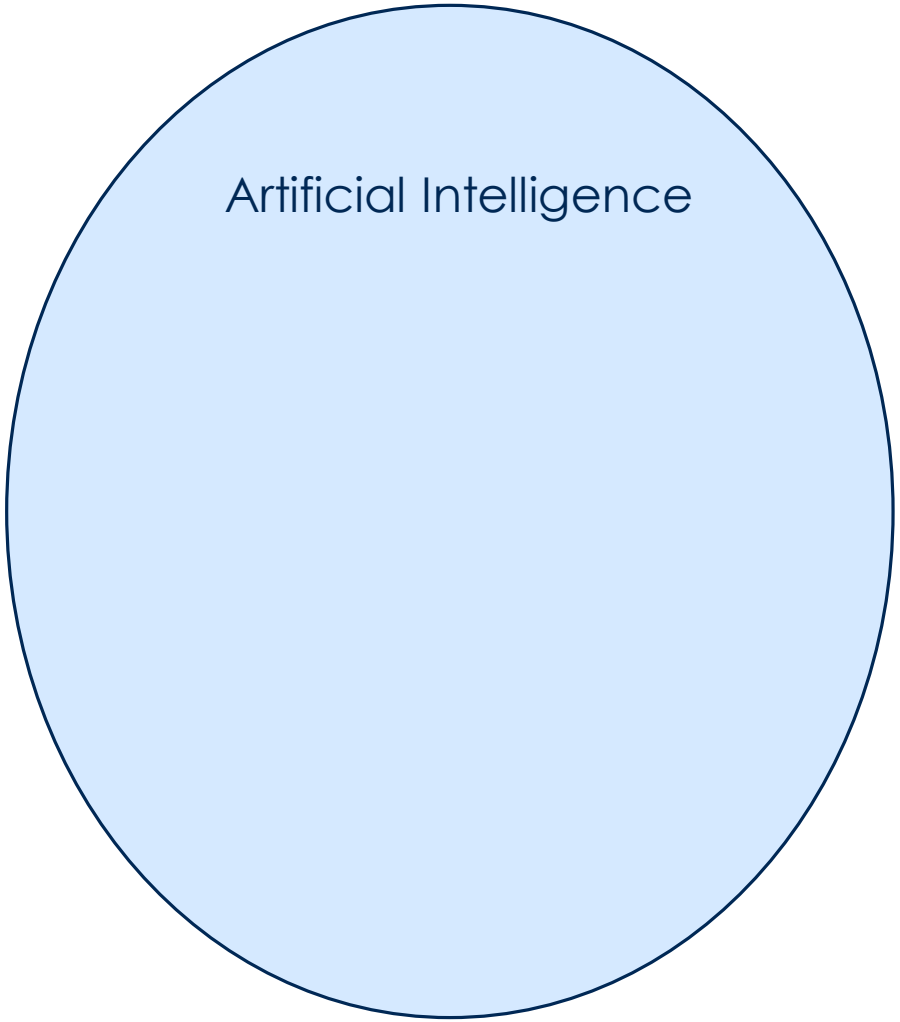
- One in 5 jobs estimated to be lost due to AUTOMATION (remember automation doesn't = artificial intelligence)
- Most citizens actually don't understand what artificial intelligence is nor its full/potential capabilities.
- Most important message of this presentation is AI is another TOOL, so we need to understand how to use it, not to be afraid of it, while understanding enough to know when to not use AI

Fear of AI Justified?



We have been engrained with fear of AI for a very long time through many forms of media. Of course there are a few examples of good AI as well. Lets first define AI and its subcomponents.

What is Artificial Intelligence / Machine Learning?



What is Artificial Intelligence / Machine Learning?

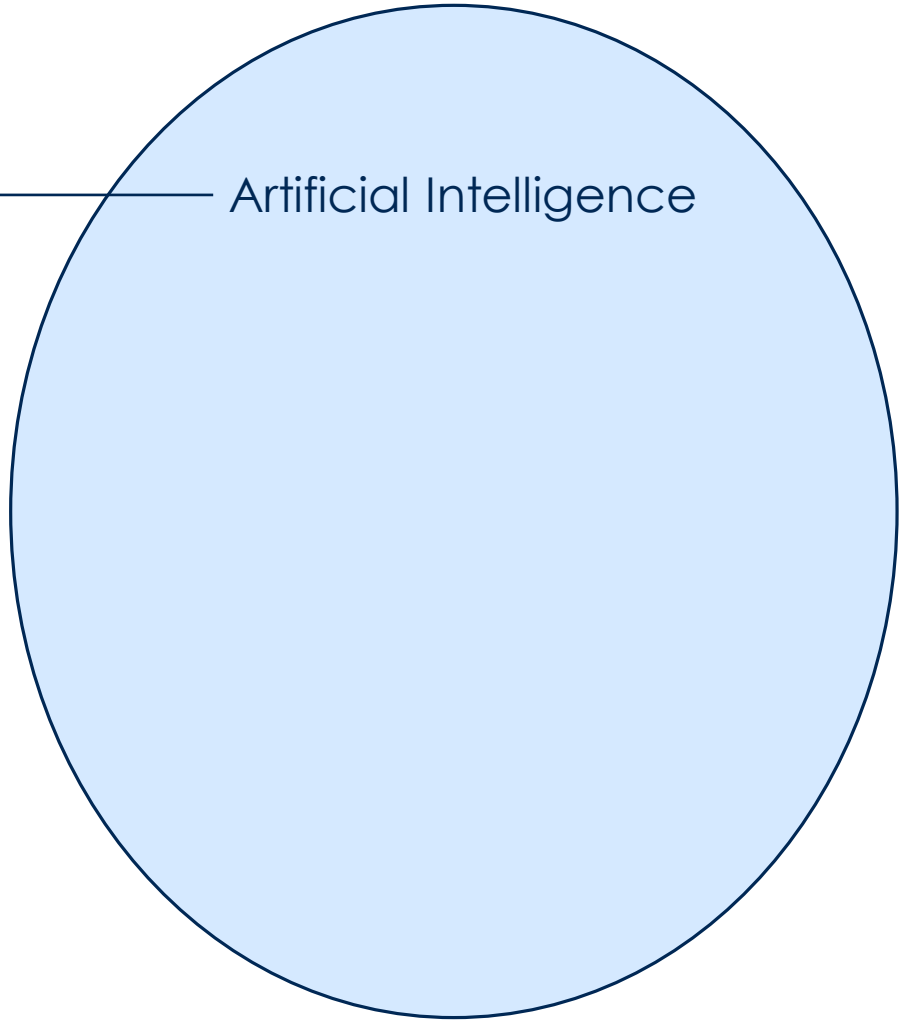
artificial intelligence

noun

Definition of *artificial intelligence*

1 : a branch of computer science dealing with the simulation of intelligent behavior in computers

2 : the capability of a machine to imitate intelligent human behavior



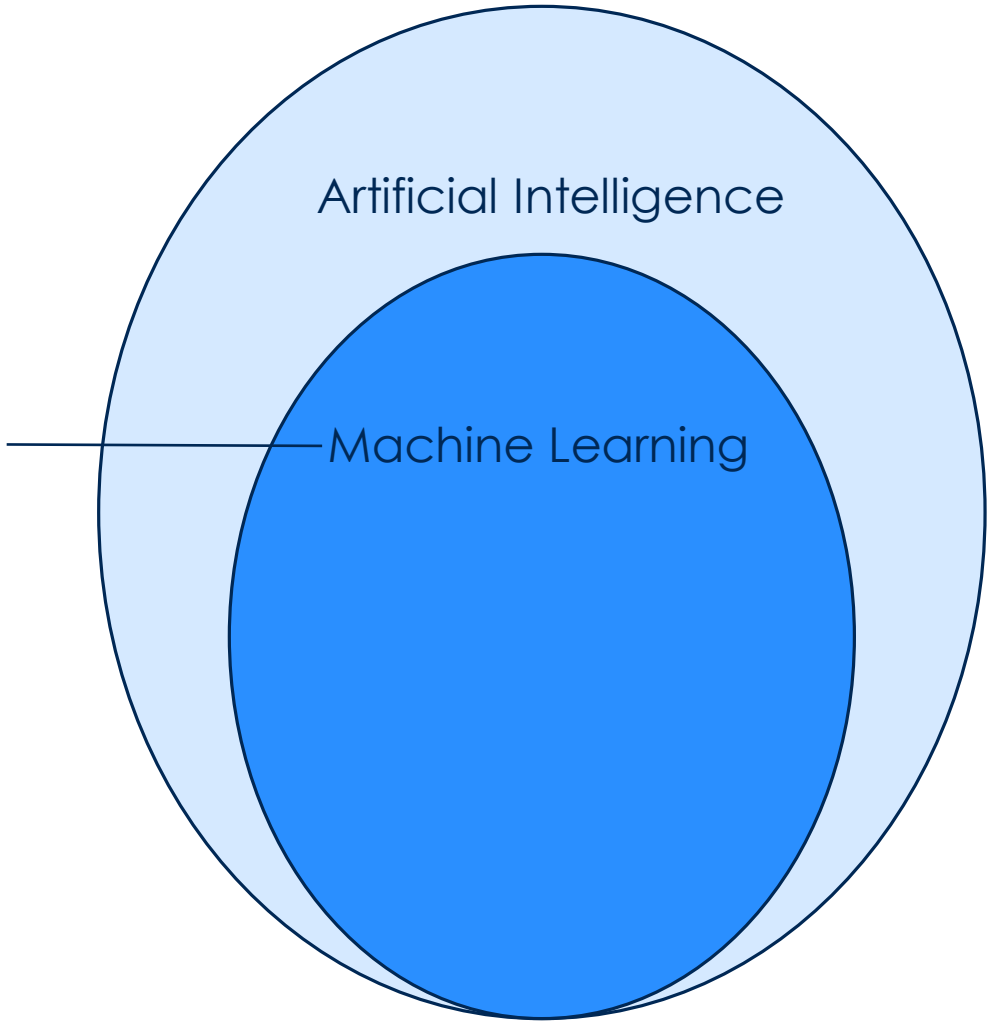
What is Artificial Intelligence / Machine Learning?

machine learning noun

Definition of *machine learning*

: the process by which a computer is able to improve its own performance (as in analyzing image files) by continuously incorporating new data into an existing statistical model

// An entire subspecialty known as *machine learning* is devoted to building algorithms that allow computers to develop new behaviors based on experience.



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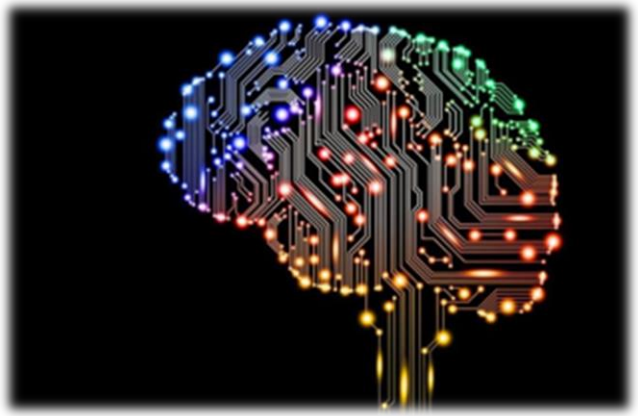
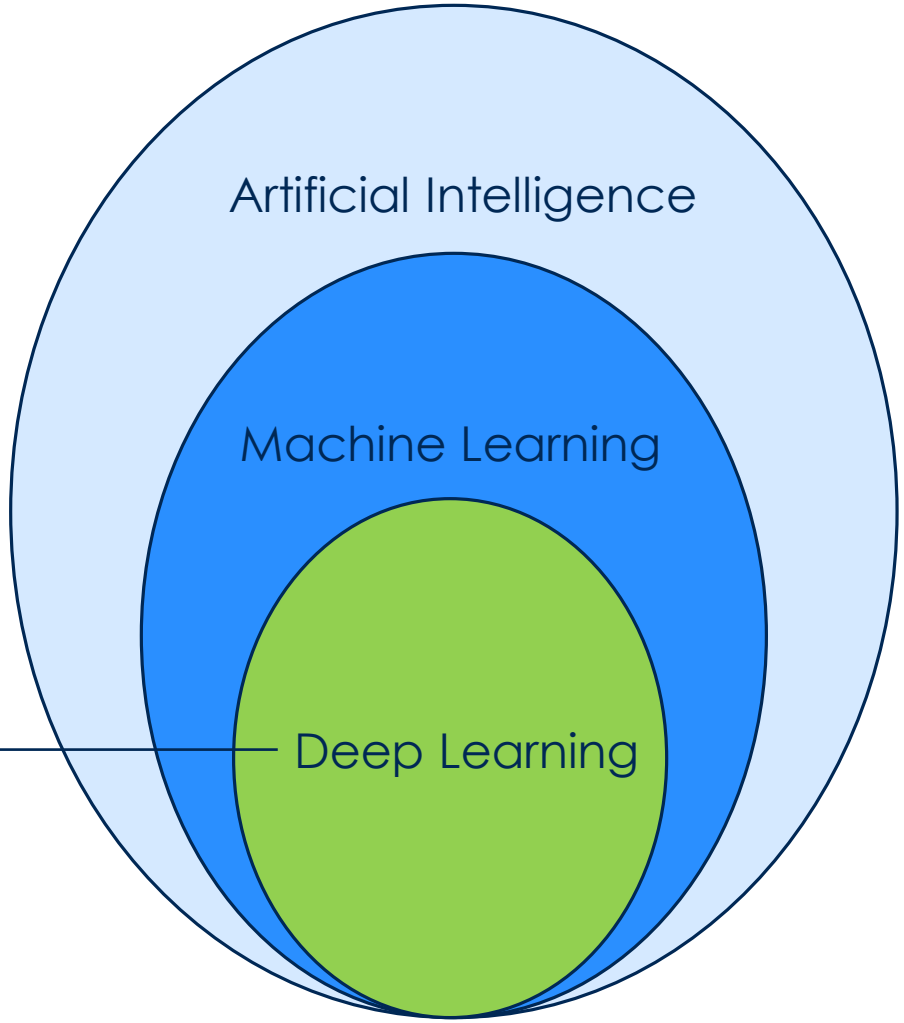


A broader branch of machine learning focused on learning data representations through layers of artificial neural neural networks.



AI/ML is Already Here and its Changing Our Lives!

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Google

amazon

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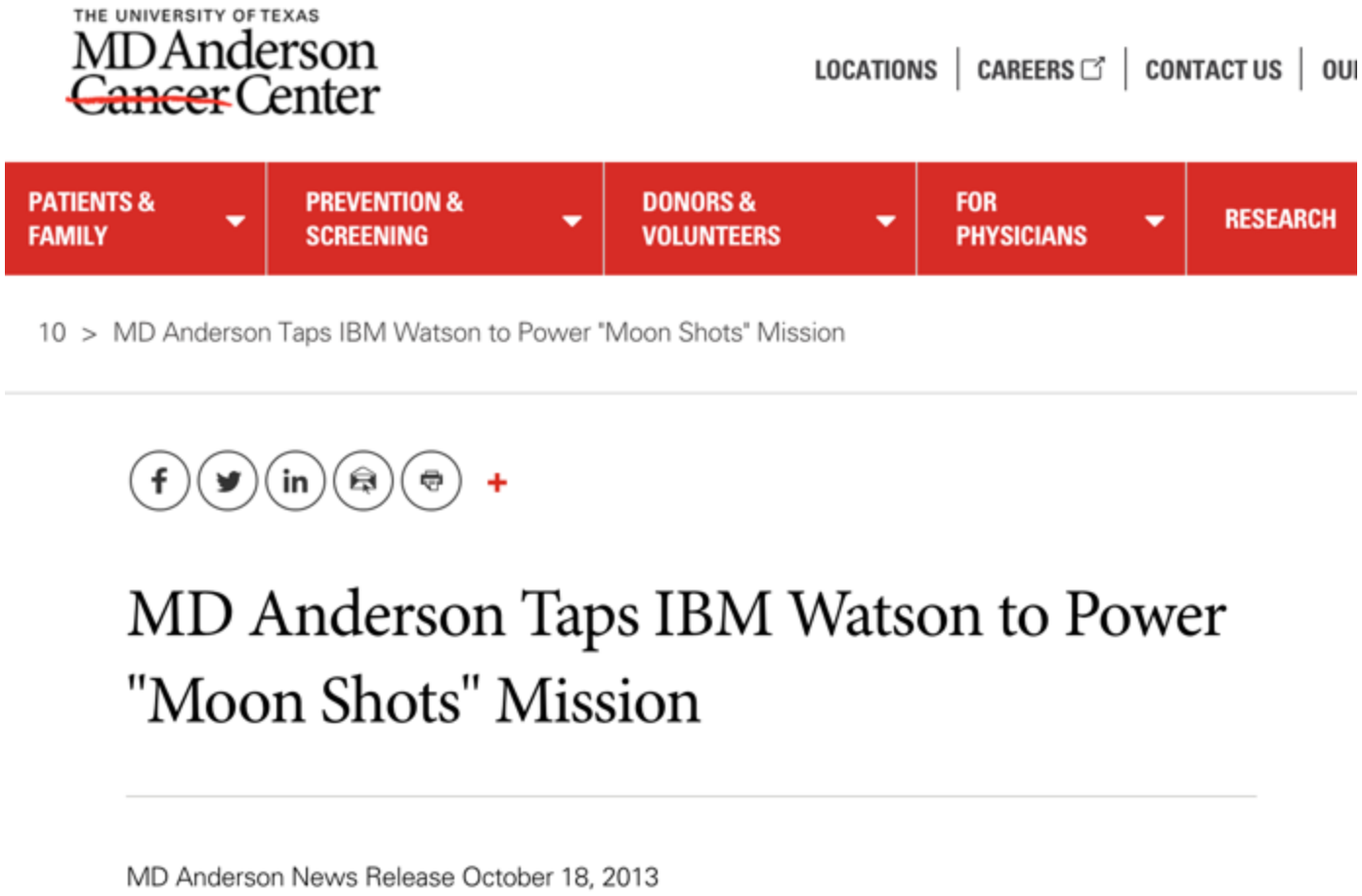
AI/ML in healthcare: Big Promises, but….



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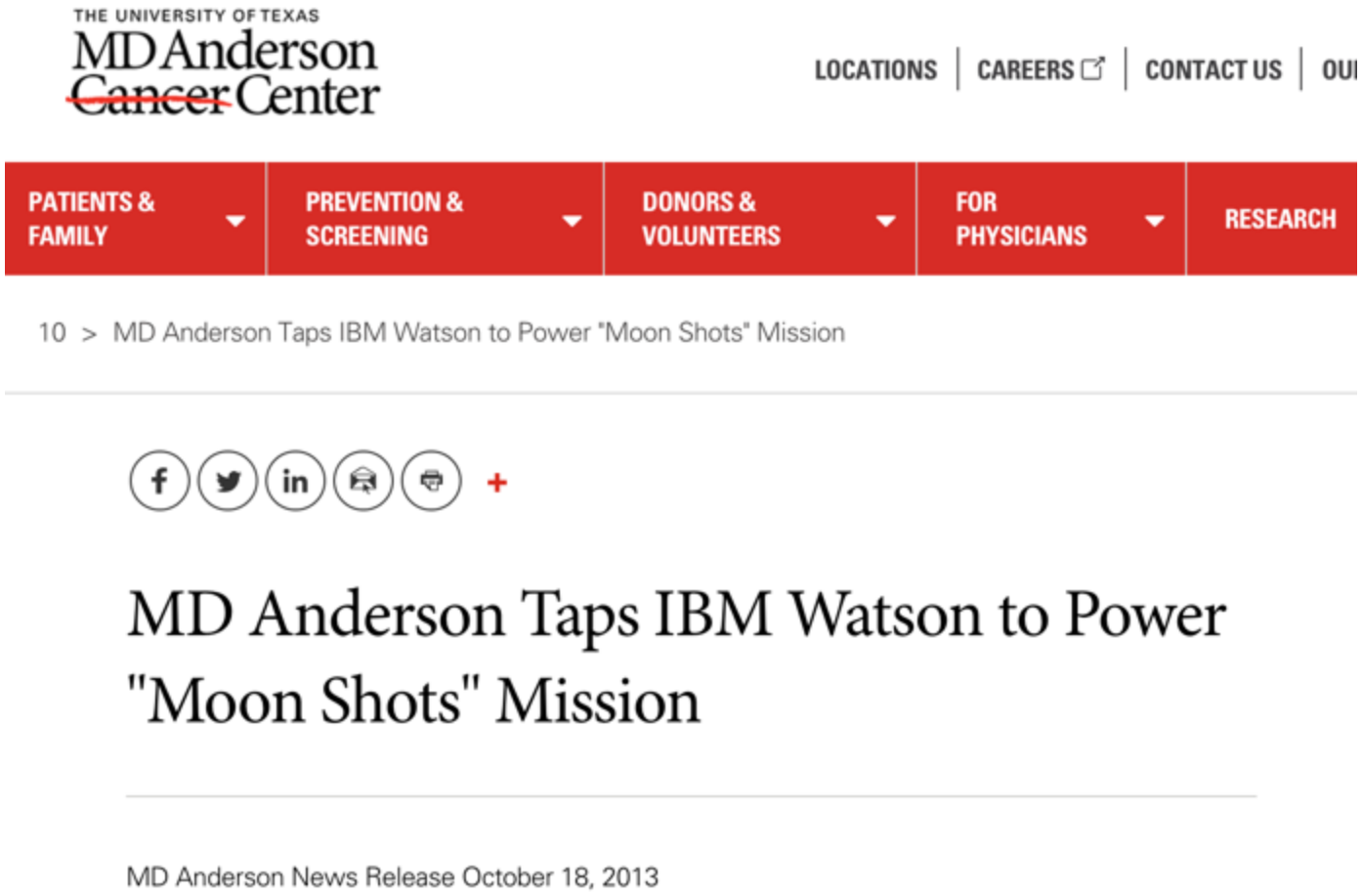

- MD Anderson partners with IBM Watson to use "Oncology Expert Advisor" for targeting cancer therapy.

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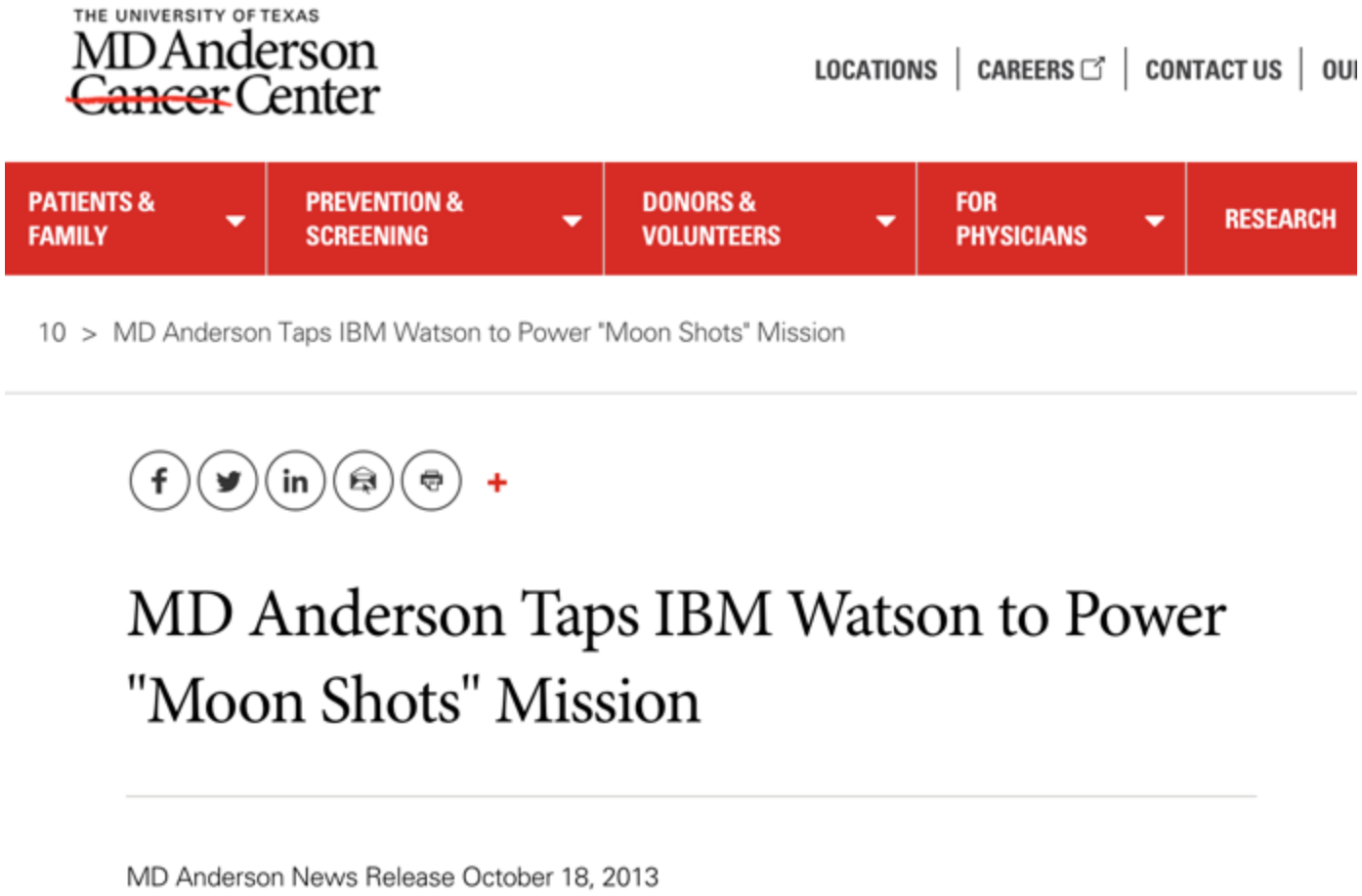
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MD Anderson Cancer Center

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10 > MD Anderson Taps IBM Watson to Power "Moon Shots" Mission

MD Anderson Taps IBM Watson to Power "Moon Shots" Mission

MD Anderson News Release October 18, 2013

- MD Anderson partners with IBM Watson to use "Oncology Expert Advisor" for targeting cancer therapy.
- *"A new era of computing has emerged, in which cognitive systems "understand" the context within users' questions, uncover answers from Big Data, and improve in performance by continuously learning from experiences"*

AI/ML in healthcare: Big Promises, but….

EDITOR'S PICK | 212,548 views | Feb 19, 2017, 03:48pm

MD Anderson Benches IBM Watson In Setback For Artificial Intelligence In Medicine

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I covered science and medicine, and believe this is biology's century.

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$62 million wasted without achieving goals

"Treating cancer is more complex than winning a trivia game, and the "vast universe of medical knowledge" may not be as significant as purveyors of artificial intelligence make it out to be…"

https://www.healthnewsreview.org/2017/02/md-anderson-cancer-centers-ibm-watson-project-fails-journalism-related/

AI/ML in healthcare: Big Promises, but….

Does a Medical Computer Scientist Exist?

Few pre-health students go into computer sciences, and "few" computer scientists go into healthcare. How do we bridge the gap?

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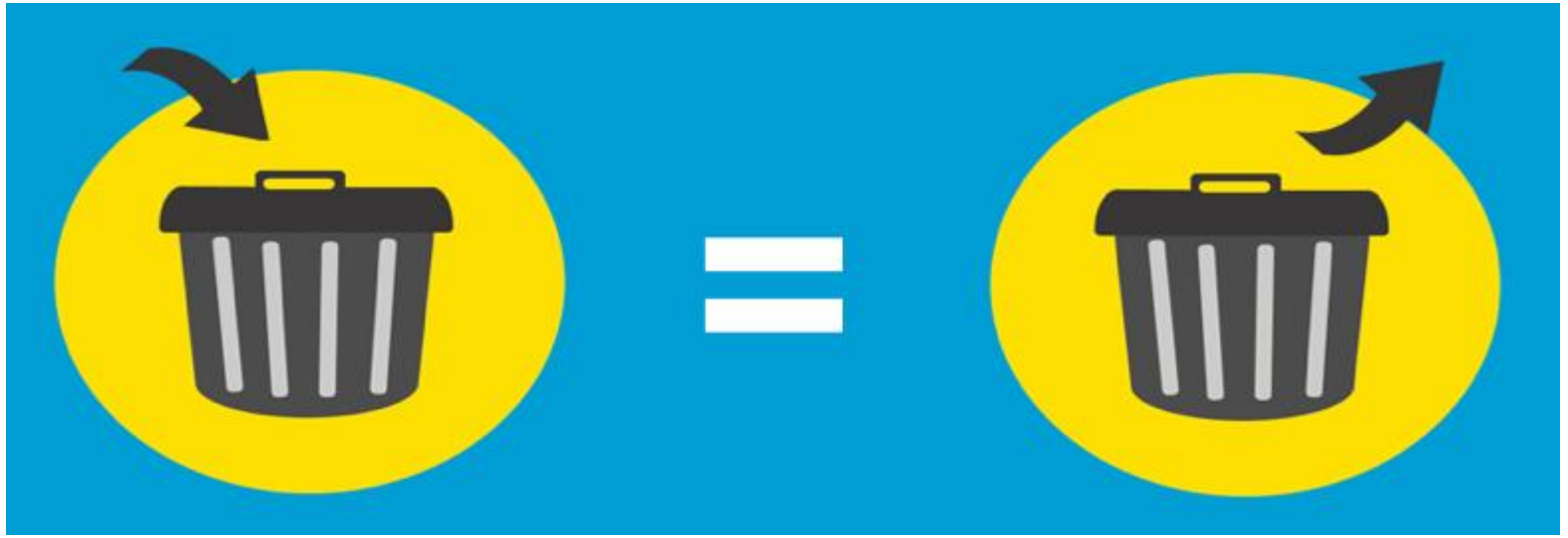

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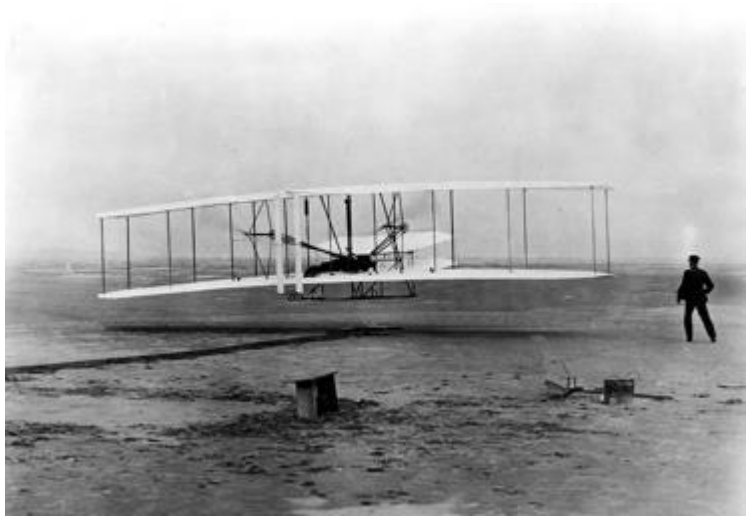
Junk in Junk out

Artificial intelligence / machine learning will only be as good as the data you provide it. We can't know what we don't know

AI/ML in healthcare: Big Promises, but….




Slow is Fast → Lets do this in a rational way…

so lets start simpler and try to address more fundamental better defined problems! <We didn't go to the moon on the first try>

Opportunities for AI/ML in Healthcare Today

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OPPORTUNITY	EXAMPLES
Well defined (clean) datasets	Laboratory utilization data

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Volume 150, Issue 6
December 2018

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FEATURED

Using Machine Learning-Based Multianalyte Delta Checks to Detect Wrong Blood in Tube Errors

Matthew W Rosenbaum, MD, Jason M Baron, MD ✉

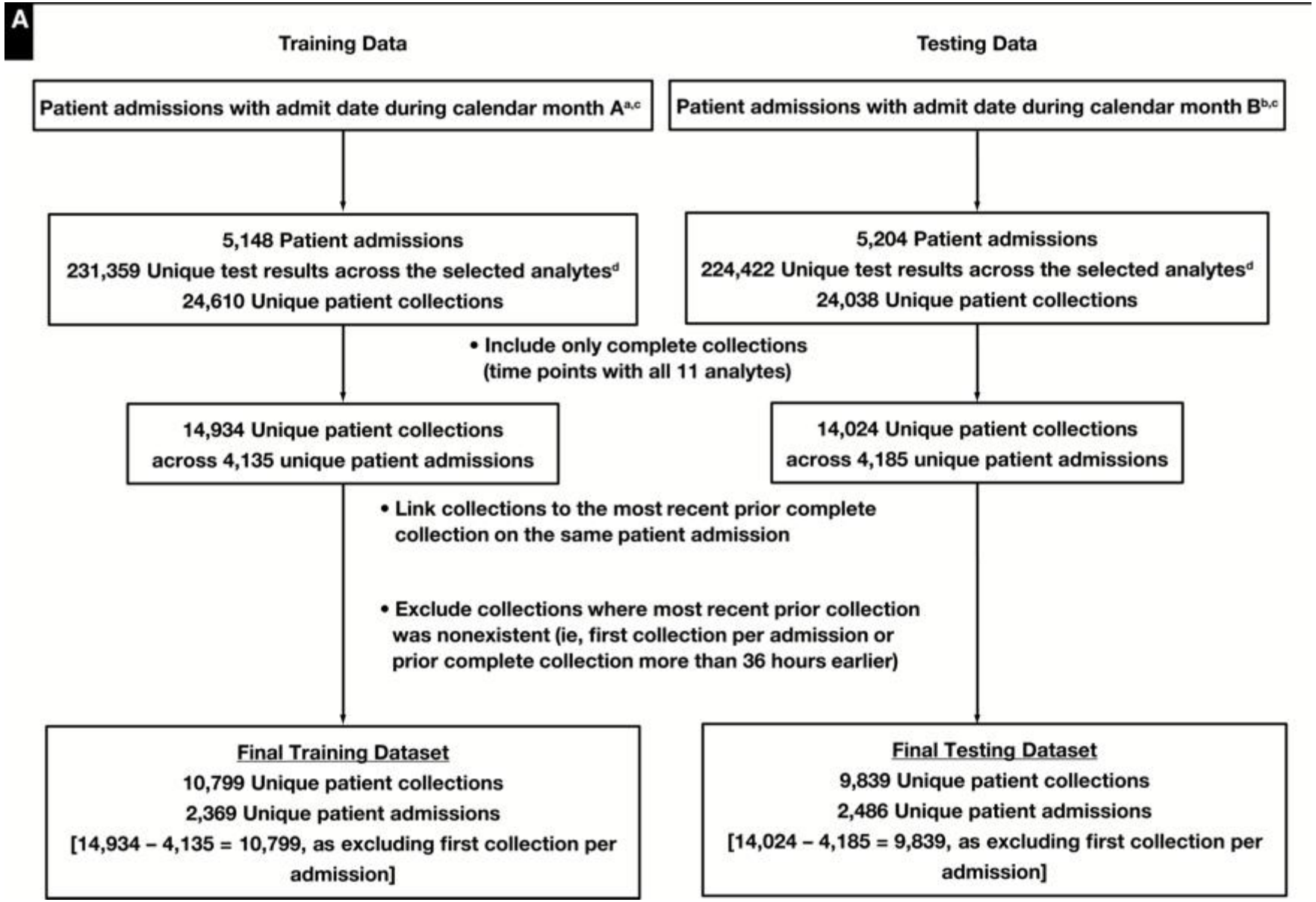
American Journal of Clinical Pathology, Volume 150, Issue 6, 24 October 2018, Pages 555–566,
https://doi.org/10.1093/ajcp/aqy085
Published: 30 August 2018

Abstract

Objectives

An unfortunate reality of laboratory medicine is that blood specimens collected from one patient occasionally get mislabeled with identifiers from a different patient, resulting in so-called "wrong blood in tube" (WBIT) errors and potential patient harm. Here, we sought to develop a machine learning-based, multianalyte delta check algorithm to detect WBIT errors and mitigate patient harm.

Study Methods: Overall Design



Study Methods

B

Original Data

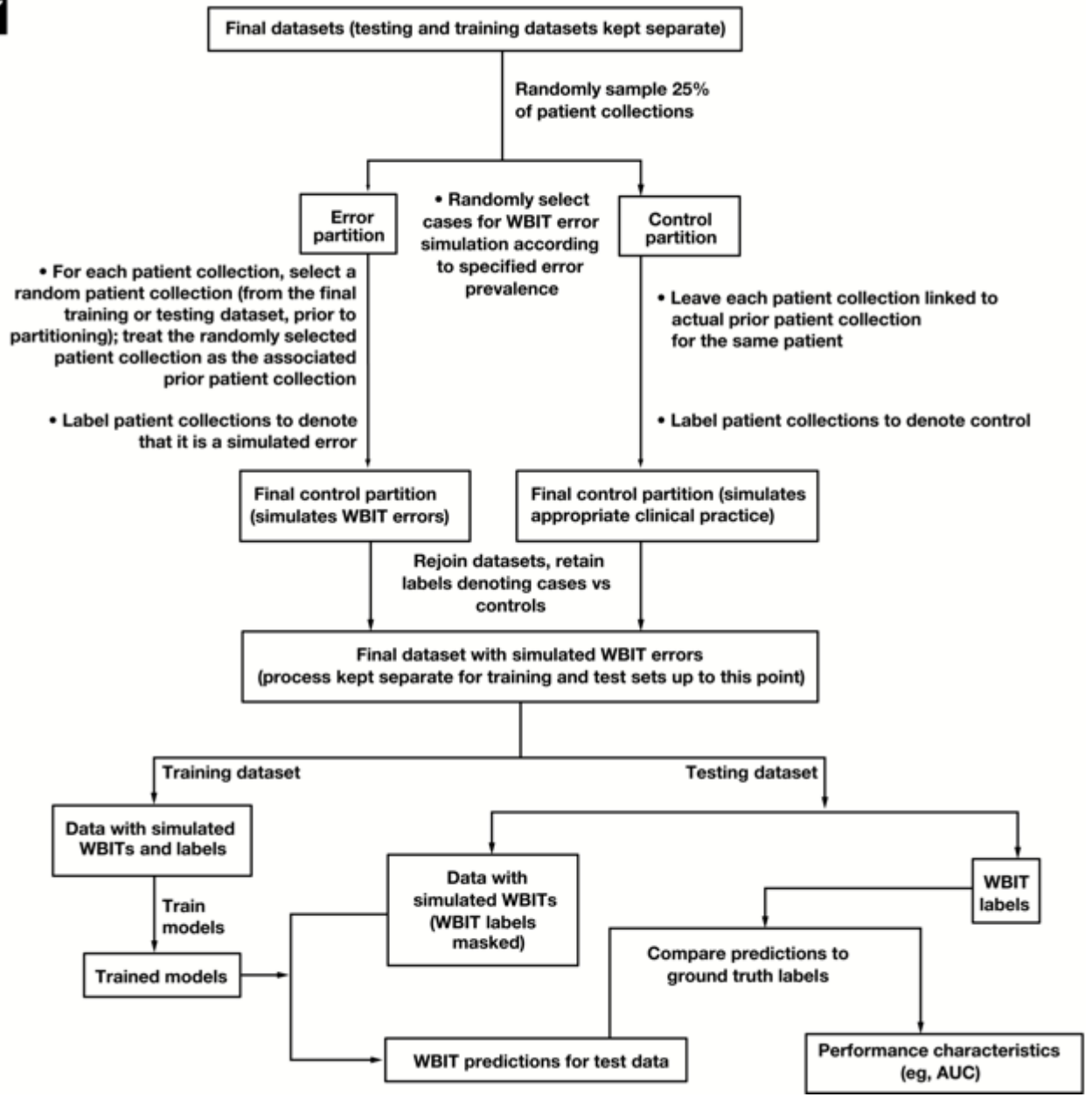
Patient admission	Collection date/time	Na	K	…	Prior Na	Prior K	…
1234567 - 1/1/1990	1/2/1990 6 AM	140	3.9	…	--	--	
1234567 - 1/1/1990	1/3/1990 6 AM	141	3.8	…	140	3.9	
2234567 - 1/1/1990	1/2/1990 6 AM	142	3.6	…	--	--	
2234567 - 1/1/1990	1/3/1990 6 AM	143	3.7	…	142	3.6	
3234567 - 1/1/1990	1/2/1990 6 AM	131	5.1	…	--	--	
3234567 - 1/1/1990	1/3/1990 6 AM	133	5.0	…	131	5.1	

After WBIT Error Simulation

Patient admission	Collection date/time	Na	K	…	Prior Na	Prior K	…	Case/ control
1234567 - 1/1/1990	1/2/1990 6 AM	140	3.9	…	--	--		Excluded, no prior results
1234567 - 1/1/1990	1/3/1990 6 AM	141	3.8	…	140	3.9		Control
2234567 - 1/1/1990	1/2/1990 6 AM	142	3.6	…	--	--		Excluded, no prior results
2234567 - 1/1/1990	1/3/1990 6 AM	133	5.0	…	142	3.6		WBIT error case
3234567 - 1/1/1990	1/2/1990 6 AM	131	5.1	…	--	--		Excluded, no prior results
3234567 - 1/1/1990	1/3/1990 6 AM	133	5.0	…	131	5.1		Control

Patient 3234567 had a specimen mislabeled with a label from patient 2234567

C



Methods of Analysis including AI/ML Techniques

Model Name	Type	Predictors
Univariate models		
Univariate absolute difference (named for each analyte)	Univariate: evaluate sensitivity/specific at various thresholds	Absolute change in consecutive results for each analyte
Univariate velocity	Univariate: evaluate sensitivity/specific at various thresholds	Absolute velocity of change between consecutive results for each analyte
Multivariate models		
Logistic regression, difference only	Logistic regression	Absolute change in consecutive results for each analyte
Logistic regression, velocity only	Logistic regression	Absolute velocity of change between consecutive results for each analyte
Logistic regression, difference and values	Logistic regression	(1) Absolute change in consecutive results for each analyte; (2) actual test results
SVM, difference only	SVM	Absolute change in consecutive results for each analyte
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SVM, support vector machines.

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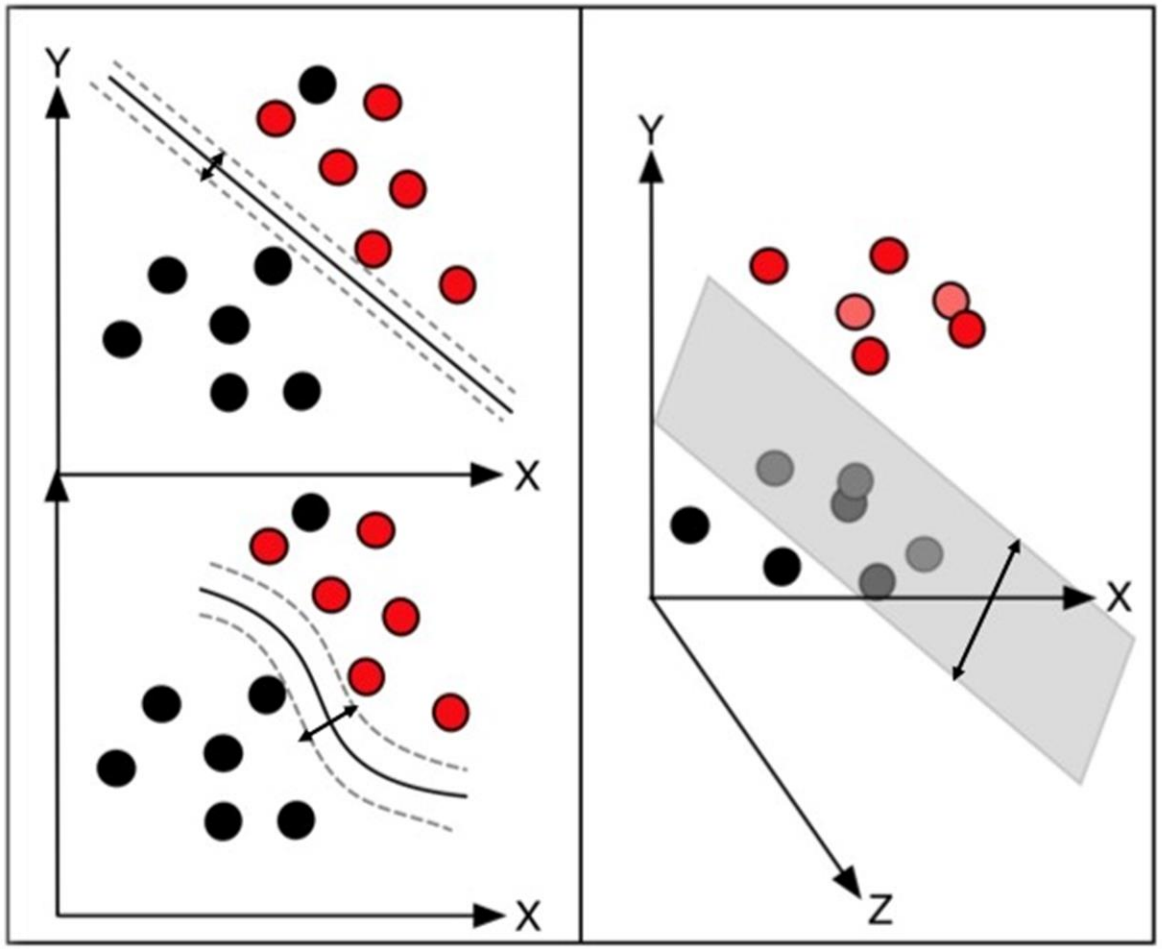
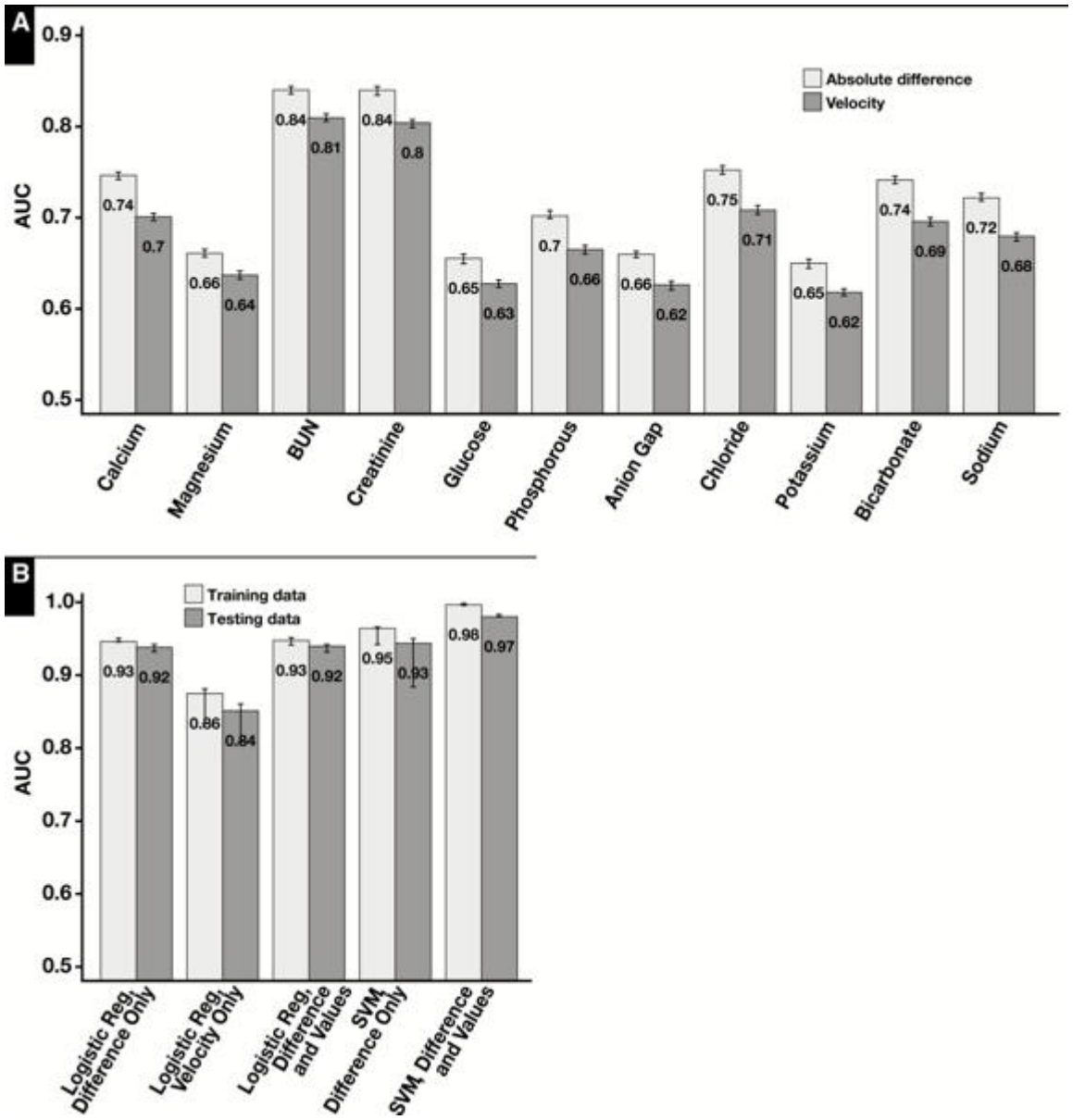
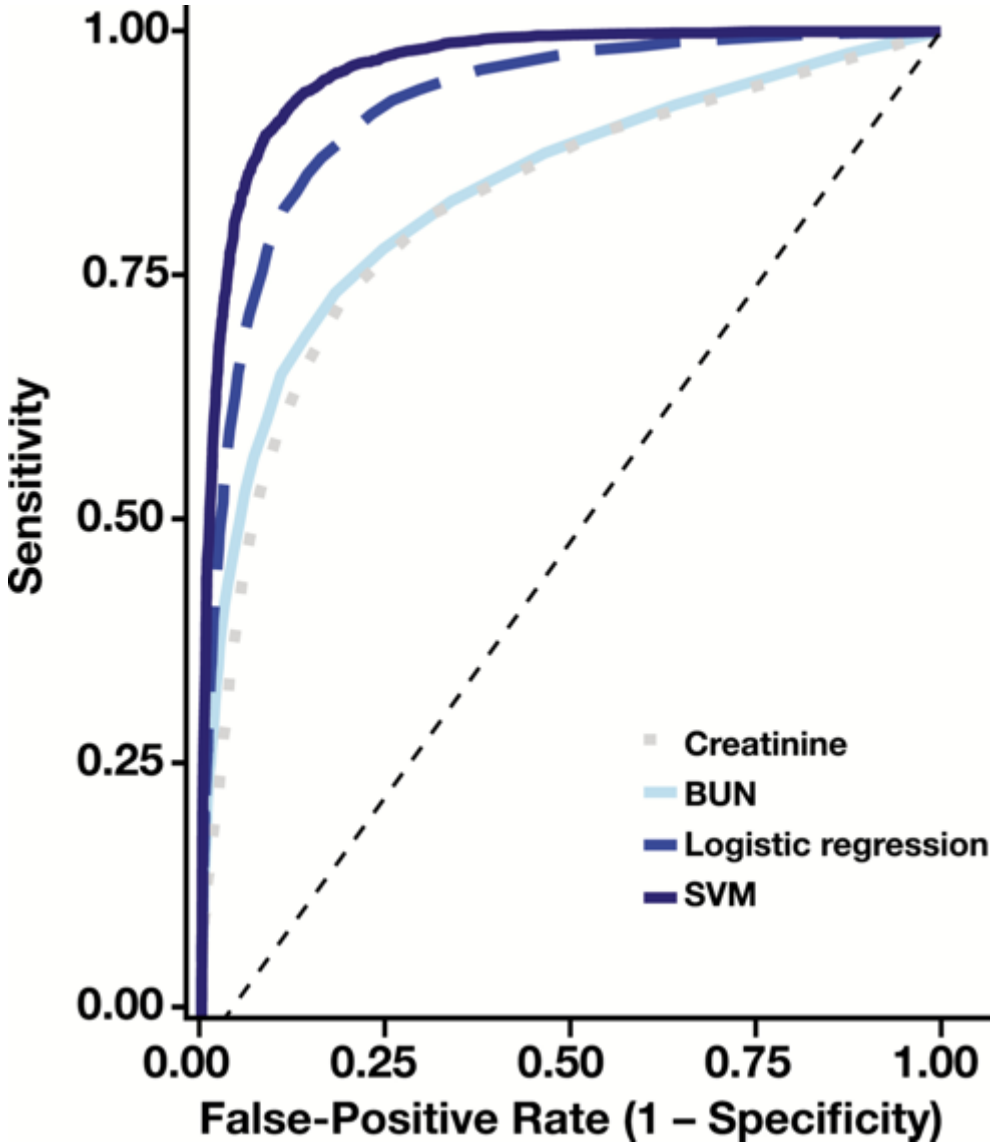
What is Support Vector Machine (SVM)



- Constructs a hyperplane (—) that that best separates groups.
- The best hyperplane maximizing the margins (---) is selected.
- Hyperplanes may exist in 3D space to improve separation of data points and further maximize margins.

Results – Predictive Power of AI/ML (SVM) for WBIT Events





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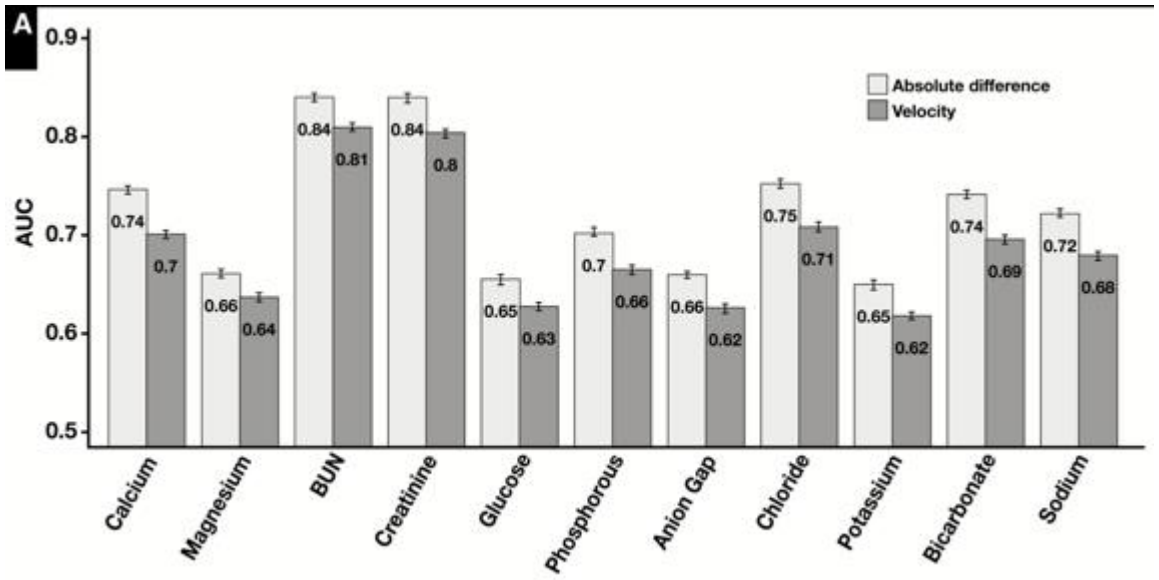
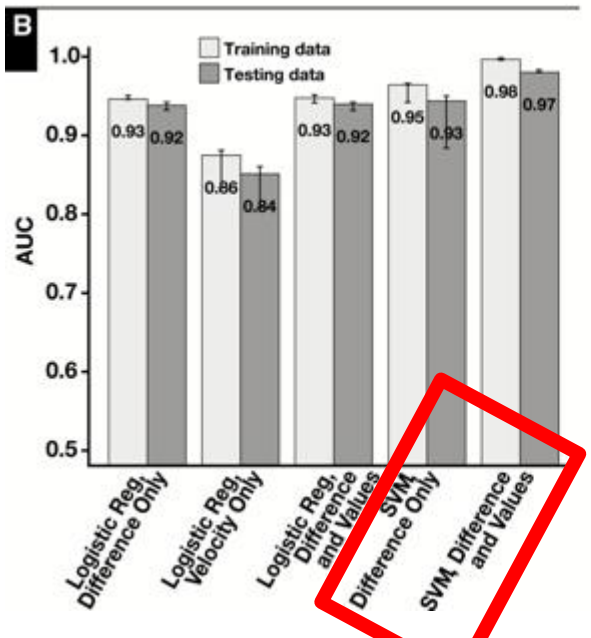
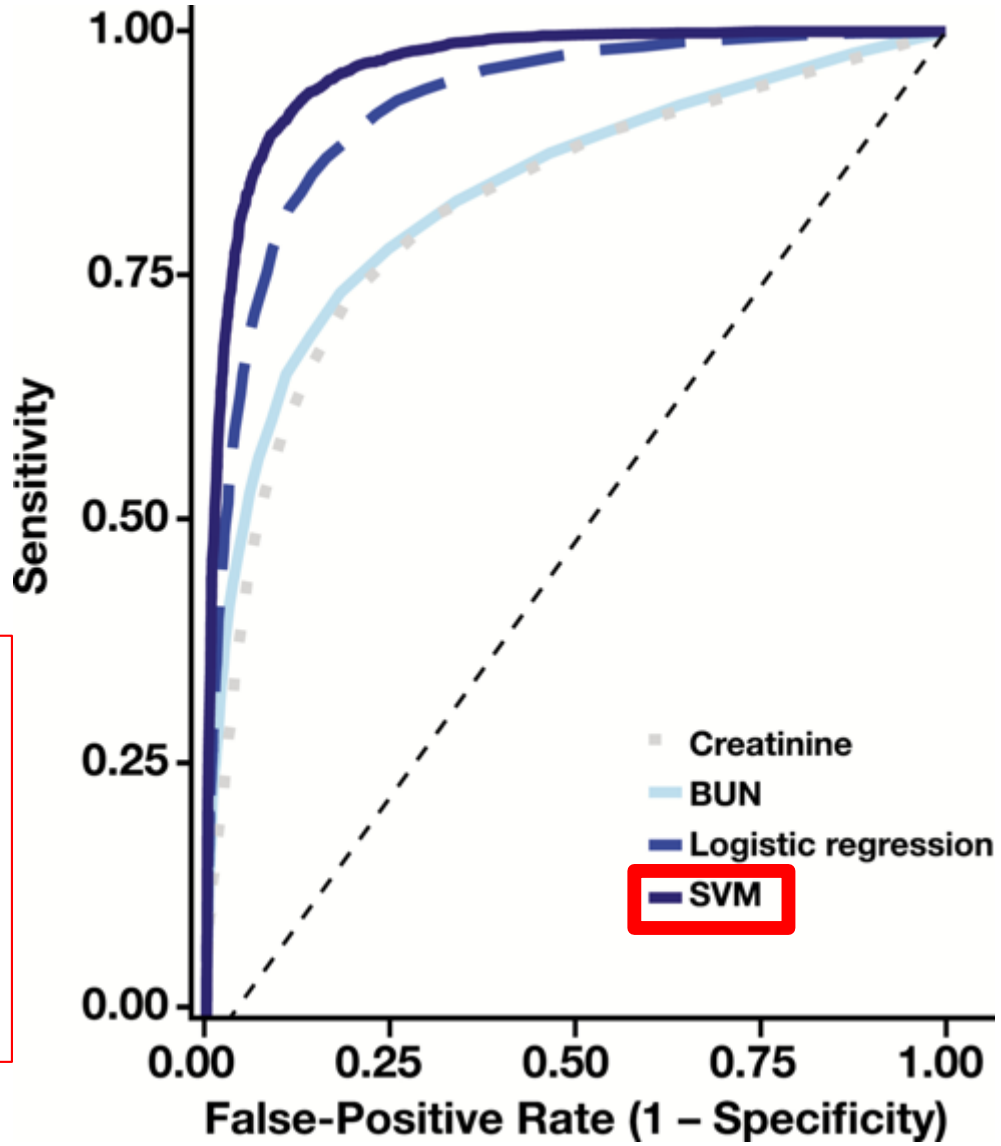




SVM performed better than other traditional statistical methods such as logistic regression when evaluating lab value differences alone and/or with values.



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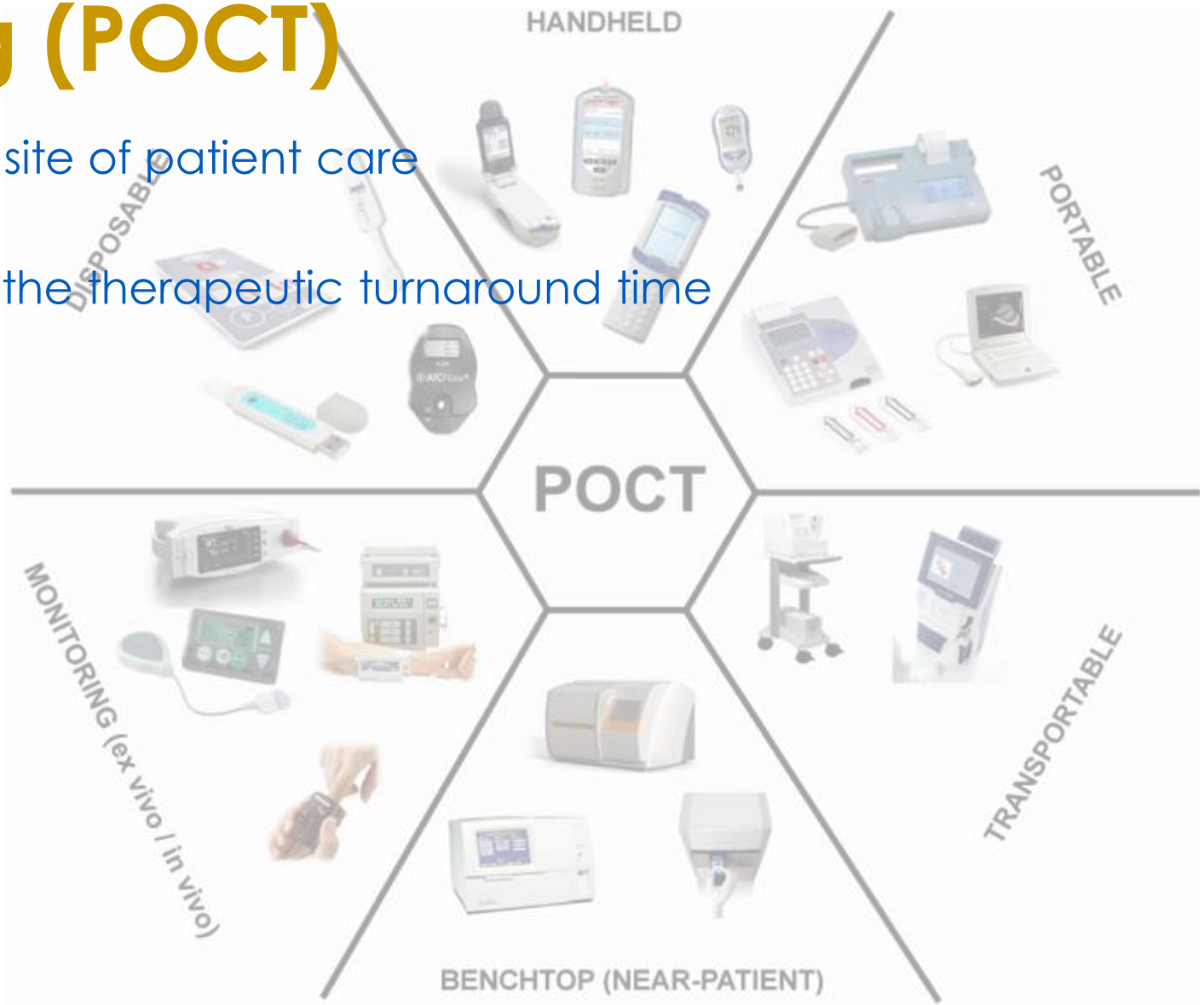
Point-of-Care Testing (POCT)

Definition: Medical testing at or near the site of patient care

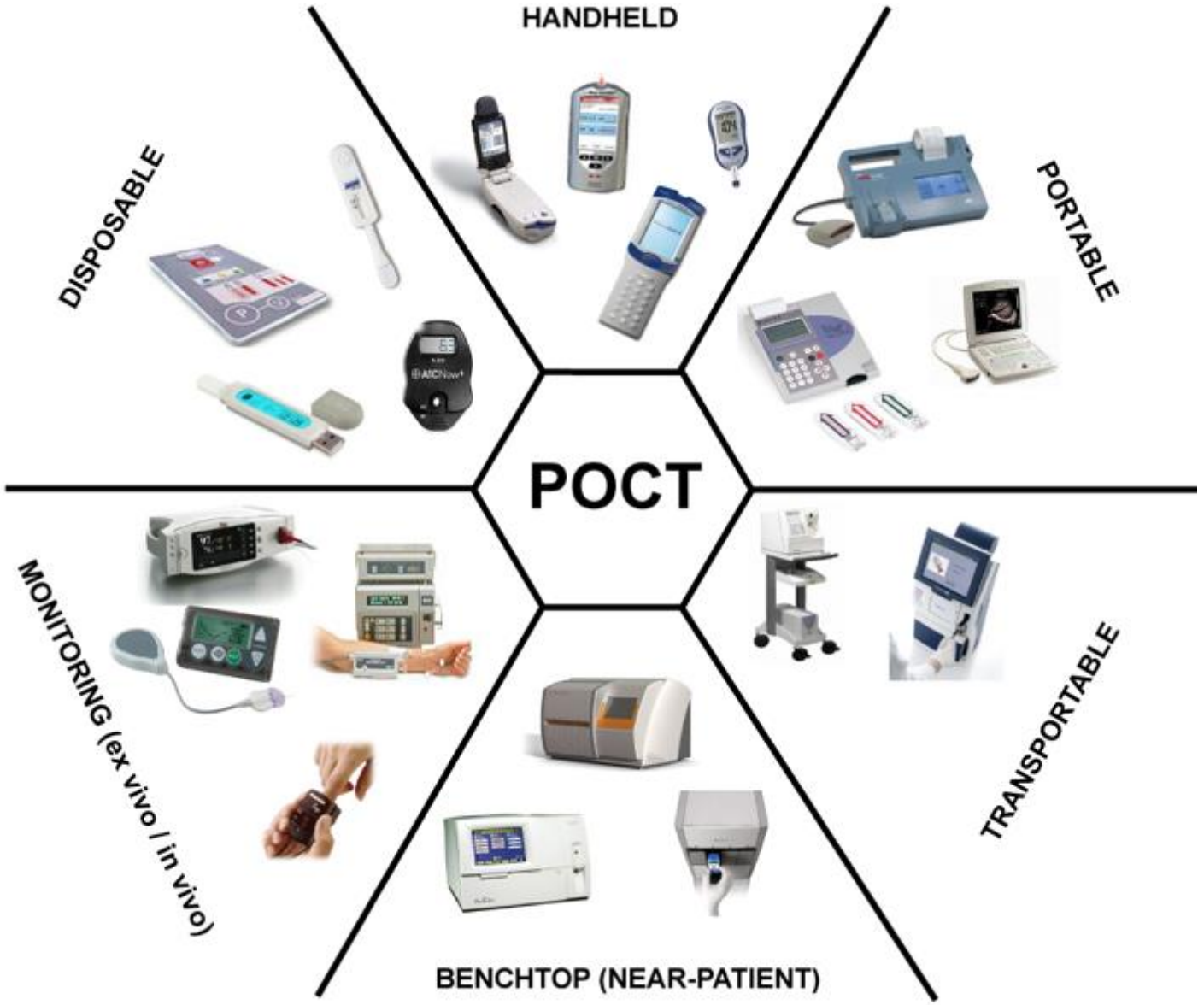
Goal: Improve outcomes by decreasing the therapeutic turnaround time



POCT Formats

POCT formats includes:

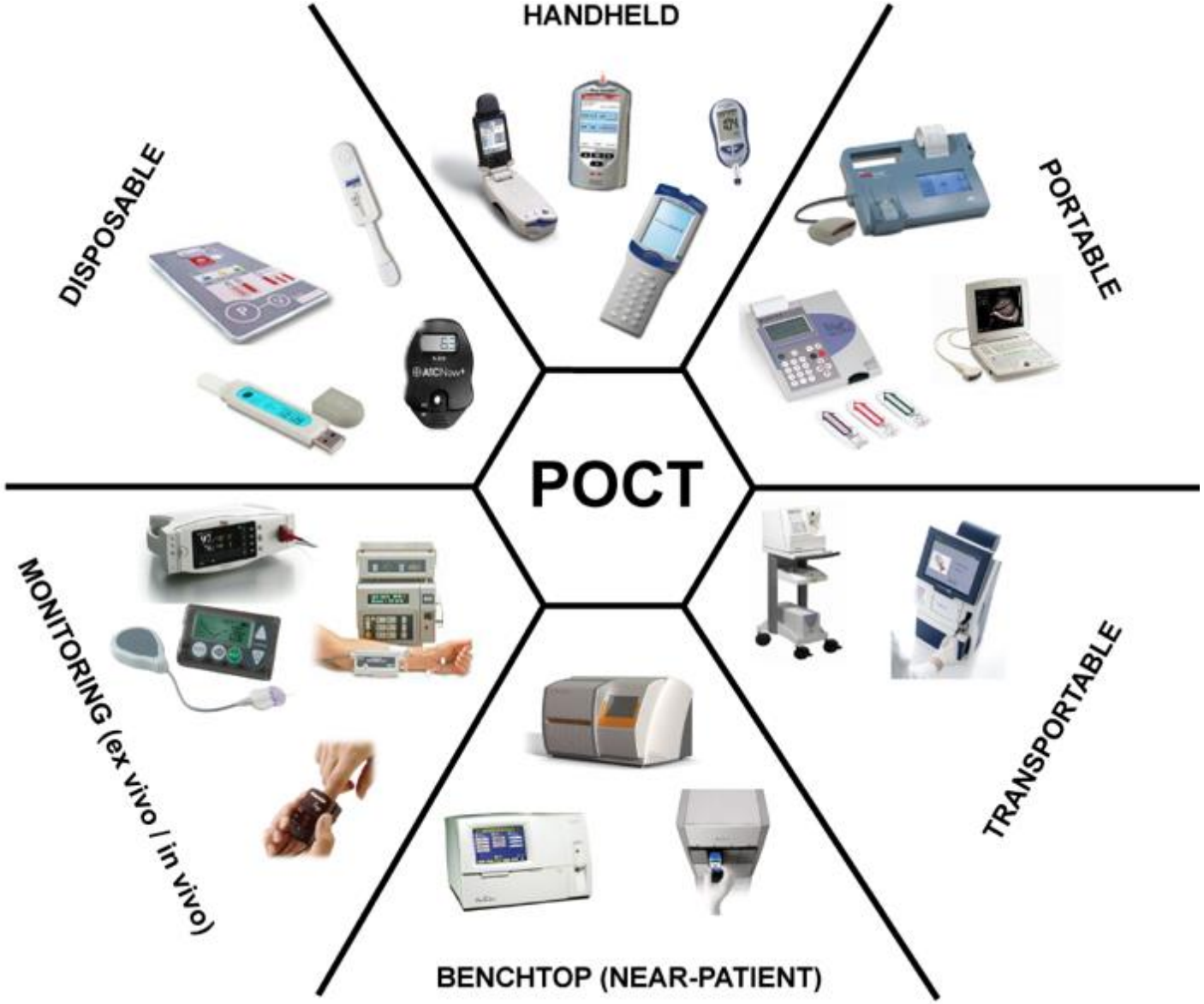
- Disposable
- Handheld
- Portable
- Transportable
- Benchtop
- Monitoring



POCT Formats

POCT formats includes:

- Disposable
- Handheld
- Portable
- Transportable
- Benchtop
- Monitoring
- **Smart devices**



Regulatory Considerations of *In Vitro* Diagnostic (IVD) Devices

Clinical Laboratory Improvement Amendment of 1988 (CLIA '88) defines three levels of complexity for IVD devices:

- **High Complexity:** Requires licensed laboratory personnel to operate the devices. Maintenance, operation, and results interpretation require high level knowledge for use.
- **Moderate Complexity:** Requires licensed medical personnel to operate. Device maintenance and operation may be simple, but results interpretation requires high level knowledge.
- **Waived:** Devices so simple to use and not prone to error. Errors that occur do not serious enough to cause harm. All personnel may be allowed to use the device.

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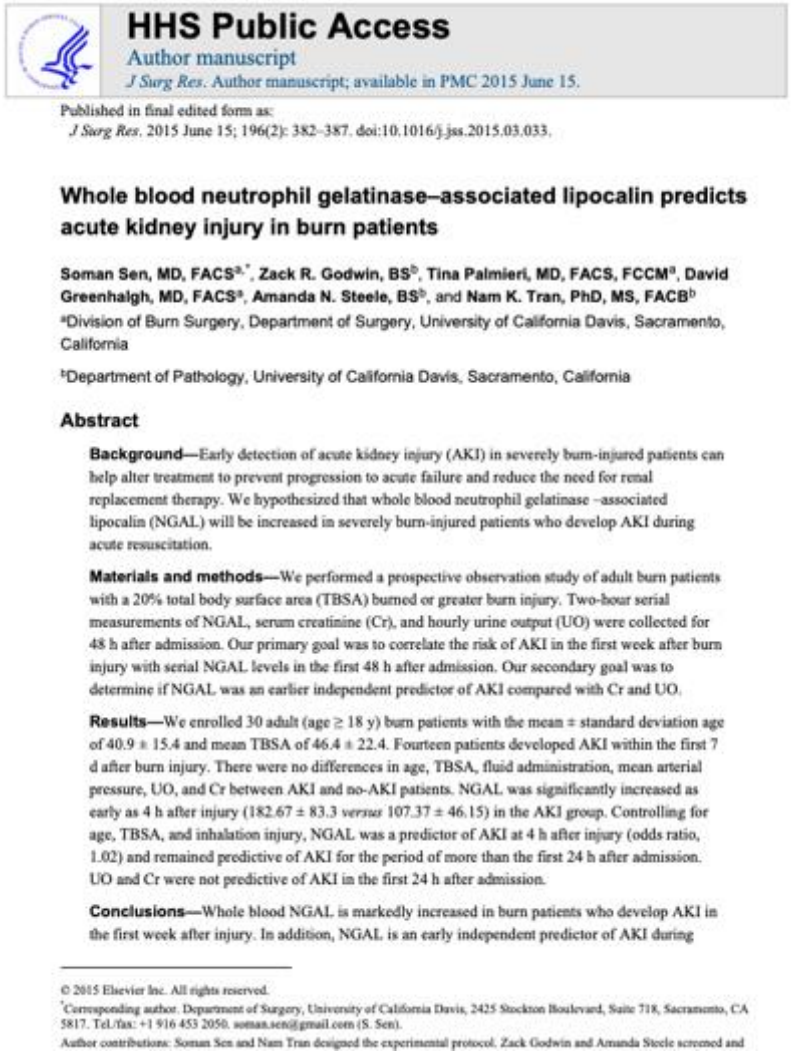
- **Waived:** Devices so simple to use and not prone to error. Errors that occur do not serious enough to cause harm. All personnel may be allowed to use the device**. <So how do we bring "lab knowledge" to non-lab settings and personnel?>**



Published in final edited form as:
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Whole blood neutrophil gelatinase–associated lipocalin predicts acute kidney injury in burn patients

Soman Sen, MD, FACS[a,*], **Zack R. Godwin, BS**[b], **Tina Palmieri, MD, FACS, FCCM**[a], **David Greenhalgh, MD, FACS**[a], **Amanda N. Steele, BS**[b], and **Nam K. Tran, PhD, MS, FACB**[b]

[a]Division of Burn Surgery, Department of Surgery, University of California Davis, Sacramento, California

[b]Department of Pathology, University of California Davis, Sacramento, California

Abstract

Background—Early detection of acute kidney injury (AKI) in severely burn-injured patients can help alter treatment to prevent progression to acute failure and reduce the need for renal replacement therapy. We hypothesized that whole blood neutrophil gelatinase –associated lipocalin (NGAL) will be increased in severely burn-injured patients who develop AKI during acute resuscitation.

Materials and methods—We performed a prospective observation study of adult burn patients with a 20% total body surface area (TBSA) burned or greater burn injury. Two-hour serial measurements of NGAL, serum creatinine (Cr), and hourly urine output (UO) were collected for 48 h after admission. Our primary goal was to correlate the risk of AKI in the first week after burn injury with serial NGAL levels in the first 48 h after admission. Our secondary goal was to determine if NGAL was an earlier independent predictor of AKI compared with Cr and UO.

Results—We enrolled 30 adult (age ≥ 18 y) burn patients with the mean ± standard deviation age of 40.9 ± 15.4 and mean TBSA of 46.4 ± 22.4. Fourteen patients developed AKI within the first 7 d after burn injury. There were no differences in age, TBSA, fluid administration, mean arterial pressure, UO, and Cr between AKI and no-AKI patients. NGAL was significantly increased as early as 4 h after injury (182.67 ± 83.3 *versus* 107.37 ± 46.15) in the AKI group. Controlling for age, TBSA, and inhalation injury, NGAL was a predictor of AKI at 4 h after injury (odds ratio, 1.02) and remained predictive of AKI for the period of more than the first 24 h after admission. UO and Cr were not predictive of AKI in the first 24 h after admission.

Conclusions—Whole blood NGAL is markedly increased in burn patients who develop AKI in the first week after injury. In addition, NGAL is an early independent predictor of AKI during

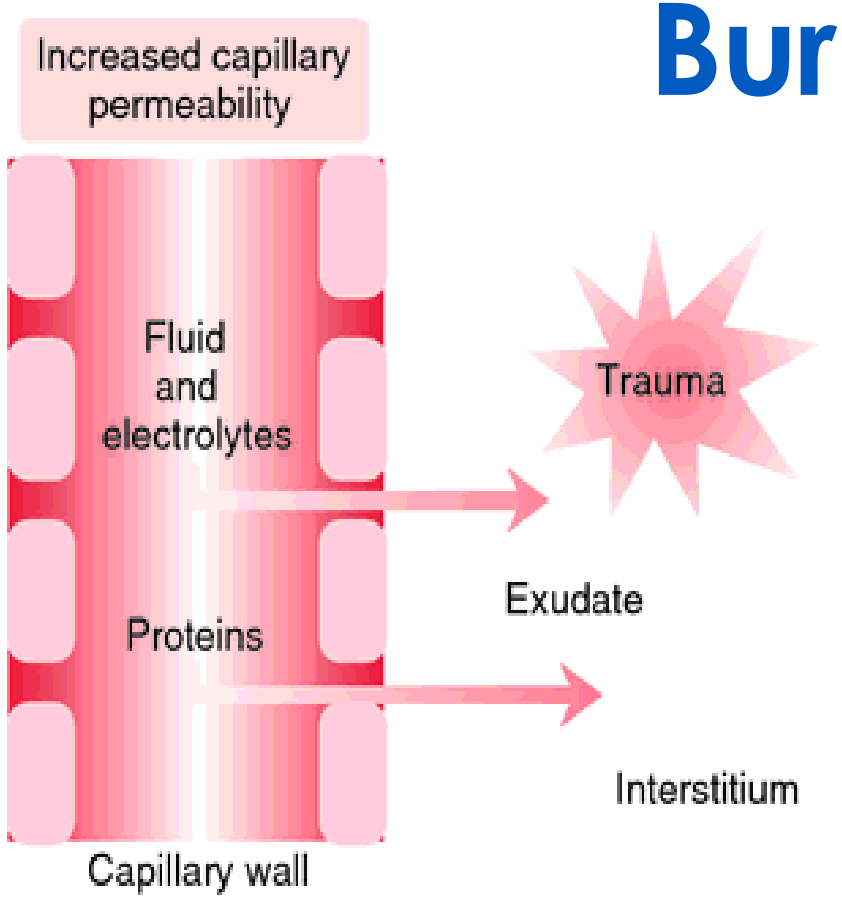
*Corresponding author. Department of Surgery, University of California Davis, 2425 Stockton Boulevard, Suite 718, Sacramento, CA 5817. Tel./fax: +1 916 453 2050. soman.sen@gmail.com (S. Sen).

Author contributions: Soman Sen and Nam Tran designed the experimental protocol. Zack Godwin and Amanda Steele screened and

Point-of-Care Testing for AKI Biomarkers in Severely Burned Patients

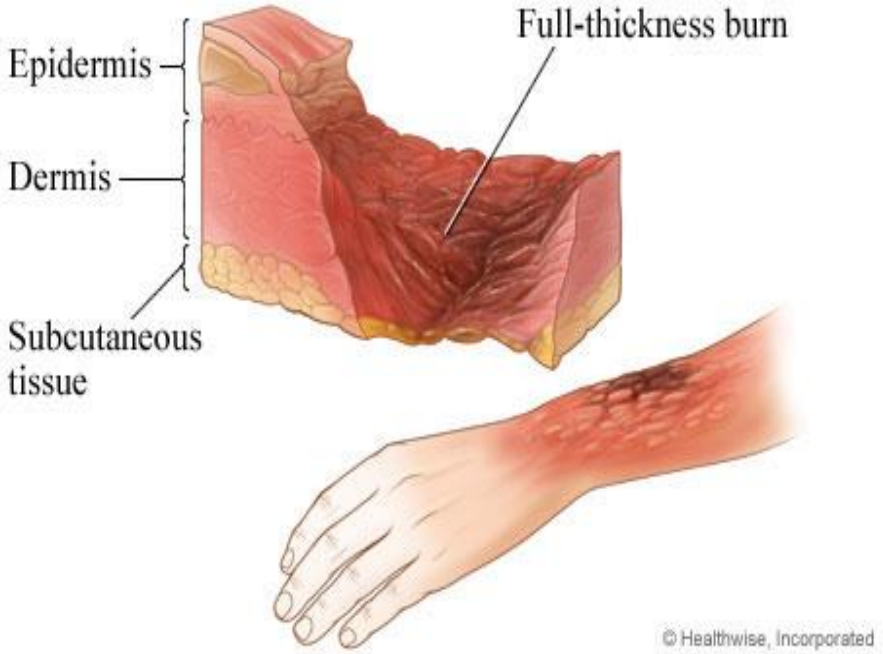
Sen S, et al. *J Surg Res* 2015;196:382-387.

Burn Shock

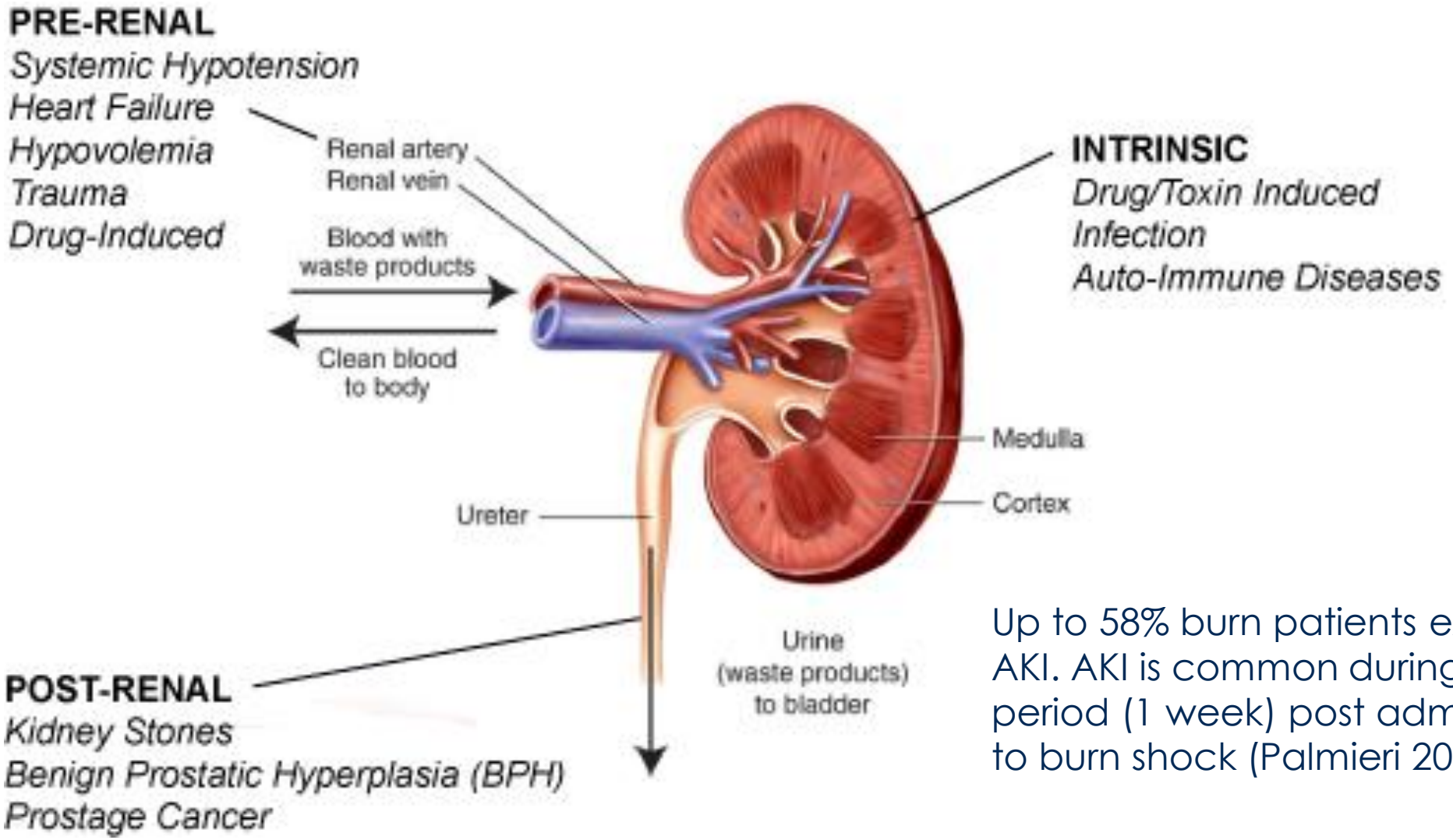


INCREASED VASCULAR LEAKAGE

EXCESSIVE EVAPORATIVE WATER LOSS



Burn-Related Acute Kidney Injury



Up to 58% burn patients experience AKI. AKI is common during the initial period (1 week) post admission due to burn shock (Palmieri 2009).

Kidney Disease Improving Global Outcomes (KDIGO) Criteria for AKI

Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (353.6 μmol/l) OR Initiation of renal replacement therapy OR, in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h OR Anuria for ≥12 h

POC Creatinine Testing

Patient Blood Drop Applied
1.2 Microliter Sample

Micro-Capillary Vent Layer
Capillary Vent

Micro-Capillary Sample Layer
Capillary Channel

Electrode Well Layer
Electrode Wells
For Measuring Creatinine,
Hematocrit, and Interferences

Base and Conductive Gold Layer
Electrochemical Measuring Surface

Electrical Contact End to Meter

POC BNP/NGAL Measurements

Multiplex BNP/NGAL Assay Specifications

Sample Volume: 240 µL EDTA whole blood

Turnaround Time: 15 - 20 minutes

Methodology: Sandwich Immunoassay

Measurable Range:

BNP	5 – 5000 pg/mL
NGAL	15 – 1300 ng/mL

1. Add sample to the device.

2. Insert device into the meter.

3. Read results on the display.

Demographics: AKI vs. No-AKI Patients

Variable	AKI (n = 14)	Non-AKI (n=16)	P-value
Age (years)	39.9 (15.5)	38.2 (13.2)	0.796
TBSA (%)	49.7 (26.0)	42.9 (18.1)	0.469
Gender (M, F)	11, 3	14, 2	0.713
Fluid Rate (mL/hr)	974.5 (452.1)	778.8 (343.8)	0.213
BUN (mg/dL)	10.2 (3.5)	9.9 (4.1)	0.137
Creatinine (mg/dL)	0.90 (0.19)	0.83 (0.13)	0.078
MAP (mmHg)	78.7 (12.5)	83.1 (6.2)	0.654
CVP (mmHg)	14.9 (11.9)	12.9 (8.1)	0.238
UOP (mL/hr)	85.5 (36.3)	88.0 (26.7)	0.362

Abbreviations: AKI, acute kidney injury; BUN, blood urea nitrogen; CVP, central venous pressure; F, female; M, male; MAP, mean arterial pressure; TBSA, total body surface area; UOP, urine output

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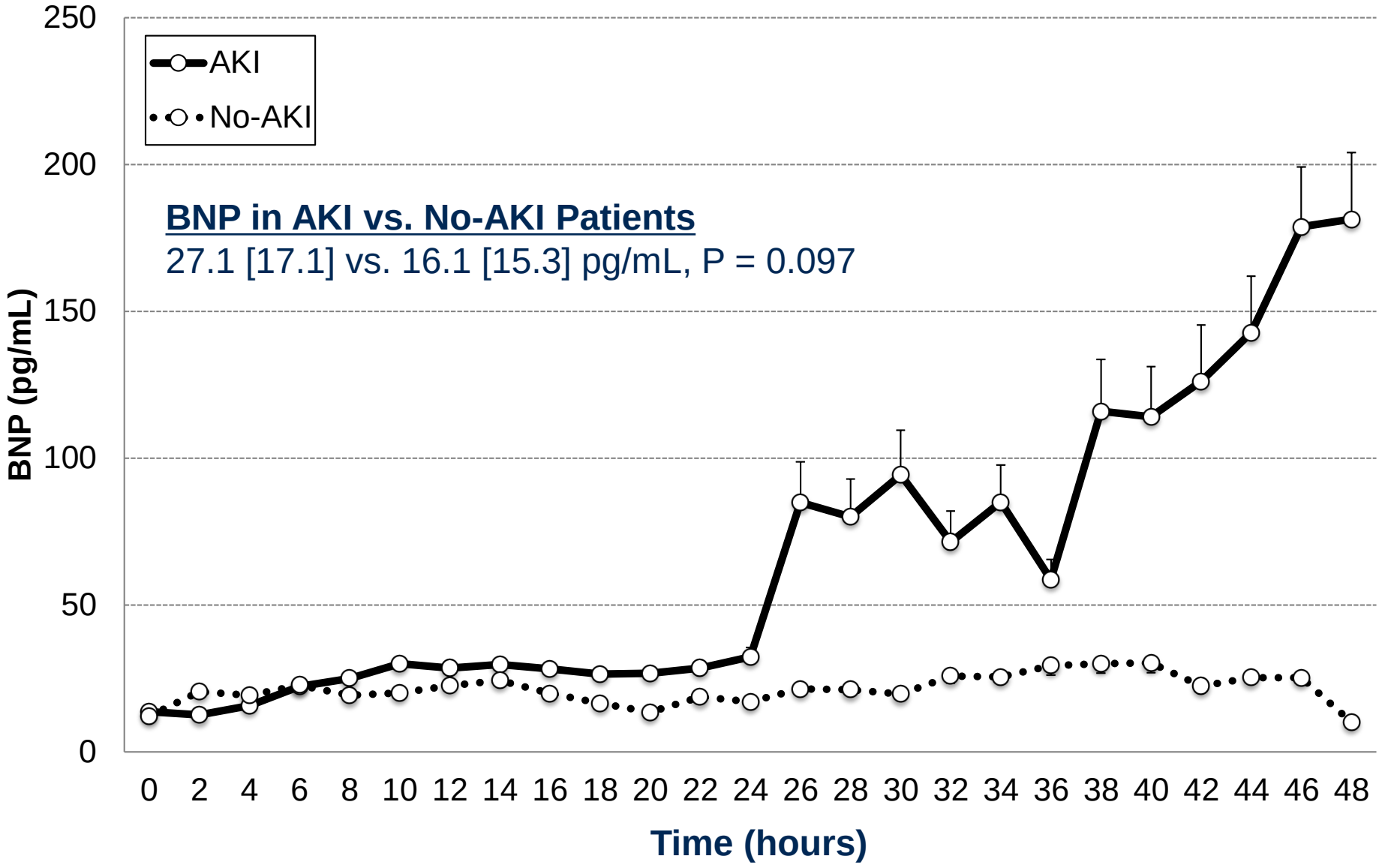
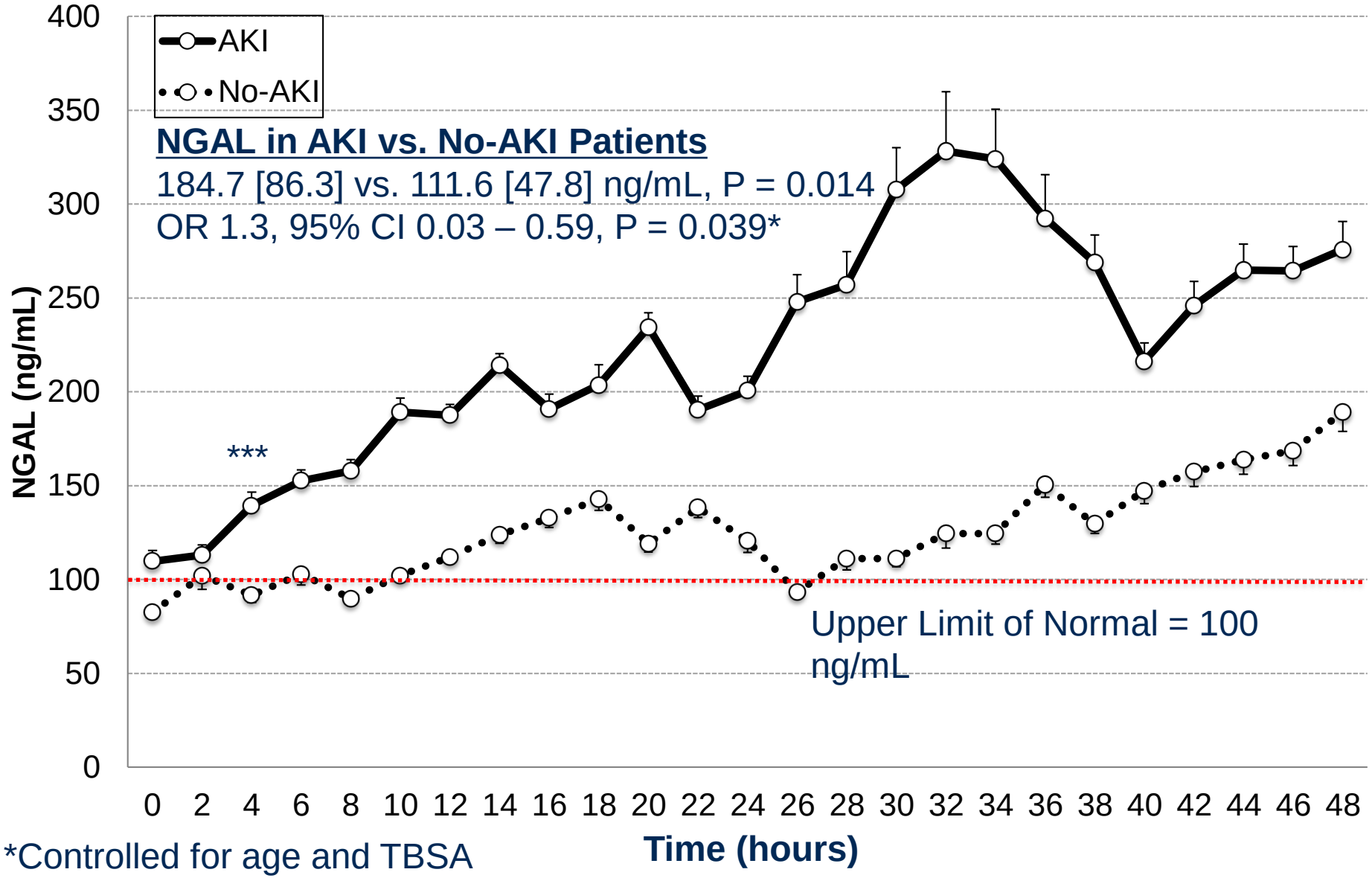
UOP (mL/h)	85.5 (36.3)	88.0 (26.7)	0.362
BNP (pg/mL)	27.1 (17.7)	16.1 (15.3)	0.097
NGAL (ng/mL)	184.7 (86.3)	111.6 (47.8)	0.014

Abbreviations: AKI, acute kidney injury; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CVP, central venous pressure; F, female; M, male; MAP, mean arterial pressure; NGAL, neutrophil gelatinase associated lipocalin; TBSA, total body surface area; UOP, urine output

BNP in AKI Patients (n = 30)

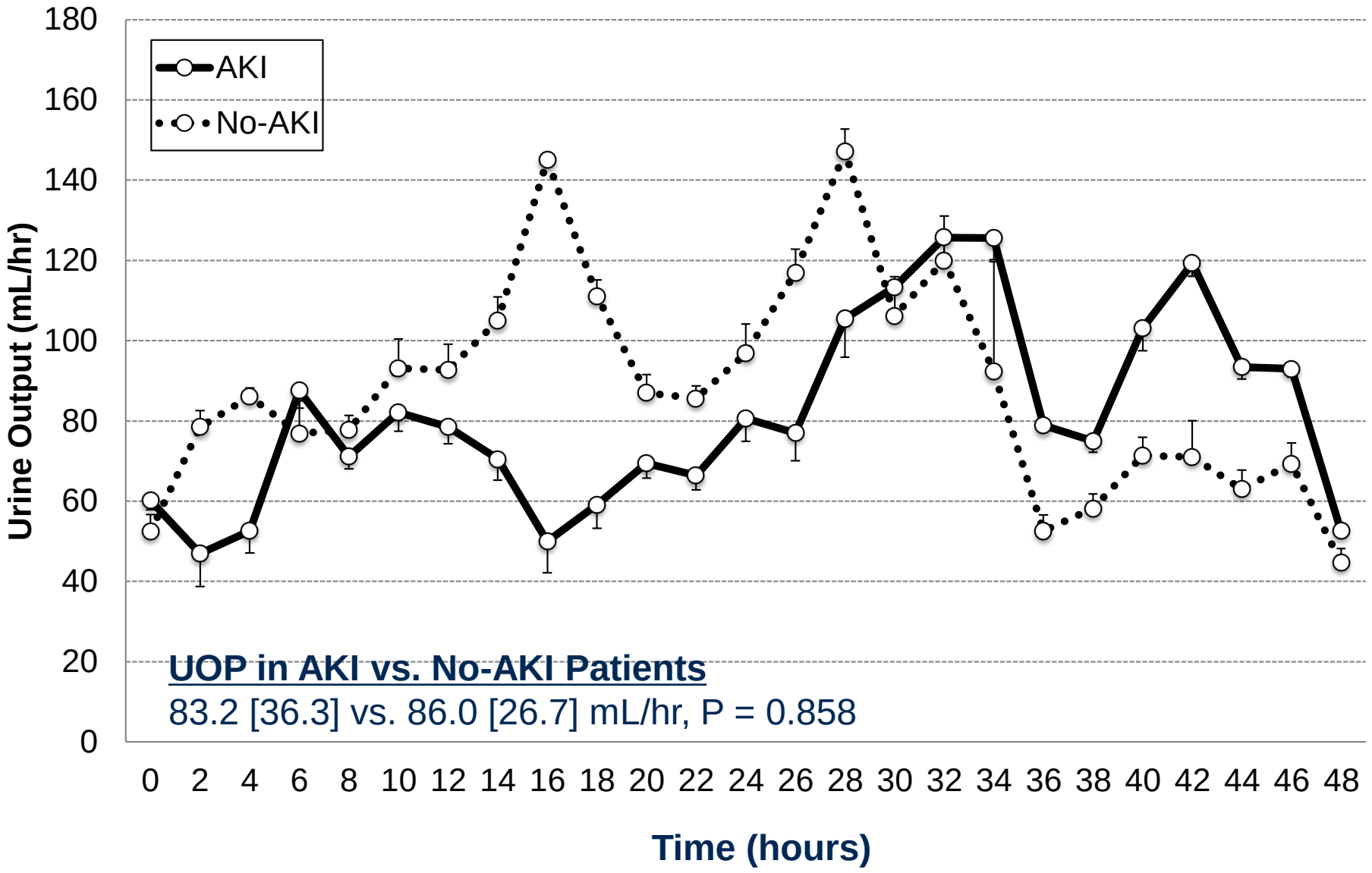


NGAL in AKI Patients (n = 30)

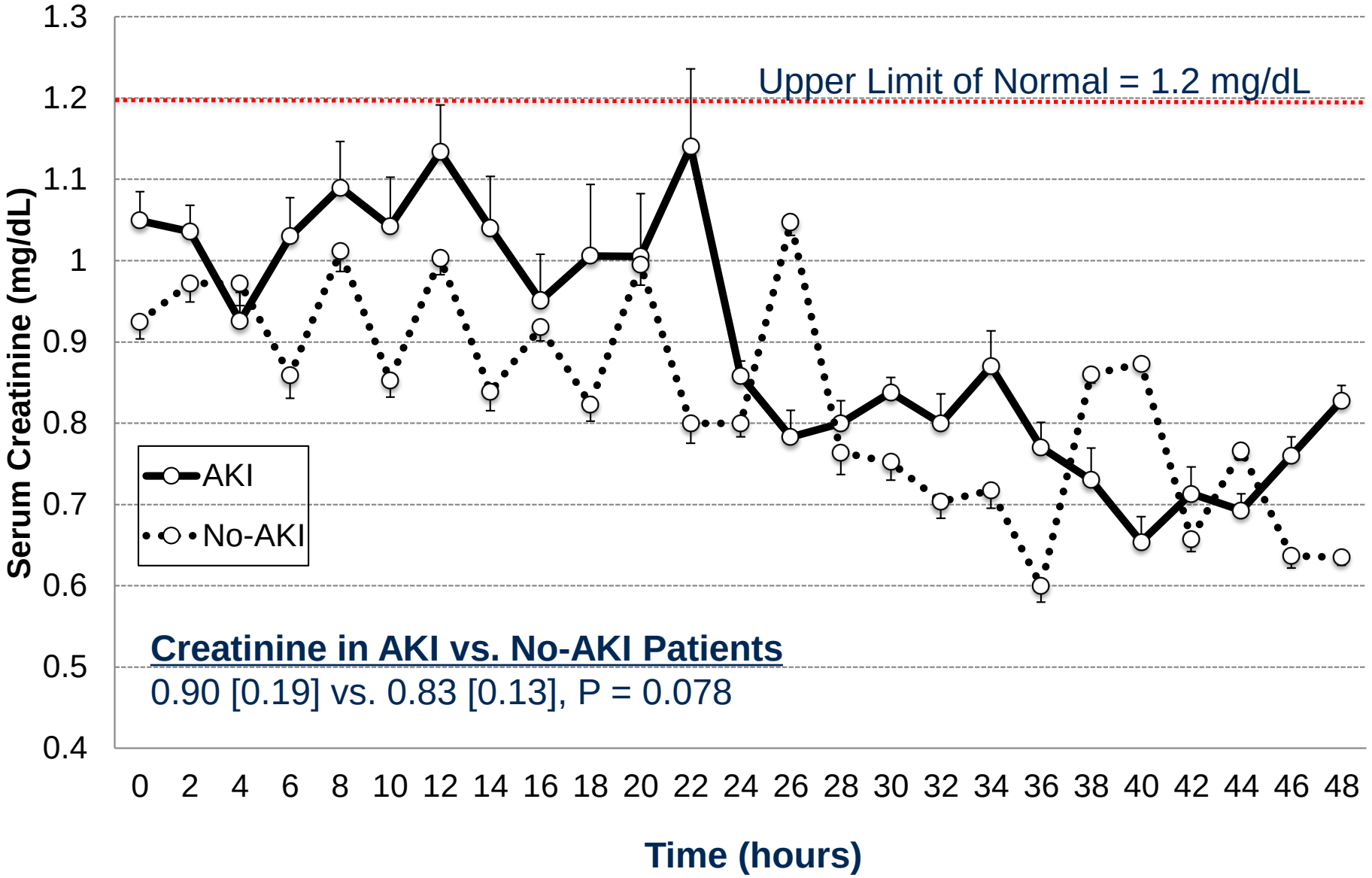


*Controlled for age and TBSA

Urine Output in AKI Patients (n = 30)



Creatinine in AKI Patients (n = 30)



Creatinine in AKI vs. No-AKI Patients

0.90 [0.19] vs. 0.83 [0.13], P = 0.078

Does anyone use NGAL today? [*at least in the United States*]

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NGAL assays in the United States are either not FDA approved or remain in the review process (not an all inclusive list of platforms)

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NGAL assays in the United States are either not FDA approved or remain in the review process (not an all inclusive list of platforms)

IGFBP-7 and TIMP-2 are potential alternative FDA approved biomarkers, but not widely adopted.

AI/ML Enhanced Detection of Burn Related AKI: A Proof of Concept

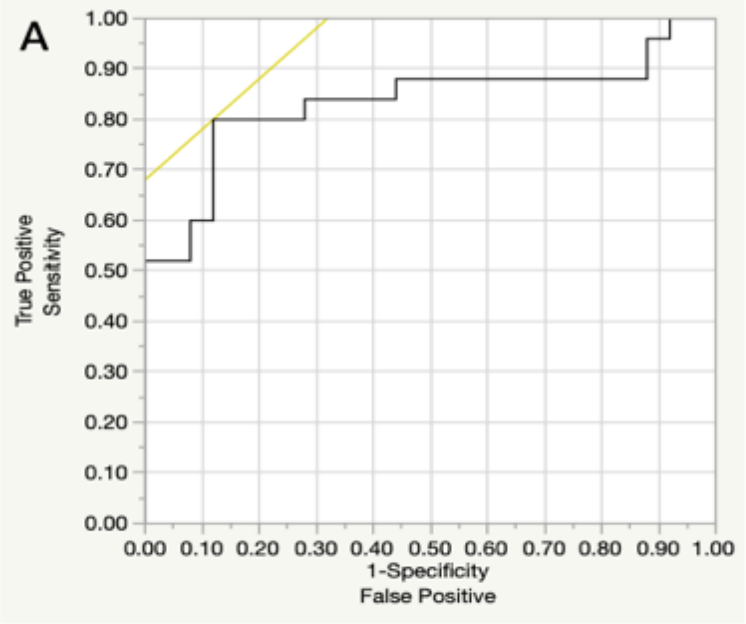
Tran NK & Rashidi R, 2019

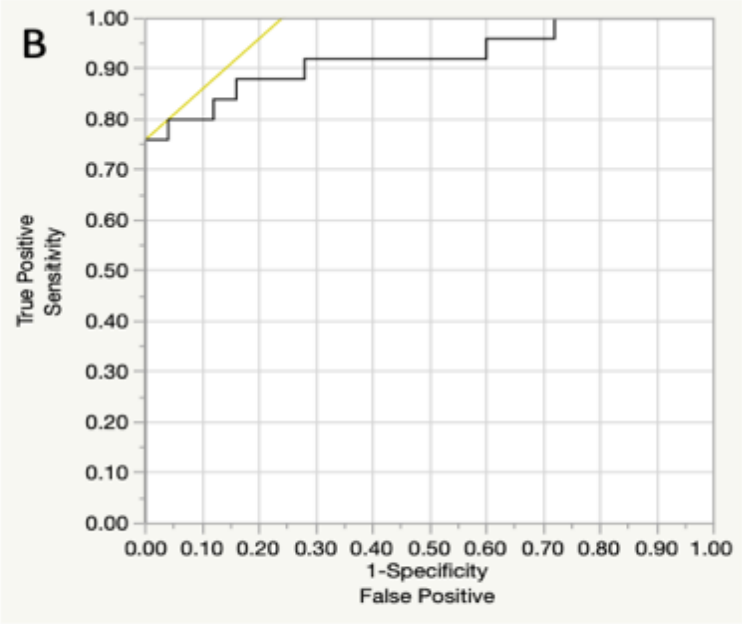
Burn AKI Study Part II: Does AI/ML Help?

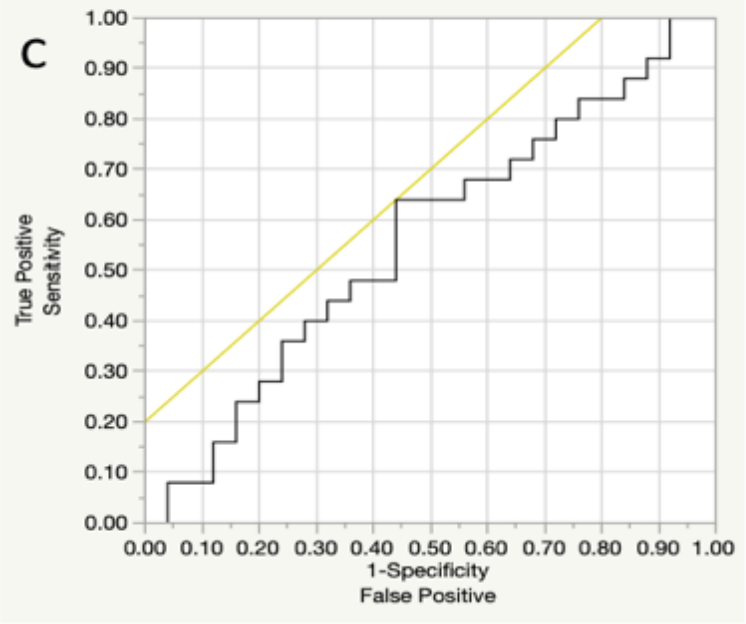
Background: UC Davis evaluated an ELISA-based NGAL assay as a potential laboratory developed test. A study was measuring plasma NGAL obtained at admission (first 24 hours) from 50 severely burned (>20% TBSA) adult patients.

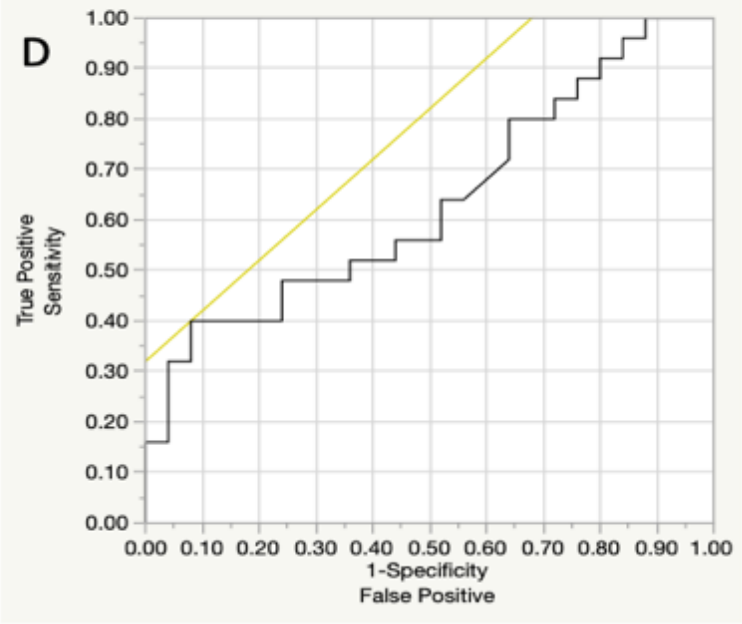
Additional Testing: Plasma creatinine and NT-proBNP measurements were also made on the same samples. Other medical data such as urine output was also collected.

Variables	AKI GROUP (n = 25)	NO-AKI GROUP (n = 25)
Mean Age (Years)	39.1 (49.2)	39.7 (15.5)
Mean Burn Size (%)	49.2 (24.1)	43.3 (18.9)
Gender (M/)	20/5	19/6
Plasma Creatinine (mg/dL)	1.21 (0.51)	0.90 (0.22)
Plasma NGAL (ng/mL)	185.1 (86.3)**	110.3 (48.1)
Plasma NT-proBNP (pg/mL)	25.7 (15.4)	16.0 (15.3)
Urine Output (mL/hr)	81.5 (31.6)	85.7 (48.9)
Time to AKI (hours)	42.7 (23.2)**	NA





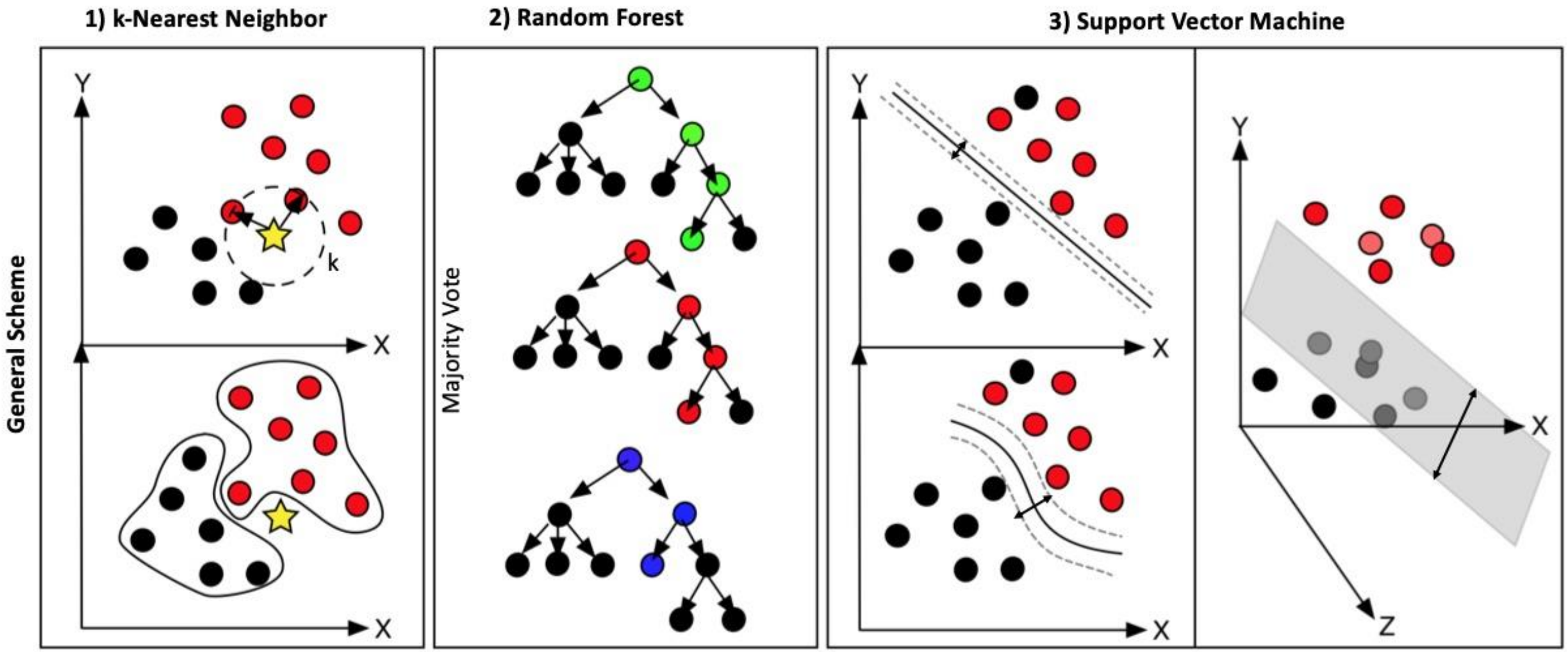




Receiver Operator Characteristic Curves for AKI Biomarkers

- Panels A-D represent ROC curves for BNP, NGAL, UOP and creatinine respectively.
- The area under the ROC curves were 0.83, 0.92, 0.56, and 0.64 respectively with NGAL exhibiting the best performance.
- So NGAL continues to perform well.

AI/ML Approaches for Consideration



- Identifies nearest neighbors (k)
- Determines distance (d)
- Groups based on d for a given k

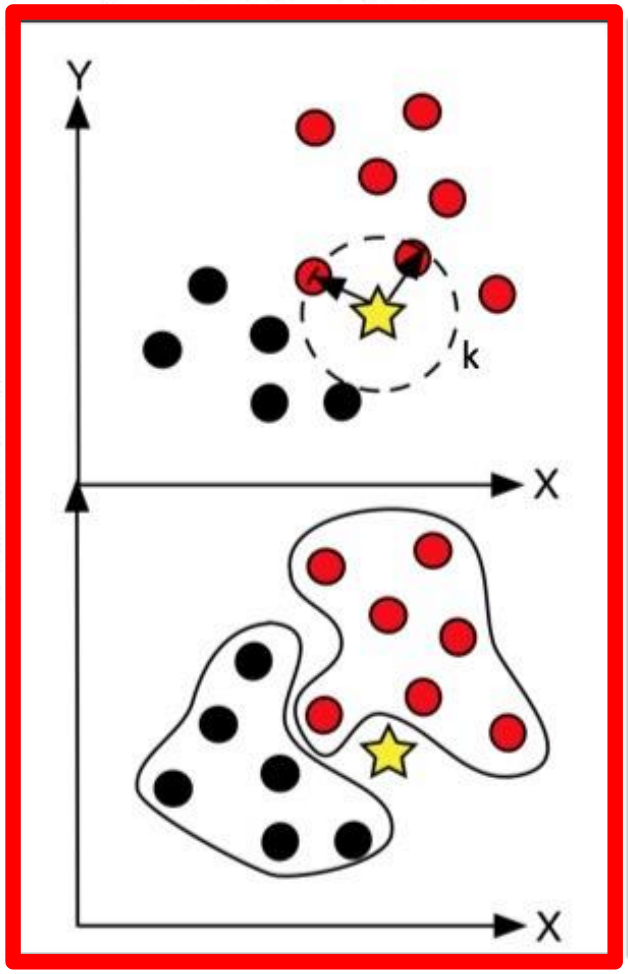
- Classification is based on given number (n) of decision trees.
- Majority voting determines final class.

- Constructs a hyperplane (—) that that best separates groups.
- The best hyperplane maximizing the margins (---) is selected.
- Hyperplanes may exist in 3D space to improve separation of data points and further maximize margins.

AI/ML Approaches for Consideration

General Scheme

1) k-Nearest Neighbor



- Identifies nearest neighbors (k)
- Determines distance (d)
- Groups based on d for a given k

2) Random Forest

- Classification is based on given number (n) of decision trees.
- Majority voting determines final class.

3) Support Vector Machine

- Constructs a hyperplane (—) that that best separates groups.
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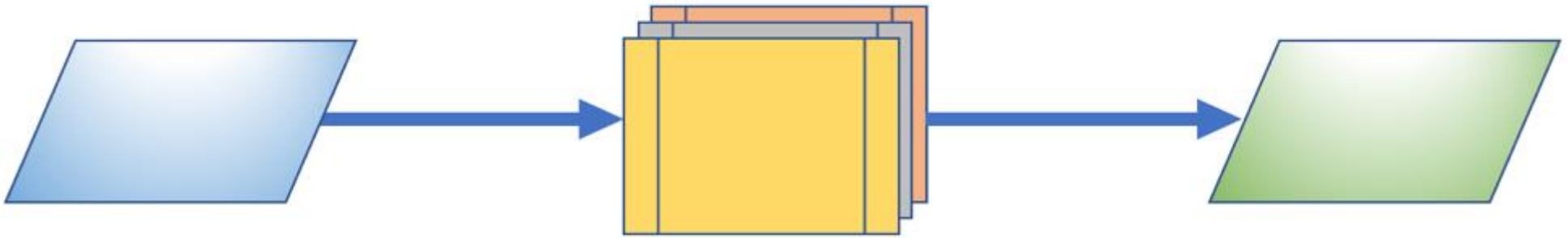
- Hyperplanes may exist in 3D space to improve separation of data points and further maximize margins.

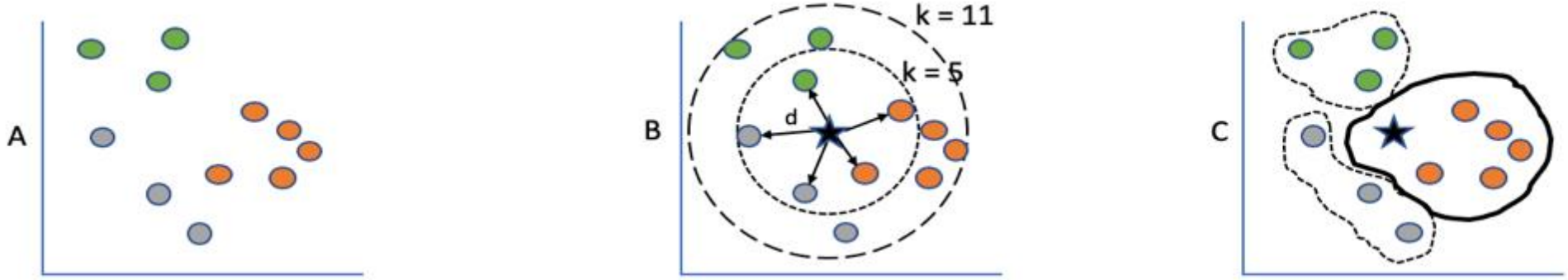
K-Nearest Neighbor Approach Conceptual Drawing



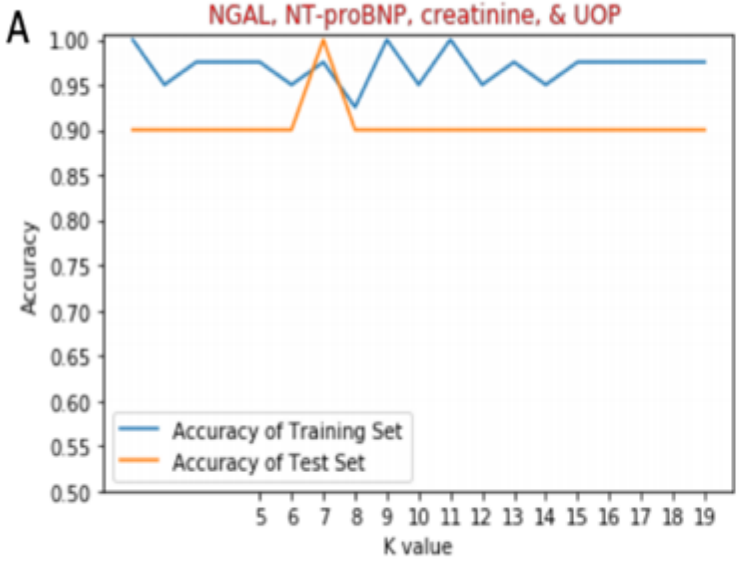
DATA INPUT

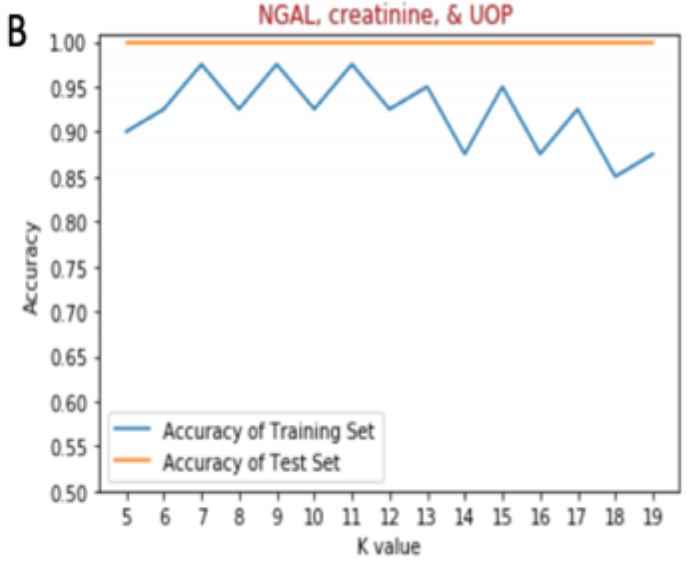
K-NEAREST NEIGHBOR CLASSIFICATION AND OPTIMIZATION (k = 0, 1, 2, … n)

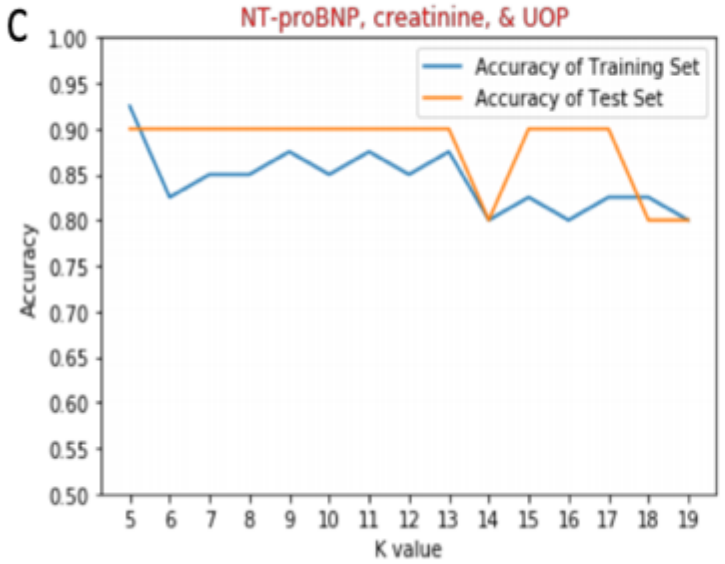
DATA OUTPUT

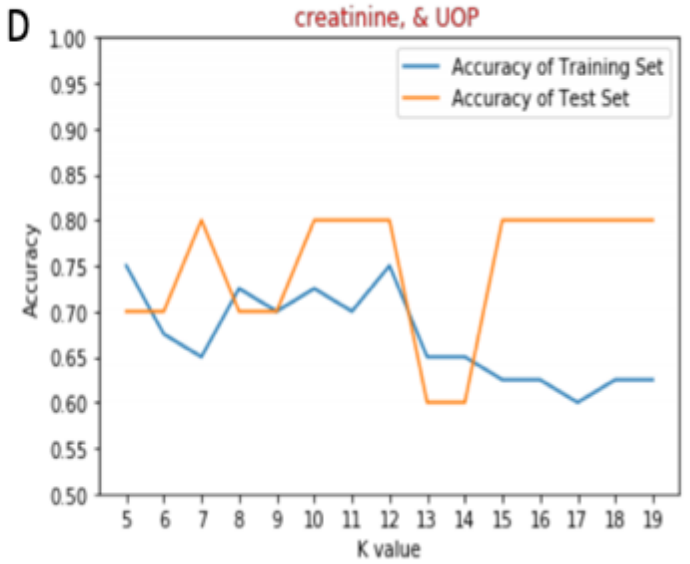


Distance Function (d) = $\sqrt{\sum_{i=1}^{k}(x_i - y_i)^2}$



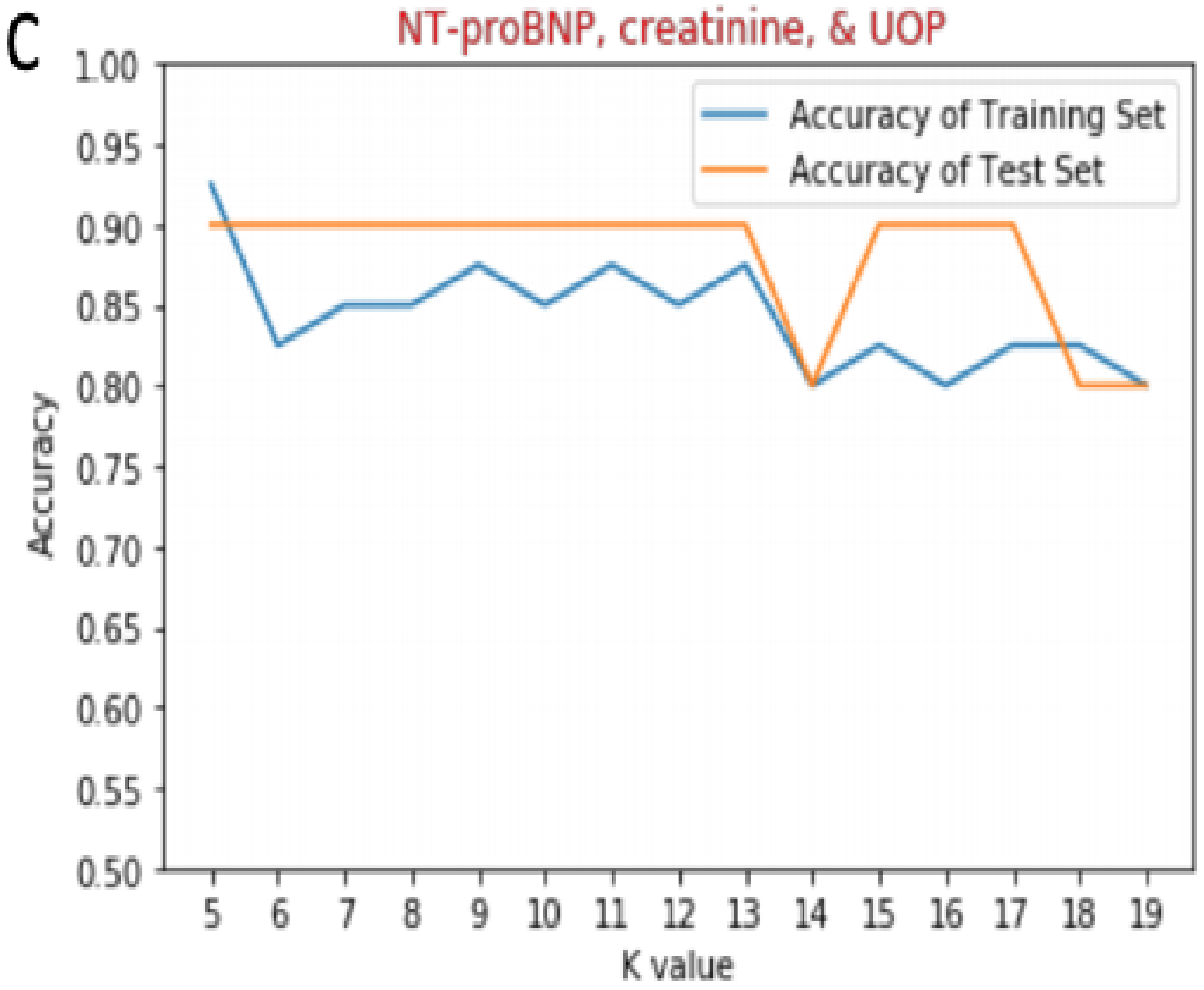






k-Nearest Neighbor Training-Testing with NGAL, Creatinine, UOP, and NT-proBNP

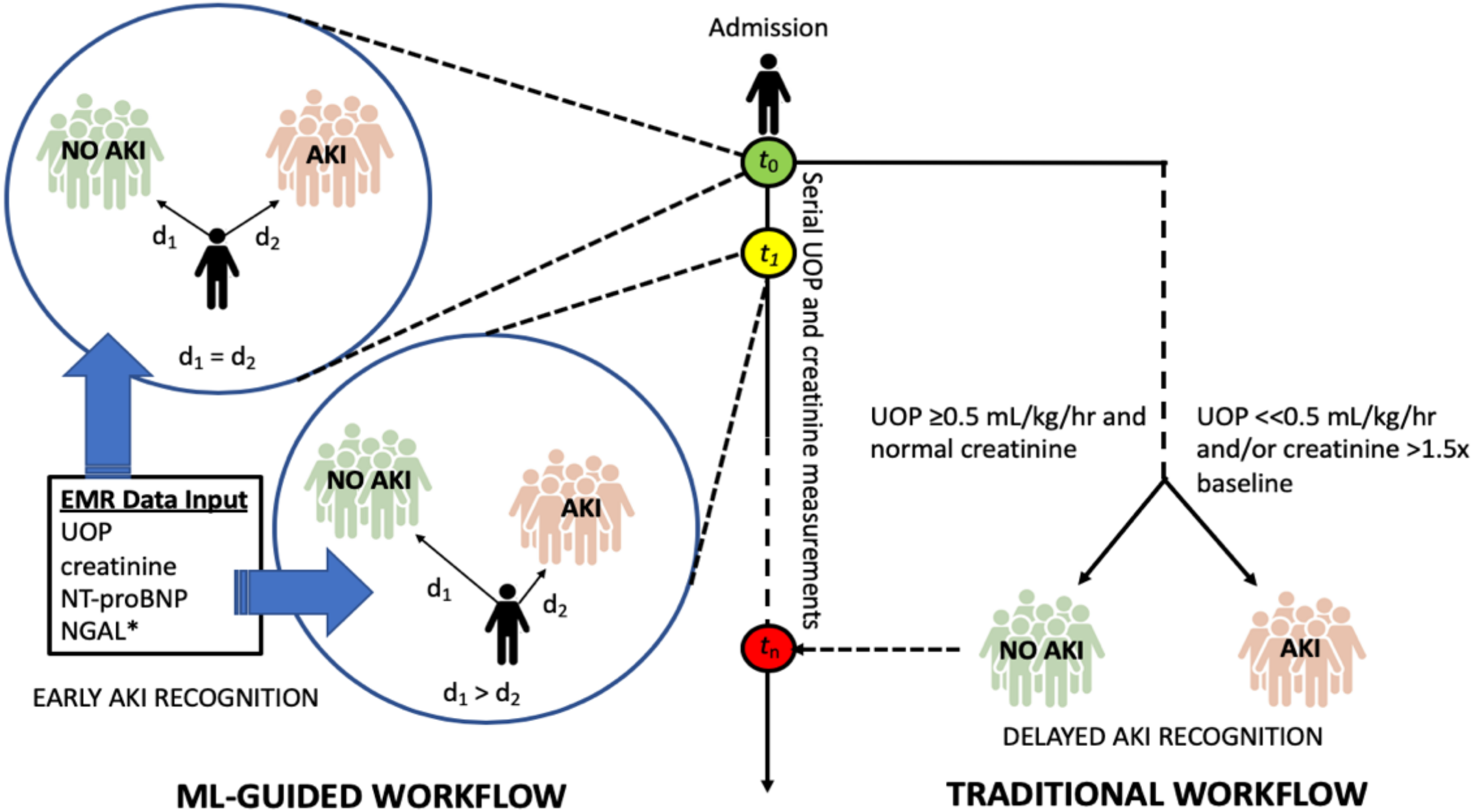
- The figure illustrates the accuracy versus *k*-value for both training and testing sets (80%-20% training-testing split).
- Panel A is the *k*-NN model that includes NGAL, NT-proBNP, creatinine, and UOP.
- Panel B excludes NT-proBNP. Panel C excludes NGAL.
- Panel D includes only UOP and creatinine.



NT-proBNP, Creatinine and UOP enhanced by AI/ML provided reasonable accuracy for predicting AKI

- Creatinine and UOP alone when used in the first 24 hours did not perform well (current standard of care).
- NGAL was of course superior to all other methods, but if you don't have NGAL…
- 90% accuracy with NT-proBNP, creatinine, and UOP enhanced by AI/ML could be a cost-effective method when NGAL (or other biomarkers) are not available.

AI/ML Real World Application for AKI?



Should we use AI/ML for AKI at UC Davis?

Not so fast!...we need to make sure we can:

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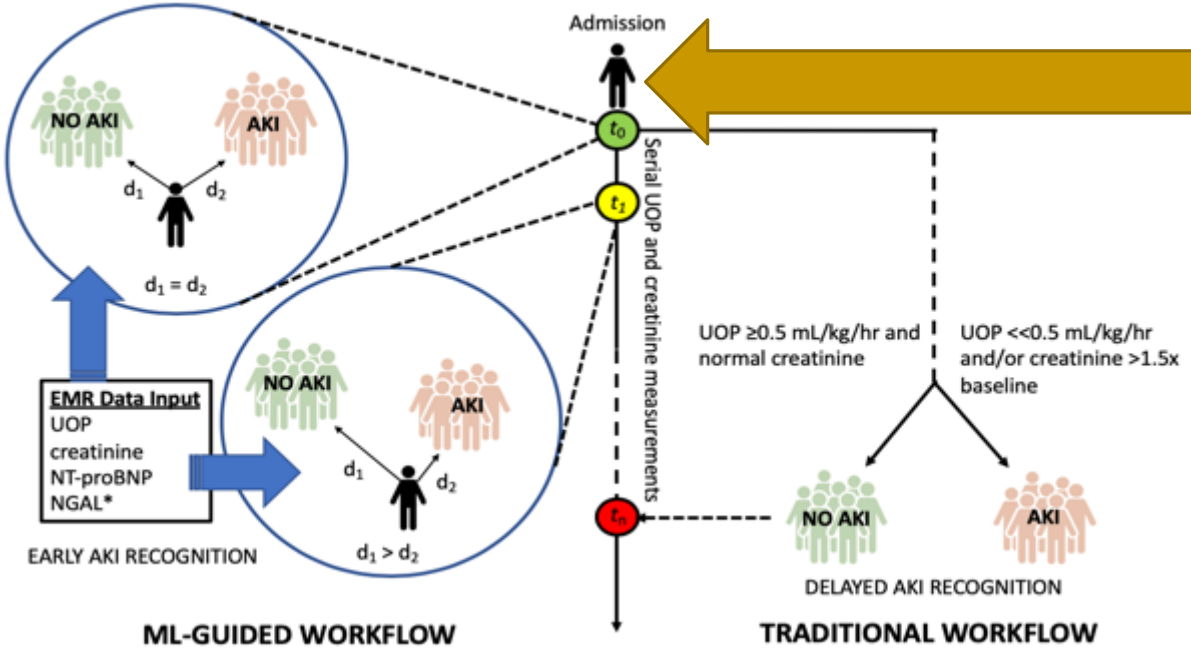

Current study now evaluates burn and non-burned patients at risk for AKI.

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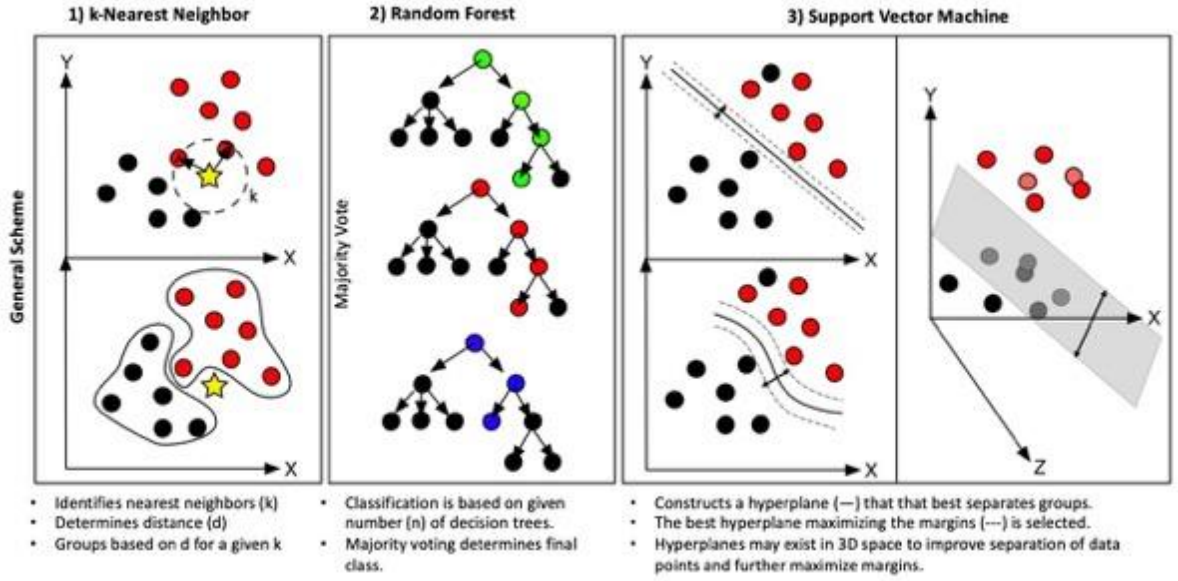
Not so fast!...we need to make sure we can:

- Generalize the data to other populations (i.e., burn vs. trauma) and test methods. We know creatinine (despite IDMS traceability) still has inter-assay differences.

- Are there better AI/ML models – should we use SVM and/or random forest?

Same new study with the combined burn and non-burn patients has compared k–NN, random forest, and SVM together.

Determine which has the better performance as well as strengths and weaknesses when faced with more heterogenous populations.



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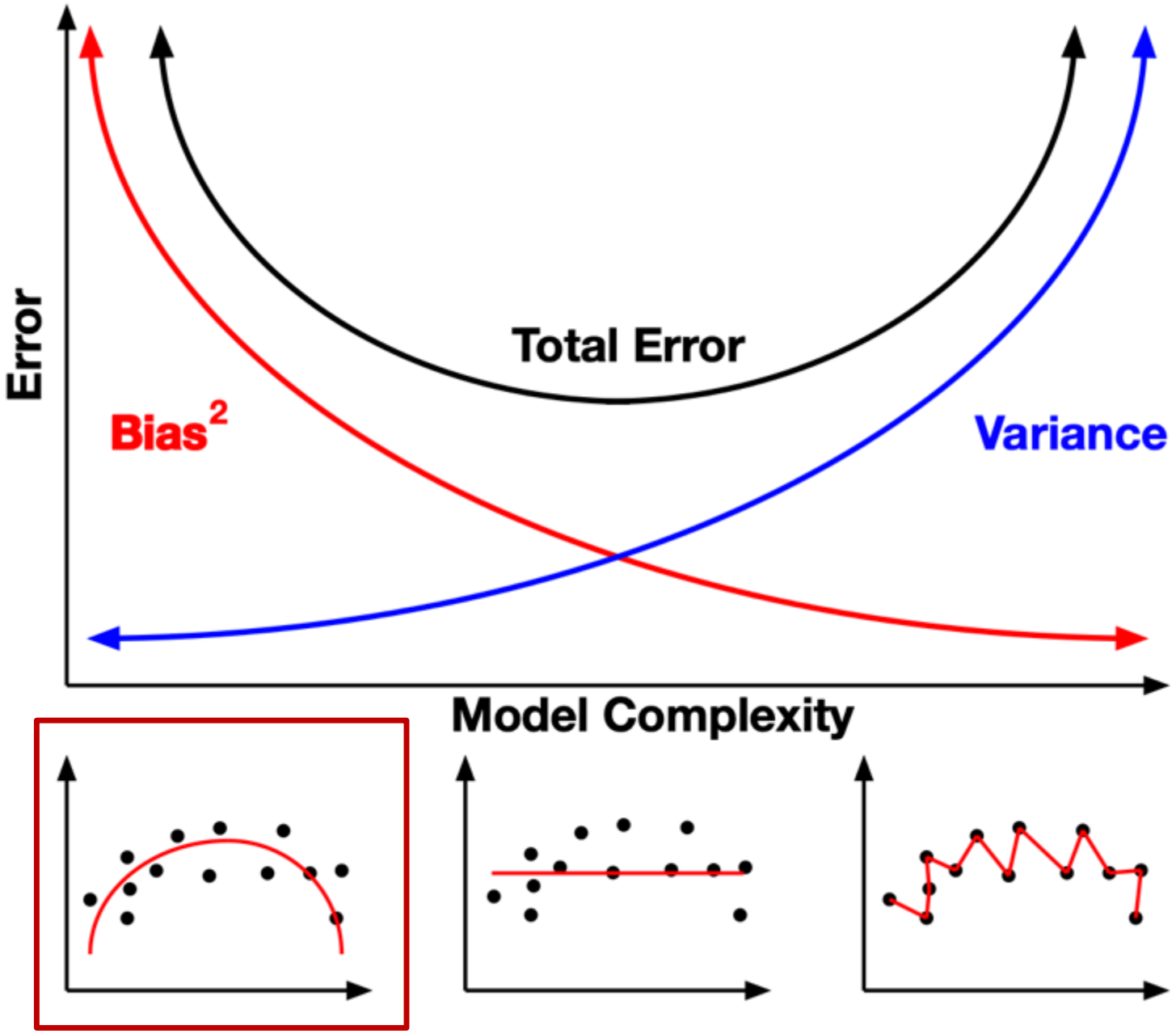
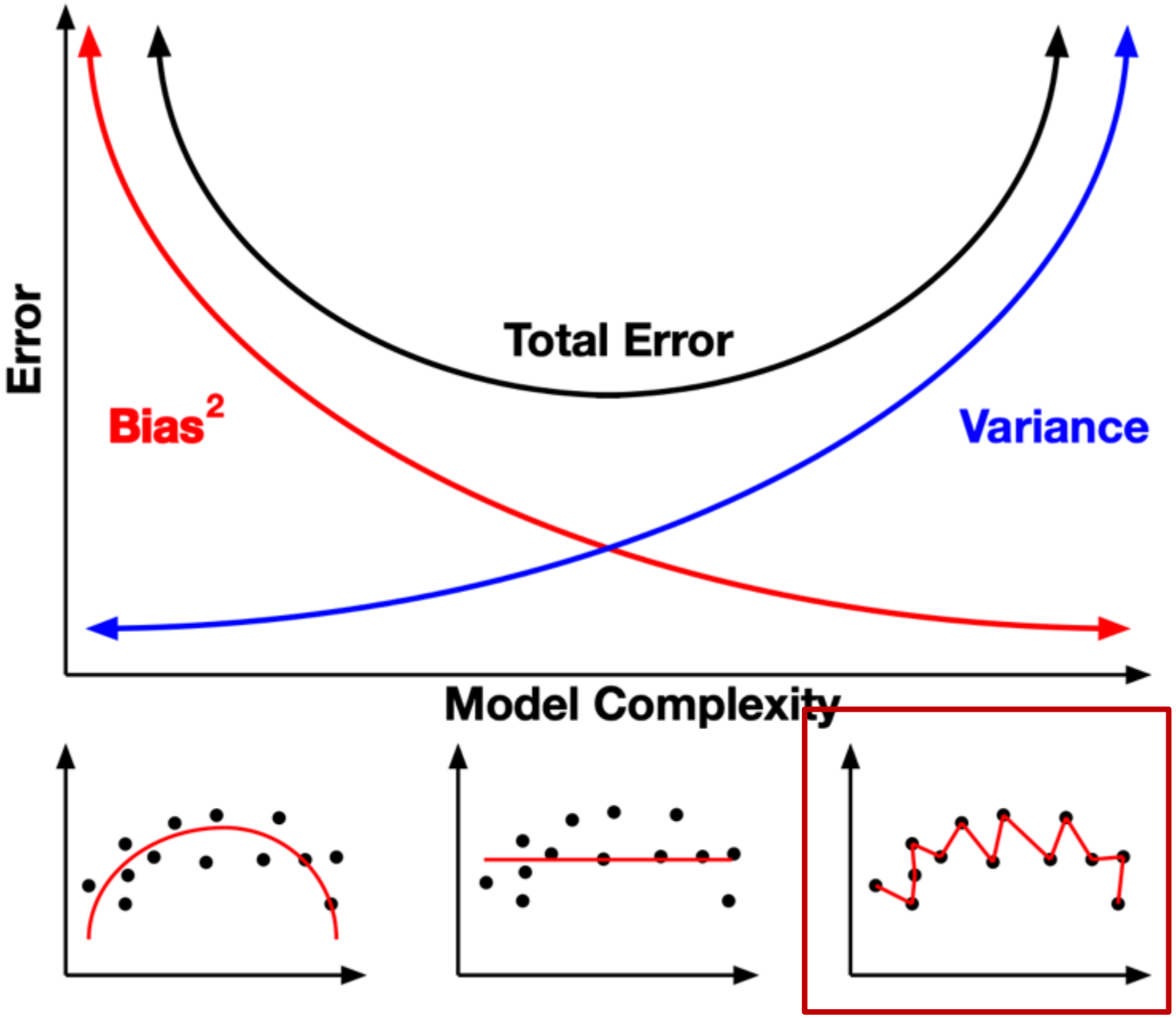
- Are there better AI/ML models – should we use SVM and/or random forest?
- **Was 50 patients enough to train/test the AI/ML. How much is enough?**



More Data isn't Actually a Good Thing

- We can understand that too little data leads to underfitting data.



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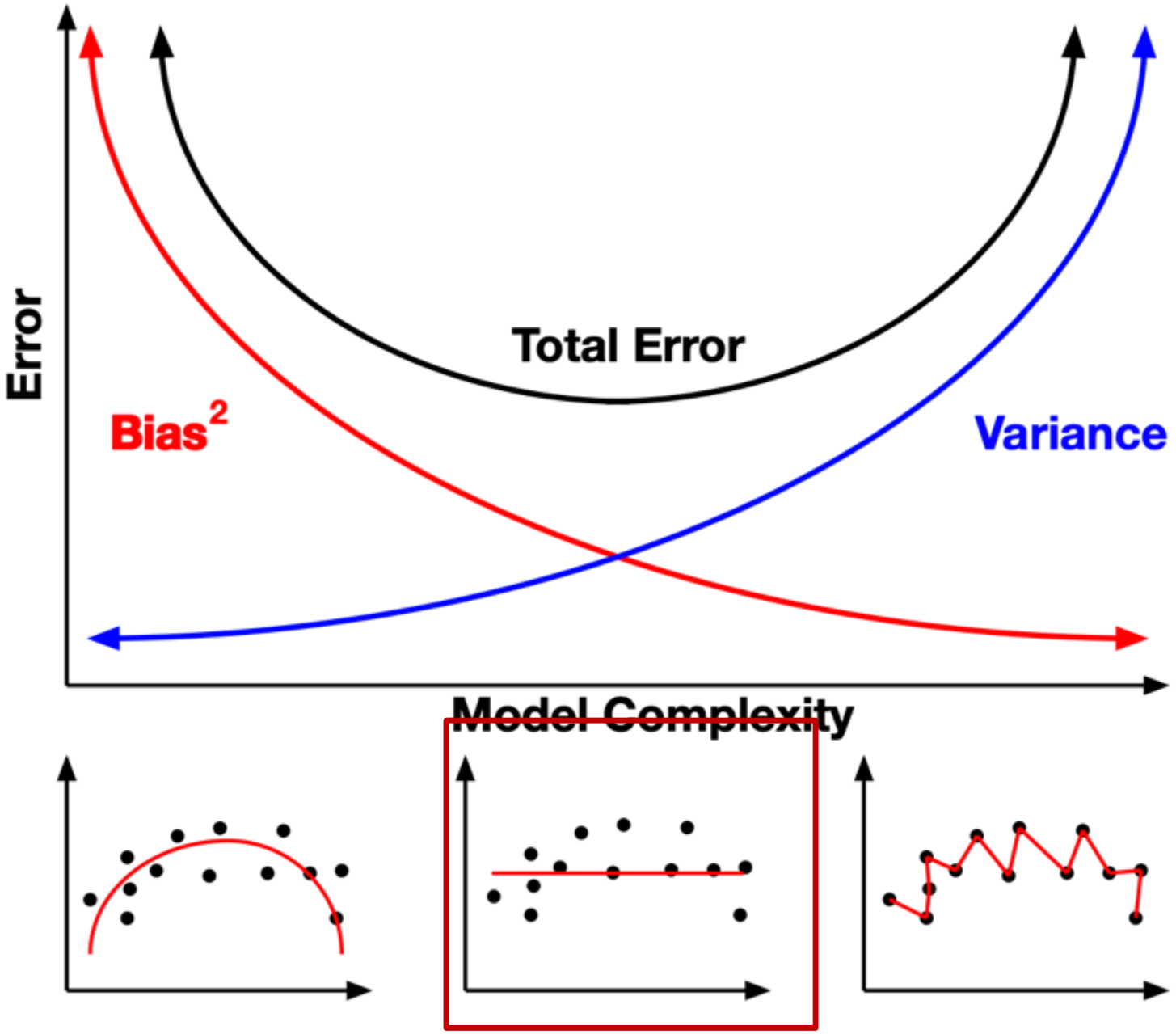
- However, too much data can lead to overfitting which also poorly predicts the desirable outcome.



More Data isn't Actually a Good Thing

- We can understand that too little data leads to underfitting data.
- However, too much data can lead to overfitting which also poorly predicts the desirable outcome.
- Validation studies are needed to find the sample size that is "just right"

Conclusions

- Fear over AI are driven by science fiction and also societal concerns of large transformative changes that could marginalize whole populations.
- This is not new, we've lived through the Industrial Revolution, Space Age, Computer Age, and now we are in Information Age (and beyond).
- However, we do have to understand and avoid overstating the promises of AI/ML. Clear examples in cancer diagnostics highlights potential pitfalls.
- Where AI/ML will immediately impact healthcare are in fundamental areas such as improvements in efficiency, safety, and serving as an adjunct (not replacement) to decision making.
- POCT is one area where AI/ML has value since device operators may have less experience than laboratorians.
- Recent studies show AI/ML could be used to enhance existing diagnostic tests for AKI.

Acknowledgements

Dr. Hooman Rashidi conducted the AI/ML modeling for the AKI study. We thank the UC Davis Burn Team for supporting the NGAL studies.

Questions?