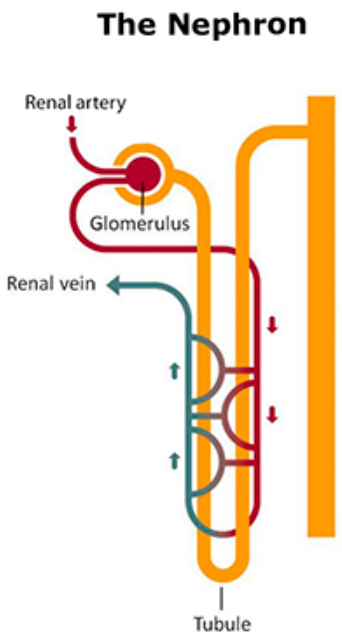
FDA Clinical Investigator Training Course:

Organ Toxicity: Kidney



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Drug-Induced Kidney Injury

A number of offenders

A range of mechanisms and manifestations

Drug development goals

- to ensure the safety of study subjects in clinical trials by enabling the detection of drug-induced kidney injury at an early and reversible stage
- to characterize a drug's risk of causing clinically significant kidney toxicity

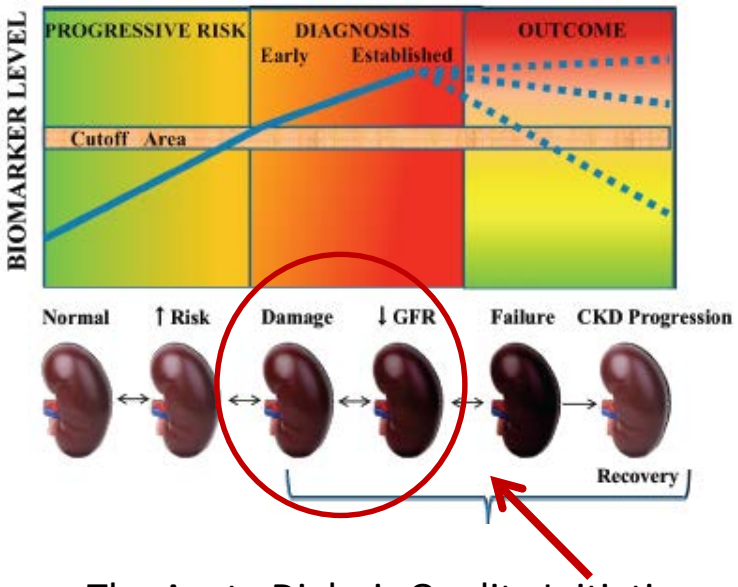
The traditional tool box

- *Blood:* serum creatinine, estimated glomerular filtration rate (eGFR, typically based on serum creatinine), sometimes serum cystatin C
- *Urine:* Urine protein:creatinine ratio, urine albumin:creatinine ratio, urine analysis and microscopy

The need for a better tool box

Creatinine's limitations as a biomarker of kidney injury

Neither sensitive…



Source: The Acute Dialysis Quality Initiative; http://www.adqi.org/

Nor specific…

Drugs can affect the tubular secretion of creatinine

-cimetadine, trimethoprim, pyrimethamine, cobicistat, etc.

Drugs can also have hemodynamic effects on renal function that may not reflect injury

-ACEIs, ARBs, diuretics, etc…

The quest for a better tool box

Requestor	Qualified Biomarker(s)	Biomarker Description	Abbreviated COU
Predictive Safety and Testing Consortium (PSTC), Nephrotoxicity Working Group (NWG)	Albumin, β2-Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, and Trefoil factor-3	Urinary nephrotoxicity biomarkers as assessed by immunoassays	Safety biomarker to be used with traditional indicators to indicate renal injury in rat
Critical Path Institute's Predictive Safety Testing Consortium Nephrotoxicity Working Group (CPATH PSTC-NWG), and Foundation for the National Institutes of Health's Biomarker Consortium Kidney Safety Biomarker Project Team (FNIH BC-KSP)	clusterin (CLU), Cystatin-C (CysC), Kidney Injury Molecule-1 (KIM-1), N-acetyl-beta-D-glucosaminidase (NAG), Neutrophil Gelatinase-Associated Lipocalin (NGAL), and osteopontin (OPN)	Urinary nephrotoxicity biomarker panel as assessed by immunoassays	Safety biomarker panel to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers

https://www.fda.gov/drugs/cder-biomarker-qualification-program/list-qualified-biomarkers

Closing Comment

- **No one size fits all** for: monitoring for drug induced kidney injury; setting exclusion criteria; or defining stopping rules for study drug administration to mitigate risk
- **If there is concern that a drug may cause kidney toxicity** *(based on preclinical data, experience with the larger pharmacologic class or a signal that emerges during drug development):*
  - Work with an expert in drug-induced kidney injury to optimize the design of your development program to mitigate risk to study subjects and adequately characterize the risk
  - Include such an expert on the Data Safety Monitoring Board overseeing your trial(s)