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**Earlier Prediction of Patient Risk for Acute Kidney Injury**  
 Jared Jaeger, PhD  
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*presented at*  
**2018 ASCLS-Idaho Spring Convention**  
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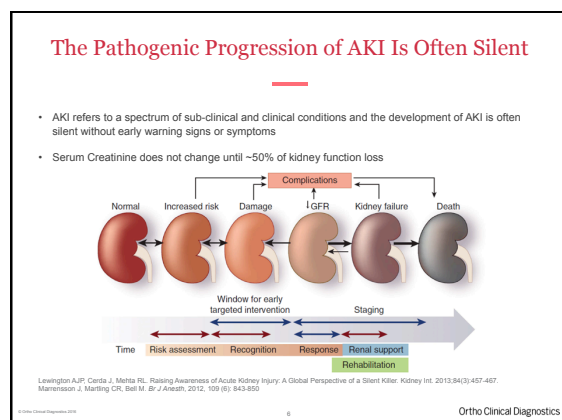
- Program Objectives**
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- Describe the importance and impact of acute kidney injury
  - Name a new diagnostic tool for prediction of acute kidney injury
  - Detail the implications of early acute kidney injury identification
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**Acute Kidney Injury:**  
A common but inappropriately managed condition with poor outcomes

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- Acute Kidney Injury & Current Diagnosis**
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- Per the 2012 KDIGO guideline, acute kidney injury (AKI) is defined as:
    - Increase in serum creatinine (sCr) by  $\geq 0.3$  mg/dl ( $\geq 26.5$   $\mu\text{mol/l}$ ) within 48 hours; or
    - Increase in sCr to  $\geq 1.5$  times baseline, which is known or presumed to have occurred within the prior 7 days; or
    - Urine volume  $< 0.5$  ml/kg/h for 6 hours.
  - AKI is further staged (stage 1-3) based on severity
  - The current AKI diagnosis relies largely on functional markers, which are not sensitive and often lead to a late or inaccurate diagnosis with adverse outcomes and high mortality
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### Acute Kidney Injury is Prevalent

- Acute kidney injury (AKI) is a common, under-recognized, but potentially reversible loss of kidney function that develops abruptly (over hours to days)
  - 7-18% of hospitalized patients developed AKI
  - Up to 50% of critically ill patients develop some stage of AKI
  - ~2 million AKI-related deaths annually worldwide
- Common causes include major surgery, sepsis, circulatory shock, nephrotoxic drugs, radiocontrast agent, etc.
- Estimated annual costs to US healthcare system attributable to hospital acquired AKI is > \$10 billion

Levingston A, P. Centa J, Mehta RL. Raising Awareness of Acute Kidney Injury: A Global Perspective of a Silent Killer. *Kidney Int.* 2013;84(3):457-467.  
 Mandelbaum T, Scott D, et al. Outcome of Critically Ill Patients with Acute Kidney Injury using the AKIN Criteria. *Crit Care Med.* 2011;39(12):2509-2514.  
 Ali T, Khan I, et al. Incidence and Outcomes in Acute Kidney Injury: A Comprehensive Population-Based Study. *J Am Soc Nephrol.* 2007;18(4):1292-1298.  
 Cherlow GM, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16:3368-3370.

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### AKI Development in Post-Surgical ICU Patients

Critically-ill surgical patients (n = 50,314 patients over 11 years)

39% developed AKI

61% no AKI

#### % Patients by AKI Severity

Hobson CE, et al. Cost and Mortality Associated With Postoperative Acute Kidney Injury. *Annals of Surgery.* 2014;00:1-8.

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### Incidence of AKI by Type of Cardiothoracic Surgery

- 43% of all cardiothoracic surgical patients had an episode of AKI during hospitalization

Type of Surgery	Mild AKI RIFLE-R (Risk) (n = 637; 22%)	Moderate AKI RIFLE-I (Injury) (n = 386; 13%)	Severe AKI RIFLE-F (Failure) (n = 242; 8%)
Bypass	328 (23%)	136 (10%)	58 (4%)
Valve surgery	151 (24%)	99 (15%)	66 (10%)
Aortic surgery	86 (18%)	92 (19%)	84 (18%)
Thoracic surgery	63 (16%)	49 (12%)	21 (5%)
Heart transplant	9 (26%)	10 (29%)	13 (38%)

Hobson CE, et al. Acute Kidney Injury is Associated with Increased Long-Term Mortality After Cardiothoracic Surgery. *Circulation.* 2009;119:2444-2453.

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### Contrast Induced-AKI

- Contrast volume is a key risk factor for contrast induced AKI (CI-AKI), especially if contrast is administered beyond the maximum acceptable contrast dose (MACD)

Brown JR, Rabb JF, Block CA et al. Does Safe Dosing of Iodinated Contrast Prevent Contrast-Induced Acute Kidney Injury. *Circ Cardiovasc Interv.* 2010;3:346-60.

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### Patients With AKI Have Higher Readmission Rates

- Patients not developing AKI after cardiac surgery had a 30-day readmission rate of 9.3% compared with patients developing AKI stage 1 (16.1%), AKI stage 2 (21.8%), and AKI stage 3 (28.6%, p < 0.001).

Brown JR, et al. Impact of postoperative acute kidney injury as a severity index for thirty-day readmission after cardiac surgery. *Ann Thorac Surg.* 2014;97(1):111-7.

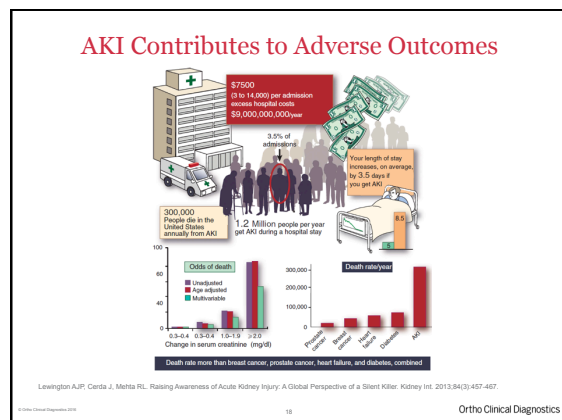
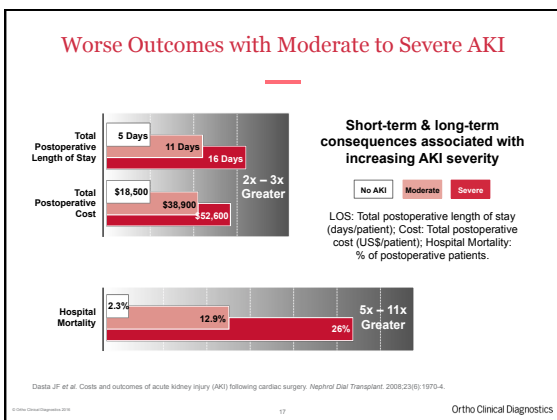
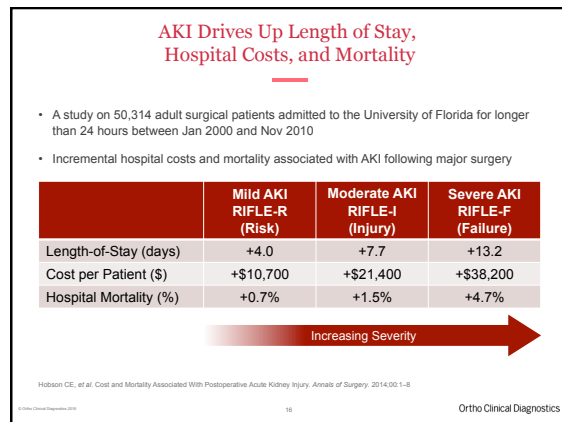
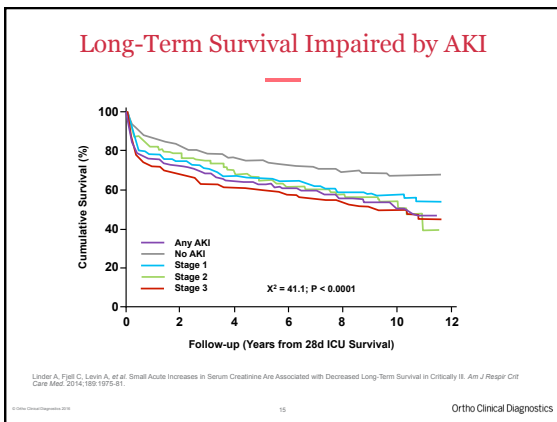
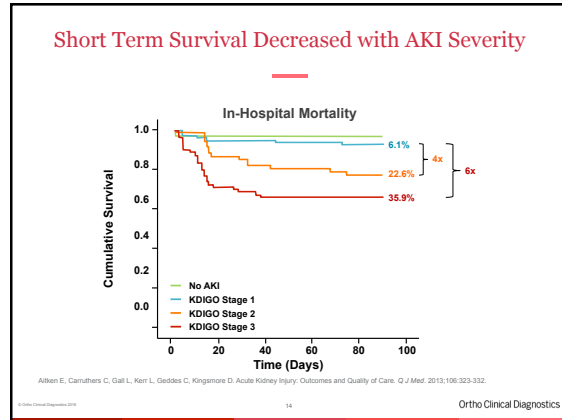
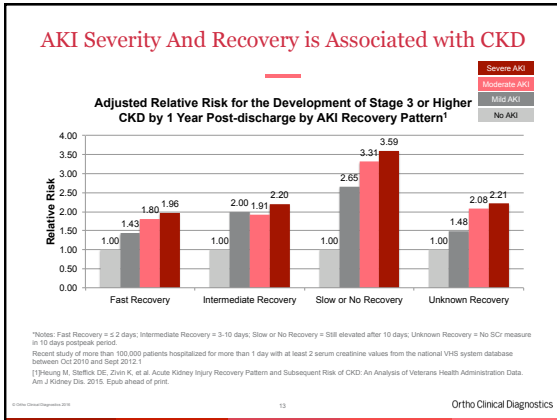
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### High Risk for AKI Survivors to Develop Chronic Kidney Diseases (CKD)

#### Rate of CKD Development Stage 3 and Higher by 1 Year Following Hospitalization

Huang M, Starfick DE, Zivin K, et al. Acute Kidney Injury Recovery Pattern and Subsequent Risk of CKD: An Analysis of Veterans Health Administration Data. *Am J Kidney Dis.* 2010; Equiv ahead of print.

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## Unmet Medical Needs in Managing AKI

## AKI is Often Poorly Recognized

- Study reports:
  - In a single hospital study with 1,500 cohorts, AKI was unrecognized in 23.5% of the patients
  - Another study of patients who died from AKI indicated:
    - 14% of all AKI cases were avoidable
    - 43% hospital acquired AKI had an unacceptable recognition delay
    - 54% had inadequate risk assessment for AKI
- The earliest reversible phases of AKI may often be missed
- Gaps exist in the care including delayed recognition, inadequate investigations, deficient monitoring, delayed and often flawed management & lack of follow-up

Altken E, et al. Acute Kidney Injury: Outcomes and Quality of Care. QJM. 2013;Jan 22.  
National Confidential Enquiry into Patient Outcome and Death. Adding Insult to Injury. 2009;1-98.  
Levington AJP, Cerda J, Matra RL. Raising Awareness of Acute Kidney Injury: A Global Perspective of a Silent Killer. Kidney Int. 2013;84(3):457-467.

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## AKI is Often Poorly Managed

- The 2009 NCEPOD Study reported:
  - Only 50% of patients who died from AKI received good care
  - Need improvements in risk assessment of AKI
- Another study with a cohort of over 1,500 patients revealed that:
  - 2 out of 3 patients with AKI were discharged without resolution in renal function
  - Significant weaknesses were found in the management of AKI including poorly kept fluid balance charts (48.2%), failure to adjust nephrotoxic drugs (38.2%) and to act on abnormal biochemistry results (41%).
- Delays in recognizing AKI will potentially lead to irreversible injury.

Levington AJP, Cerda J, Matra RL. Raising Awareness of Acute Kidney Injury: A Global Perspective of a Silent Killer. Kidney Int. 2013;84(3):457-467.  
NCEPOD. The National Confidential Enquiry into Patient Outcome and Death. Evidence & Emergency Surgery in the Elderly and Age-Old Patients. 2010.  
Altken E, et al. Acute Kidney Injury: Outcomes and Quality of Care. QJM. 2013;Jan 22.

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## There Is A Need for Better Assessment Tools


- Early recognition and management of patients at risk for AKI is crucial since there are no specific therapies to reverse established AKI
- There is a growing consensus that better diagnostic and predictive tools are needed to reduce the burden of AKI, particularly tools to provide earlier diagnosis of AKI, at stages where early intervention permits better patient results
- The identification of novel AKI biomarkers has been designated a top priority by the American Society of Nephrology.

KDIGO Clinical Practice Guideline. Kidney Inter. Suppl. 2012;2:1-138  
National Confidential Enquiry into Patient Outcome and Death. Adding Insult to Injury. 2009;1-98.  
Levington AJP, Cerda J, Matra RL. Raising Awareness of Acute Kidney Injury: A Global Perspective of a Silent Killer. Kidney Int. 2013;84(3):457-467.  
American Society of Nephrology Renal Research Report. J Am Soc Nephrol. 16:1886-1903. 2005.

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## New Markers for AKI Risk Assessment

The NEPHROCHECK® Test



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## The Discovery and Validation of Two New Markers

**Discovery Stage**  
340 proteins analyzed

TIMP-2 & IGFBP7 were the best two biomarkers

**Validation Stage**

[TIMP-2] + [IGFBP7] validated as the best biomarker

**Endpoint**

Within 12 hrs

Kaushal et al. Critical Care 2013, 17:R25

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### New Biomarkers for AKI Risk Assessment

**Diagram Description:** A schematic diagram of a nephron. It shows the afferent arteriole entering the glomerulus, where filtration occurs into Bowman's space. The filtrate then moves through the renal corpuscle and tubule. Reabsorption of solutes and waste occurs from the tubule back into the blood flow. Secretion of additional waste occurs from the blood flow into the tubule. Finally, the waste is excreted in the renal tubule.

- Tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7) are produced by renal tubular cells and are involved in G1 cell cycle arrest
- TIMP-2 and IGFBP-7 are known to be involved in the response to a wide variety of insults (inflammation, oxidative stress, ultraviolet radiation, drugs, and toxins) and are elevated in earliest stages of stress, which may explain why they correspond to risk of AKI.

Kellum JA and Chavakis LS. Cell cycle arrest and acute kidney injury: the light and the dark side. Nephrol Dial Transplant 2016;31(1):16-22.

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### TIMP-2 and IGFBP-7 Outperform Existing Biomarkers

**Forest Plot Data (Approximate AUC values):**

Biomarker	AUC (with 95% CI)
[TIMP-2]*[IGFBP-7]	0.82
Urine TIMP-2	0.78
Urine IGFBP-7	0.75
Urine NGAL	0.72
Plasma Cystatin C	0.68
Urine KIM-1	0.65
Plasma NGAL	0.62
Urine IL-18	0.60
Urine pi-GST	0.58
Urine L-FABP	0.55

**The AKIRISK Score is expressed as:**  

$$[\text{TIMP-2}] * [\text{IGFBP-7}] \text{ (ng/mL)}^2 / 1000$$

Kashani K, et al., Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Critical Care 2013, 17:R25

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### [TIMP-2]\*[IGFBP-7] Demonstrated a Compelling Specificity Profile

**Urine NGAL (ng/mL)**

**[TIMP-2]\*[IGFBP-7] ((ng/mL)<sup>2</sup> / 1000)**

**Chart Description:** Two bar charts comparing specificity profiles. The left chart shows Urine NGAL (ng/mL) and the right chart shows [TIMP-2]\*[IGFBP-7] ((ng/mL)<sup>2</sup> / 1000). Both charts compare various biomarkers across three patient groups: Reasons for ICU Admission (Acute Conditions), Chronic Conditions, and Maximum AKI Stage Within 12 h of sample collection. The [TIMP-2]\*[IGFBP-7] chart shows significantly higher specificity for the Maximum AKI Stage group compared to other biomarkers.

Kashani K, et al., Critical Care 2013, 17:R25

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### The NEPHROCHECK® Test Intended Use and Indications

The Astute Medical NEPHROCHECK® Test System is intended to be used in conjunction with clinical evaluation in patients who currently have or have had within the past 24 hours acute cardiovascular and or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment. The NEPHROCHECK® Test System is intended to be used in patients 21 years of age or older.

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### The NEPHROCHECK® Test System

**The NephroCheck® Test System**

**Intended Use:** The Astute Medical NephroCheck® Test System is intended to be used in conjunction with clinical evaluation in patients who currently have or have had within the past 24 hours acute cardiovascular and or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment. The NephroCheck® Test System is intended to be used in patients 21 years of age or older.

**Interpretation:**

Positive AKIRISK Score (> 0.3)	What It Means
Positive AKIRISK Score (> 0.3)	Patient could develop moderate to severe AKI in the next 12 hours of evaluation.
Negative AKIRISK Score (≤ 0.3)	Patient might not develop moderate to severe AKI in the next 12 hours of evaluation.

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### Case Studies: AKI Risk Assessment

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### Case Studies

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Clinical Trial

Case 1  
Case 2  
Cardiac Surgery Patients

Case 3  
Case 4  
Septic Shock Patients

Cases are from Astute-sponsored observational studies.  
Results from case studies are not predictive of results in other cases.  
Results in other cases may vary.

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### Case #1: 60 year-old male

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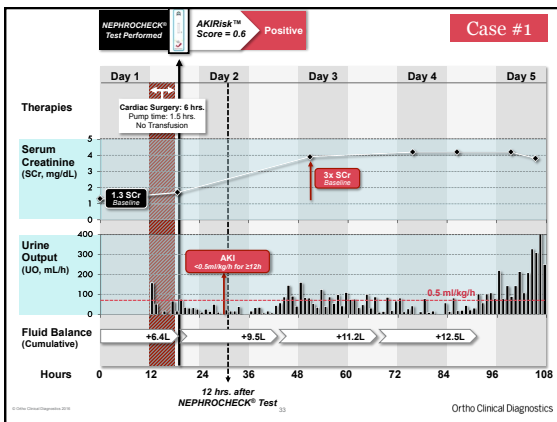
**Past History**

- Coronary Artery Disease
- Congestive Heart Failure
- Hypertension
- COPD
- Type 2 Diabetes Mellitus

**Current Condition**

- Cardiac Surgery Postop (Elective CABG & AVR)
- **Baseline serum creatinine (SCr) = 1.3 mg/dL @ time of enrollment**

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### Case #2: 54 year-old female

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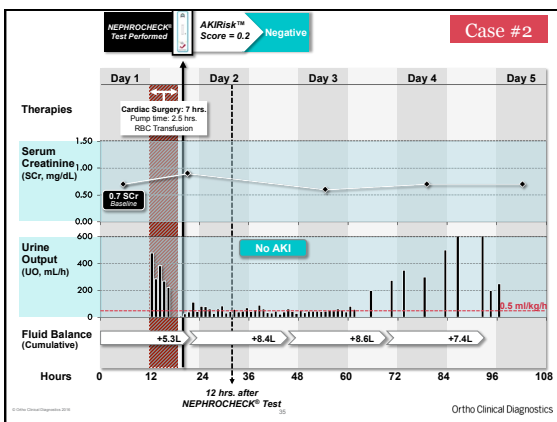
**Past History**

- Coronary Artery Disease
- Congestive Heart Failure
- Hypertension

**Current Condition**

- Cardiac Surgery Postop (Elective AVR & Pacemaker Insert)
- **Baseline serum creatinine (SCr) = 0.7 mg/dL @ time of enrollment**

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### Case #3: 59 year-old male

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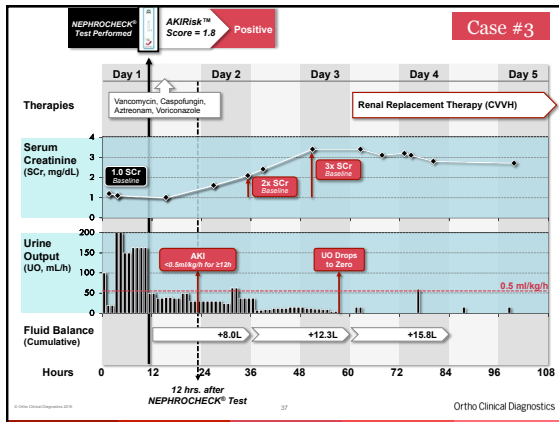
**Past History**

- Atrial fibrillation
- Diabetes Mellitus (DM)
- No chronic kidney disease (CKD)

**Current Condition**

- Pneumonia (PNA)
- Septic shock
- Respiratory failure (on ventilator)
- **Baseline serum creatinine (SCr) = 1.0 mg/dL @ time of enrollment**

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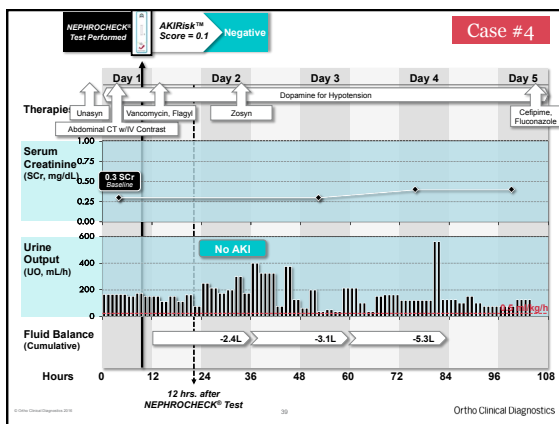
**Case #4: 66 year-old female**

**Past History**

- Peripheral vascular disease
- Carotid endarterectomy
- Femoral-femoral bypass
- Ilio-femoral bypass
- Carotid to subclavian bypass
- COPD
- Ischemic colitis
- Anemia

**Current Condition**

- Ischemic colitis
- Septic shock
- **Baseline serum creatinine (SCr) = 0.3 mg/dL @ time of enrollment**



So What?

**Enhance the Lab's Value**

- Educate?
- Make a difference?
- Impact patient care?
- Practical:
  - Budget, Capital Allocation, Staffing?
  - Rewarding place to work?

**Why is there an Opportunity ?**

- Specialization of Physicians
  - How well are physicians doing with test utilization initiatives?
  - Are different specialties collaborating?
  - Who is bringing them together?
- Affordable Care Act
  - New metrics for hospitals (readmissions, complication rates...)
  - Reimbursement penalties
  - More to come...

Source: <http://housedocs.house.gov/energycommerce/ppacacon.pdf>

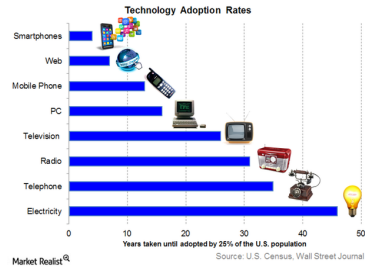
### How can labs become more relevant?

- Test Interpretation
- Test Utilization
- Test Selection
  - Implementation of new protocols – e.g., Sepsis protocol in ED
  - Impact of new medications and therapies on test selection
- Patient diagnostic algorithms
- Quality Initiatives
- Risk Management

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### New Technology Adoption Rate



\*Source:

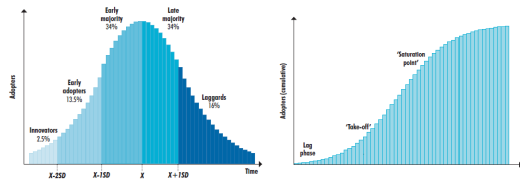
<http://finance.yahoo.com/news/tech-employment-tough-road-short-123550370.html>

Accessed February 2016

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### New Technology Adoption Curve



Where does your lab fit relative to technology adoption?

Source: World Health Organization 2010; WHO/HSS/EHT/DIM/10.6

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### Summary

- Acute kidney injury is a common but often inappropriately recognized and managed condition in hospitalized patients and is associated with higher patient mortality and morbidity as well as higher hospital and healthcare cost
- There is a growing consensus that better diagnostic and predictive tools are needed to reduce the burden of AKI, particularly tools to provide earlier diagnosis of AKI, at stages where early intervention permits better patient results

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### Summary

- Two urinary biomarkers (TIMP-2 and IGFBP-7) have been discovered in human observational clinical trials and are specifically corresponded to risk of AKI
- The NephroCheck® Test, which is based on the measurement of urinary TIMP-2 and IGFBP-7, is available as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours for patients 21 years of age or older

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### Questions?

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