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The Development of Urinary Biomarkers for Kidney Disease Is the Search for Our Renal Troponin

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The practice of nephrology is long recognized to treat and comfort on the basis of a blend of science and art. As nephrologists, we do an amazing job of monitoring kidney function with rather rudimentary measures such as serum creatinine and urine output. When patients ask what are the "normal" values for each of these measures, we all answer in a similar and somewhat nonspecific manner reflecting the "art" of interpretation: What is normal creatinine? Answer: It is like golf: High

is bad, low is good. What is a normal amount of urine? Answer: Depends on how much you drank and ate.

The new field of biomarkers for kidney injury or disease is an exciting and rapidly advancing scientific area. Recent developments in the study of several urinary biomarkers of kidney injury have focused on NGAL, NAG, and KIM-1. Two articles in this issue of *JASN* are part of a growing literature that will shift the balance between the art and science of understanding—shifting toward new evidence that anticipates changes in kidney function more reflective of better science.[1,2] As we read this rapidly growing literature and seek out our "renal troponin," we can take a lesson from our cardiology colleagues: Our ultimate goal is to identify patients with a clinical syndrome earlier to initiate promptly a therapy that ultimately affects outcomes in a more positive way. It is these last two points that will be essential in prioritizing our future research agenda.

The new study by Siew et al.[1] provides data to support the use of urinary NGAL as a predictor of acute kidney injury (AKI) in the intensive care unit. More than 400 critically ill patients in intensive care were enrolled, had urinary NGAL measured, and were followed prospectively to identify those with AKI defined as an increase in serum creatinine of >0.3 mg/dl or 50%. Median values of urinary NGAL were significantly higher on enrollment in patients who experienced AKI during the subsequent 48 h (190 *versus* 57 ng/mg; $P < 0.001$).

The new study by Paragas et al.[2] also provides data to support the ability of urinary NGAL to discriminate among different types of kidney disease in patients with HIV infection. Patients with HIV-associated nephropathy had significantly greater values of urinary NGAL than those with HIV without chronic kidney Disease (CKD), those with HIV and CKD (not HIV-associated nephropathy), and those with a variety of non-HIV glomerular lesions. The choice of multiple comparison groups allows the reader to consider the effect of HIV infection, CKD, both, or neither and the multiple types of kidney diseases in relation to the level of urinary NGAL.

Although these new studies will play a foundation role in the future validation of these biomarkers, they are not without limitations. Minor methodologic issues can be discussed, such as the use of a dichotomized outcome of AKI. Although the definition is widely accepted and common in the literature, arguably, AKI exists on an exaggerated spectrum from the damage of a single tubular cell to acute cortical necrosis. Underscoring this continuum is a recent article examining NGAL and other urinary biomarkers after cardiac surgery.[3] In that study, regardless of whether the patient was considered to have or have not experienced AKI (using the same definitions used by Siew et al.[1]), a rise from the baseline value with subsequent fall back to baseline was seen over time. Stated another way, even patients without any significant change in creatinine experienced a rise and fall in their urinary NGAL. In the study in this issue of *JASN*, there were also statistical differences in *mean* peak concentrations of NGAL between those with and without AKI.[1] Furthermore, it is clear that considerable overlap exists in the ranges of NGAL for groups with and without

AKI. This strongly suggests that considerably milder degrees of AKI, including those that cannot be detected with serum creatinine, may result in a rise in NGAL. This overlap is also present in the article by Paragas et al.[2] examining HIV in relation to kidney disease.

These limitations help to frame the challenges that we as a renal community will experience as we seek to validate these biomarkers and implement their use in a way that cardiologists use troponin. First, we must be very careful to approach the development of these biomarkers as a way to augment rather than replace the rather familiar tools of serum creatinine and urine output in detecting new clinical presentations of renal injury such as AKI. We might consider the analogy of how troponin measurements do not replace the electrocardiogram in acute coronary syndrome. Second, we need to validate the level of biomarker elevation that is truly clinically significant. As we examine the literature, clearly we will have increasingly more sensitive abilities to identify patients with subclinical or exceptionally mild disease. With continued research in the development of biomarkers will come the increasingly important task of defining the relevant thresholds for elevation above which therapy should be instituted or additional diagnostic tests triggered. Finally, we need to prioritize studies in which treatment of the patient will be affected and early knowledge of the disease or injury will benefit outcome. Hopefully, the development of strategies to treat AKI more actively and successfully will soon follow the discovery of how to diagnose AKI earlier and earlier.

The second application, as explored in the article by Paragas et al.,[2] may have a more immediate impact. Our ability to differentiate between particular histologic lesions using urine studies rather than biopsy will represent a major leap ahead in the early initiation of therapy for CKD. Our subsequent ability to follow disease activity and success of treatment using these biomarkers rather than urine sediment or serial biopsies will also need to be demonstrated, and when that time comes, there will be a major advantage in the monitoring and modulation of therapies.

Before we adopt these biomarkers in such a role, we must not forget that these urine studies are actually intermediate outcomes. They will need to be validated in the rigorous manner as outlined by the McMaster criteria.[4] Although they clearly correlate with the event of interest, we must further understand how a change in their measure represents a change in the event under study. This may seem a daunting task, but if the cardiologists can do it with troponins, then so can we.

DISCLOSURES
None.

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Does Idiopathic Hypercalciuria Trigger Calcium-Sensing Receptor–Mediated Protection from Urinary Supersaturation?

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Kidney stone formation is common, affecting 5 to 6% of the American adult population, and highly recurrent. Approximately 70% of stones are composed predominantly of calcium oxalate (CaOx) with small amounts of calcium phosphate (CaP); another 10% are largely CaP. The physicochemical requirement for stone formation is supersaturation of urine with respect to the stone minerals. In the case of calcium stones, supersaturation is driven by urine calcium concentration, which is a function of calcium excretion and urine volume. For CaP, supersaturation is also controlled by urine pH, because solubility of this salt decreases as urine pH rises; CaP stones are seen largely in patients with urine pH >6.

Biopsies of renal medullary papillae of stone formers, taken during percutaneous nephrolithotomy, demonstrate that stone formers are also characterized by specific patterns of mineral deposition in tissue. Common idiopathic CaOx stone formers have interstitial deposits of CaP in the medullary interstitium, so-called Randall's plaques, which begin in the thin loops of Henle and extend downward toward the base of the