Clinical Chemistry 60:2
294–300 (2014)

Biomarkers for Acute Kidney Injury: Where Are We Today? Where Should We Go?

Moderator: John C. Lieske[1,2*]
Experts: Lakhmir Chawla,[3,4] Kianoush Kashani,[5] John A. Kellum,[6] Jay L. Koyner,[7,8] and Ravindra L. Mehta[9]

Acute kidney injury (AKI)[10] is an important health problem. Patients who develop AKI have markedly increased in-hospital mortality, and they have an increased likelihood of morbidity and mortality over the long term even if they do survive. Current treatments focus on supportive care and avoiding the potential for injury, such as from nephrotoxic drugs and intravenous contrast agents. Potentially more-specific therapies have been identified with animal models, but they have not demonstrated efficacy in subsequent human clinical trials, in part because AKI is difficult to identify before there is loss of organ function, at which point the damage may be irreversible. Therefore, there has been much interest in the development of biomarkers for identifying AKI in its earliest stage, when interventions might be more successful. There is also keen interest in stratifying the patients at greatest risk for AKI so that preventive treatments can be initiated in a timely fashion. In this Q&A, 5 researchers with vast clinical experience in AKI and biomarker development discuss the current status of the field (for suggested readings on this topic, see the Data Supplement that accompanies the online version of this Q&A at http://www.clinchem.org/content/vol60/issue2).

What aspects of AKI do you study?

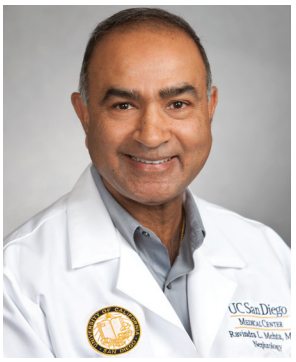
Lakhmir Chawla: I am involved in the study of inflammation and AKI, AKI biomarkers, AKI risk prediction, AKI as a cause of chronic kidney disease (CKD), and AKI therapeutics.

Kianoush Kashani: I am currently working on risk stratification models for prediction of AKI, novel biomarkers of early detection of AKI, derivation and validation of a renal angina model, and development and validation of electronic surveillance tools for early detection of AKI.

[1] Professor of Medicine, Division of Nephrology and Hypertension, and [2] Director, Renal Testing Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [3] Associate Professor of Anesthesiology and Critical Care Medicine and [4] Associate Professor of Medicine, George Washington University, Washington, DC; [5] Assistant Professor in Internal Medicine, Division of Nephrology and Hypertension, Division of Pulmonary and Critical Care, Mayo Clinic, Rochester, MN; [6] Professor, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA; [7] Director, Inpatient Renal Replacement Therapy, and [8] Assistant Professor of Medicine, Section of Nephrology, University of Chicago, Chicago, IL; [9] Professor of Clinical Medicine and Associate Chair for Clinical Research, Department of Medicine, UCSD Medical Center, San Diego, CA.
* Address correspondence to this author at: Division of Nephrology and Hypertension, Mayo Clinic, 200 First St. SW, Rochester, MN 55905. Fax 507-266-9315; e-mail lieske.john@mayo.edu.
Received April 27, 2013; accepted May 21, 2013.
[10] Nonstandard abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; PICARD, Progress to Improve Care in Acute Renal Disease; ADQI, Acute Dialysis Quality Initiative; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease: Improving Global Outcome (group); NGAL, neutrophil gelatinase-associated lipocalin; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; L-FABP, liver fatty acid–binding protein; TIMP-2, tissue inhibitor metalloproteinases inhibitor-2; IGFBP7, insulin growth factor–binding protein-7; FDA, US Food and Drug Administration; TRIBE-AKI, Translational Research Investigating Biomarker Endpoints-AKI (study); EARLY-ARF, Early Intervention with Erythropoietin Does Not Affect the Outcome of Acute Kidney Injury (trial); EMEA, European Medicines Agency.

John Kellum: I am interested in all forms of AKI, but mainly those that arise as a consequence of critical illness—so sepsis-induced AKI is at the top of the list. I study the epidemiology and pathophysiology of AKI and evaluate novel markers and therapeutics in both animals and humans.

Jay Koyner: My work has focused on the investigation of novel biomarkers of AKI with the goal of diagnosing AKI before a significant increase in serum creatinine or a decrease in urine output, the currently accepted gold standards. Thus, I have prospectively followed patients undergoing cardiac surgery or in the setting of critical illness [intensive care unit (ICU) admission], attempting to determine if biomarkers can forecast who will have more-severe/more-progressive AKI at the time of clinical AKI (increased serum creatinine).



Ravindra Mehta: I have been interested in the epidemiology, treatment, and outcomes of AKI in critically ill patients. My areas of research have focused on defining the natural history of AKI in ICU patients through the Progress to Improve Care in Acute Renal Disease (PICARD) prospective observational cohort study, an assessment of nondialytic and dialytic interventions and the influence of process of care on patient outcomes. As a founding member of the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN), I have been involved in the development of the RIFLE and AKIN diagnostic and staging criteria for AKI and their subsequent refinement through the Kidney Disease: Improving Global Outcome (KDIGO) group. In collaboration with the University of Alabama in Birmingham, we have established a National Institutes of Health–funded O'Brien Center for AKI research that provides investigators core resources for clinical and translational research. Utilizing this core resource, we have developed an international prospective registry of AKI in the ICU patients that has enrolled over 1000 patients from 17 centers across the world. We have also studied the epigenetic changes associated with recovery from AKI and provided assays for various AKI biomarkers. I am currently the principal investigator on an international multicenter prospective study evaluating the potential genetic contribution to drug-induced kidney injury with a genomewide association study approach.

What do you see as the most important recent advances in the care of patients with AKI? What are the greatest areas of need?

Lakhmir Chawla: The first and most obvious are the discovery and validation of multiple AKI biomarkers that have the capacity to improve the time to diagnosis of AKI and offer insights related to the severity, prognosis, and recovery of AKI. A second important insight is the fact that patients who suffer from AKI are at risk for the future development of CKD. While this connection remains a strong association, multiple putative injury pathways have been demonstrated, and my personal bias is that this is likely causal. A third important advance is the clinical trials of renal replacement therapy dosing in patients with severe AKI. Multiple large clinical trials have helped determine the appropriate dose range that should be used to treat the vast majority of patients with AKI.

Kianoush Kashani: There is good and bad news. The bad news is that there has not been any major breakthrough in the treatment of AKI, and, indeed, most interventions to avoid progression of AKI have been very disappointing.

The good news is that amongst scientists, clinicians, and patients, the awareness of AKI has significantly improved within the last decade. The volume of studies focused on AKI has significantly increased, and this has created more opportunities to advance the science. A large number of clinicians in multiple specialties and subspecialties consider AKI a serious adverse event, and many have implemented protocols to comply with consensus recommendations, including the KDIGO guidelines.

Community involvement and professional and political will are all required to increase the awareness about the gravity of this entity and the desire to mitigate the problem. In my opinion, the road to improvement in the care of patients with AKI includes but is not limited to the following actions:

1. Invent and discover novel tools and biomarkers of early detection of AKI,
2. Design and conduct large-scale studies on prophylactic and therapeutic interventions for AKI,
3. Develop biomarkers of AKI recovery to be able to monitor the response to the above-mentioned interventions, and
4. Continue large-scale epidemiological studies to evaluate the extent of impact generated by the above-mentioned interventions.

John Kellum: The first major advance is that we now have a consensus regarding what AKI is and how it should be defined. We now recognize that small changes in renal function can herald significant pathology that can have long lasting consequences. This is a huge advance over where we were just a decade ago. This advance has allowed for much better epidemiology of AKI and identification of conditions that cause it. In turn, this has opened up new avenues of research as to the mechanisms underlying AKI, and this, we hope, will lead to new therapies. The second major advance concerns the discovery of new biomarkers of AKI. These markers permit earlier recognition and even risk stratification for AKI. Next, we need to harness these advances to discover therapies that can prevent AKI, mitigate the damage, and/or enhance recovery.

Jay Koyner: The international acceptance of consensus definitions of AKI amongst nephrologists, intensivists, and health professionals has advanced our knowledge of the epidemiology, natural history and long-term outcomes of those with AKI. These definitions have (1) standardized AKI research, (2) paved the way for the recent explosion of biomarker studies, (3) informed our understanding of volume overload in the setting of AKI, and (4) led to the understanding that episodes of AKI have long-term deleterious consequences for a patient's renal function. However, despite these advances, those with AKI still suffer from a relative lack of effective prophylactic and therapeutic treatment options. By and large, patients with AKI are treated with supportive measures (e.g., acute dialysis, avoidance of nephrotoxins, maintaining adequate renal perfusion), and this care has essentially been unchanged over the last 10 years. While large randomized multicenter trials have answered questions about the dose of dialysis in the setting of AKI, we still do not have evidenced-based answers for the optimal timing of dialysis initiation or if there is a benefit from specific dialysis modalities. Patients with AKI desperately need therapeutic options that will treat their underlying tubular injury/dysfunction, rather than supportive measures that simply control their fluid balance and fix their deranged electrolytes.

Ravindra Mehta: The availability of standardized diagnostic and staging criteria for AKI, which have now been validated worldwide in multiple settings, has established the existence of a high disease burden linked to adverse outcomes. Studies have demonstrated large gaps in the recognition, management, and follow-up of patients with AKI. These findings have prompted an urgent need for raising awareness of AKI worldwide and for the development of practical strategies for early recognition and effective response to improve outcomes for this disease. Considerable progress has occurred in our understanding of the basic mechanisms and pathways of AKI, which have been facilitated with advances in technology. Preclinical studies have provided guidance for the development of specific biomarkers of kidney damage and established potential targets for therapeutic interventions. Several kidney-specific biomarkers have been tested in prospective studies; however, they have not been incorporated in the routine clinical management of AKI patients. Biomarker utilization has been hindered by several factors, including regulatory issues limiting availability in some countries, lack of standardized assays, identification of the best biomarkers for each purpose (risk assessment, diagnosis, determination of cause for differential diagnosis and prognosis), and the recognition that the thresholds may be different in each setting, particularly when there is underlying CKD. It is likely that further advances in AKI management will require incorporation of sensitive and specific biomarkers to enhance recognition and early and effective response for disease management.

What biomarkers show the greatest promise for detecting AKI?

Lakhmir Chawla: A large host of biomarkers have been identified that appear to detect AKI earlier than serum creatinine and urine output. It should be mentioned that multiple new biomarkers currently in development appear to have promise as well. Of the biomarkers that have been established in large cohorts, 6 have shown the most promise: neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule 1 (KIM-1), liver fatty acid–binding protein (L-FABP), tissue inhibitor metalloproteinase inhibitor 2 (TIMP-2), and insulin growth factor–binding protein 7 (IGFBP7). Each of these biomarkers has shown promise in various facets of AKI management. Unfortunately, at this time none of these biomarkers has gained US Food and Drug Administra-

tion (FDA) approval, and consequently the biomarkers remain unavailable in the US for clinical use.

Kianoush Kashani: Within the last decade, many biomarkers of AKI have been discovered and studied. Some of the markers obviously perform better than others in the early detection of AKI. Most of these markers were found not to be very specific for AKI in follow-up studies. In my opinion, an ideal AKI biomarker should have the following characteristics:

1. It is syndrome specific. For example, if a marker is to detect AKI, it should not show signals in CKD.
2. It is disease specific so that it can be used in differential diagnosis. For example, markers should be able to distinguish AKI due to tubular injury from glomerular injury or interstitial disease.
3. It needs to be adequately sensitive to the injury. Its sensitivity should be clinically relevant; that is, it should not be so sensitive that it identifies injuries that are not clinically important. On the other hand, it should be sensitive enough to allow detection of clinically significant AKI.
4. A marker is useful when it can estimate the extent of the damage.
5. It needs to be identifiable early in the course of AKI progression so that it can be used for identification of patients who may benefit from early preventive or therapeutic intervention.
6. Not only should the ideal marker show signals early during the injury, but its concentration should also decline after the injury has subsided or the underlying process has been removed.
7. It needs to be able to predict short- and long-term outcomes of AKI, including the need for renal replacement therapy and quality-adjusted life-years.
8. Low turnaround time is particularly essential in early detection of AKI. Point-of-care measurement of markers with low coefficients of variation would be ideal.
9. The marker needs to be easy to measure.
10. Measurement cost should be reasonable.

Unfortunately, none of the available biomarkers have all of the above-mentioned criteria. Particularly among the adult patient population with other comorbidities, the function of the available biomarkers is poor. NGAL is one of the most studied biomarkers of AKI. This marker has an excellent function in the pediatric population after timed injury (cardiopulmonary surgery). However, its performance in adult patients with other comorbidities is not as robust. KIM-1, IL-18, and L-FABP are other well-studied biomarkers that have the same limitations as NGAL. Recently, 2 novel biomarkers, IGFBP7 and TIMP-2, were validated in a large-scale trial. These markers reflect arrest in the cell cycle G_1-to-S transition. In this study, the sensitivity and specificity of a panel of these markers were good. However, before any final judgment, these results need to be replicated in other, independent studies.

John Kellum: Biomarkers are not just about detecting AKI—indeed, once damage has occurred we've already lost part of the battle. The first role for biomarkers is to aid in risk prediction, to tell us which patients should be monitored closely and in which patients we should consider more expensive but safer treatment options. For this indication, I believe, new markers like TIMP-2 and IGFBP7 are clearly helpful. Next, we would like to know if a patient with reduced renal function has AKI and whether a patient with AKI will progress or renal function will recover. NGAL appears to have value in this space, as does KIM-1. KIM-1 may also be very helpful in detecting early renal injury from drugs and toxins. Finally, all of these markers may identify patients who have sustained some degree of subclinical AKI and may be at risk for progression.

Jay Koyner: Several biomarkers have shown tremendous promise, so it is hard to single out just one. Some have shown promise in the early detection of AKI following cardiac surgery (plasma NGAL, urine IL-18), while others have demonstrated the ability to detect AKI in the setting of critical illness (urine cystatin C, TIMP-2, and IGFBP7) and others have shown the ability to predict AKI progression at the time of clinical AKI (plasma NGAL, urine microalbumin). Serum creatinine has been the sole marker to detect AKI for so long that perhaps some physicians may have the misguided notion that, in the future, only 1 novel biomarker will be needed to detect AKI. However, in the near future physicians will likely use a panel of biomarkers (traditional and novel) to diagnose AKI, with different combinations excelling in certain clinical settings (sepsis, cardiac surgery, nephrotoxin) as well as at different clinical time points (in the emergency room, time of ICU admission, onset of clinical AKI).

Ravindra Mehta: This will depend on what criteria are used for diagnosing AKI. Currently, the detection of AKI is based on establishing a functional change, either through a change in urine output or an increase in serum creatinine. Over the last few years, the biomarker field for AKI has rapidly expanded with the identification of different molecules emanating from the injured kidney or reflecting altered kidney function. These molecules have ranged from constitutive proteins released by the damaged kidney (e.g., α and π glutathione *S*-transferases, L-FABP) to molecules upregulated in response to injury (e.g., KIM-1 and NGAL) or nonrenal tissue products that are filtered, reabsorbed, or secreted by the kidney (e.g., cystatin C).

I believe that each of these biomarkers will have role in detecting AKI, depending on the context. For instance, oliguria is a sensitive and specific marker of AKI but will likely have value only when there is accurate monitoring of urine flow, e.g., in an ICU with an indwelling Foley catheter and consistent recording of the data. Similarly, while urinary NGAL may be increased earlier than serum creatinine, it may not be as specific in the setting of a pyelonephritis. At the current time, all of the damage and functional markers have promise; however, they need much more extensive evaluation before being considered as a substitute for current criteria.

How do you envision clinicians using biomarkers in the care of patients with AKI?

Lakhmir Chawla: AKI biomarkers will be used in 3 different phases of AKI: early diagnosis, early prognosis assessment, and recovery.

Kianoush Kashani: Instead of reinventing the wheel, we can adopt what has been done by other subspecialties to improve the chance of success in implementation of biomarkers.

Oncologists use a panel of genetic markers to make a decision on the nature of each cancer and design a target-specific treatment plan. This has resulted in significant improvement in the treatment of cancer patients in recent years. The available functional and injury markers of AKI, and the ones that will be discovered in the future, could be used in such a fashion. Each marker potentially represents one or more mechanisms during the injury and/or recovery. The sum of information gained by the panel of markers can potentially be more meaningful than relying on markers separately. We can create a map of the injury process, and using marker panels can place each patient in the appropriate location on this map. This would allow us to design a focused and individualized care plan for each patient with AKI.

Cardiologists have used biomarkers of myocardial injury to plan for appropriate and early interventions to preserve myocardial mass. They have been able to collaborate with emergency room physicians, intensivists, and other care providers to measure and report these markers. To be able to use AKI biomarkers in a more efficient way, we need to collaborate with other care providers to utilize the markers in patients who have a high risk for AKI. Cardiologists use their biomarkers after initial risk-stratification processes. Indeed, any use of biomarkers in low-risk patients would be associated with increased cost with no value added.

John Kellum: Whenever clinical uncertainty exists. Sometimes AKI is obvious, and one doesn't need a biomarker. Often, however, we are faced with clinical uncertainty. Take, for example, a patient with oliguria who has responded to fluids. Has the risk of AKI been mitigated, or will the creatinine rise over the next 6–12 h? Can such patients safely be discharged, or should they remain in a monitored environment? What about a patient presenting with an increased creatinine? Will the patient progress, or will renal function improve? Is this a case of AKI or CKD or both? What is the prognosis? Biomarkers may also address the etiology of AKI and help guide clinical decision-making that way.

Jay Koyner: Physicians will utilize biomarkers to diagnose AKI before there are changes in traditional markers, such as urine output and serum creatinine. Additionally, biomarkers may be used to help prognosticate long-term clinical outcomes, including the risks of inpatient mortality and of developing post-AKI CKD. Biomarkers at the time of clinical AKI (once creatinine is already increased or the urine output has already dropped) will be used to differentiate those with volume-responsive AKI (e.g., from renal hypoperfusion) from those with true intrarenal tubular injury (e.g., acute tubular necrosis from renal ischemia); this is not currently possible with serum creatinine and urine output. Finally, a quick check of ClinicalTrials.gov demonstrates several studies that utilize biomarker values in conjunction with clinical factors to enroll/stratify subjects in therapeutic trials investigating novel and previously tested treatment options.

Ravindra Mehta: Since AKI has a wide spectrum of manifestations, ranging from unrecognized alterations in serum creatinine to anuric renal failure, the clinical context and setting strongly influence the natural history of the disease. Biomarkers can be used for risk assessment, diagnosis and staging, differential diagnosis, predictive value for prognosis for recovery of renal function or progression, and establishing appropriate time points for intervention. It is highly unlikely that a single biomarker will fulfill all these needs; however, individual biomarkers may be well suited for a specific purpose. I believe that the optimal utilization of biomarkers will require a combination of markers of functional change and kidney damage to characterize the underlying state of kidney health that represents changes in function or damage, alone or in combination. The magnitude of change could inform the underlying severity. For instance, measurement of NGAL or KIM-1 along with serum creatinine following exposure to a nephrotoxic antibiotic may demonstrate initial changes in the damage markers alone without changes in serum creatinine. This may represent a subclinical early phase of injury that could progress to a

functional change. Alternatively, in a dehydrated patient who is oliguric, serum creatinine may be increased without increases of NGAL or KIM-1, suggesting a functional change that is potentially reversible. Sequential measurements would further define disease progression or resolution and guide interventions. However, biomarker-based management will require correlating the data with the clinical context and associated concomitant events to improve management. Which damage and functional biomarkers would work best for each purpose (risk assessment, diagnosis, differential diagnosis, or prognosis) will need to be defined in well-designed large prospective clinical studies. For instance, the recent identification of 2 biomarkers associated with cell cycle arrest performed better than NGAL and KIM-1 in predicting progression in severity. I envision that the clinical utilization of biomarkers will be incremental and will be guided by physician experience in specific settings and will benefit from a standardized approach.

What are the major obstacles to the development and use of AKI biomarkers?

Lakhmir Chawla: The major limitation in the US is availability. In addition, in order for these biomarkers to be widely used, the issues regarding platform and cutpoint values need to be addressed. Different laboratory platforms often generate slightly different results. In order for clinicians to have confidence in the markers, these logistical issues will need to be addressed. Fortunately, this process is under way in Europe and Japan, and as various companies complete their validation studies, we should have availability in the US within 12–18 months for some of these biomarkers.

Kianoush Kashani: There are many reasons that the field of AKI is not as advanced as for other diseases, including:

1. A false perception exists in the medical community regarding the lack of need for AKI biomarkers.
2. Until recently, clinicians had no specific definition of AKI.
3. Only in the past decade has the medical community realized that the kidney is one of the vital organs that, if injured, can independently increase mortality and morbidity.
4. The management of advanced AKI is very effective; that is, renal replacement therapy can maintain the metabolic milieu of the body in the case of severe kidney injury.
5. The clinical implementation of biomarkers needs a change in management to achieve a culture shift; this will require time and entail cost.
6. Currently, there is no effective treatment for AKI. Therefore, large numbers of clinicians question the need for AKI biomarkers.
7. In the majority of AKI cases, there is no biopsy sample available to compare tissue damage with biomarker concentrations.
8. The mechanism of AKI and its recovery are very complex, and pinpointing a single molecule may not represent the whole picture.
9. Most AKI biomarkers are not kidney or disease specific.
10. In the majority of cases, AKI biomarkers are compared with an AKI definition based on functional markers, such as serum creatinine and urine output. However, not all kidney injuries are associated with functional changes, and not all functional changes result from AKI. Therefore, it seems we are comparing apples to oranges.

John Kellum: Actually, the field has moved pretty quickly. It's very helpful that we have access to urine, which is very close to the site of action in the tubules. So, the markers we have are actually very good. The next required step, though, is education. We need to teach clinicians how to use these markers, and to do that we need a better understanding of exactly what they tell us. Studies evaluating the ROCs of the markers are too limited, and an ROC curve is not the be-all and end-all.

Jay Koyner: Countless small and several large-scale multicenter studies have been published [Translational Research Investigating Biomarker Endpoints-AKI (TRIBE-AKI), Early Intervention with Erythropoietin Does Not Affect the Outcome of Acute Kidney Injury (EARLY-ARF) trial, and Evaluation of Novel Biomarkers from Acutely Ill Patients at Risk for Acute Kidney Injury Trial (Astute Medical Sapphire)]. These studies have demonstrated an ability to accurately and reliably diagnose AKI earlier than serum creatinine, in a variety of clinical settings. While some of these studies require further validation, several biomarkers are ready for wide-scale use. To this end, in Europe and Asia several biomarkers are clinically available. Unfortunately, none of these assays are clinically available in the US; however, through continued collaborations between physician scientists, industry sponsors, the FDA, and the newly formed Kidney Health Initiative, I suspect that nephrologists and physicians in the US will have access to these clinical assays soon.

Ravindra Mehta: Several barriers have limited biomarker utilization in AKI. Emerging biomarkers all have different test characteristics (in serum and urine), diverse platforms for evaluation, and a lack of stan-

dardization in the way data are expressed. Additionally, there are considerable differences in the regulatory assessment for biomarker approval in different countries. Concern about the costs and reimbursement for biomarker assays further influences the enthusiasm for clinical implementation. The evidence base for biomarker performance has also been influenced by the large number of studies emphasizing the potential benefit of one biomarker over another without clear evidence of added benefit to clinical criteria. Finally, there have not been any specific clinical recommendations for applying these emerging biomarkers to optimize patient management. The results from the recent ADQI conference on biomarker utilization in AKI will be published shortly and will provide a framework for the clinician to incorporate biomarkers in clinical practice.

Are there any AKI biomarkers that are ready for prime time today?

Lakhmir Chawla: Of the main 6 biomarkers, 3 appear to have utility for early diagnosis of AKI: NGAL, TIMP-2, and IGFBP7. Other biomarkers, such as KIM-1, L-FABP, and IL-18, also appear to have an important capacity to assess kidney injury and prognosis. However, for each of these biomarkers the platform and cutpoint values will need to be determined before clinicians can effectively use these promising AKI biomarkers.

Kianoush Kashani: In a recent systematic review of AKI biomarkers, the authors concluded that current markers are not quite ready for prime time in the adult population with other comorbidities. This was felt to be due to a lack of sufficient sensitivity and specificity of these markers in the populations of interest.

Among the biomarkers of kidney function, certainly serum creatinine and cystatin C have been implemented in clinical practices across the nation. Urine output, although found to be very sensitive and a valuable functional marker, has not gained the momentum due to its limitations. In the majority of studies, urine output has not been reported, due to the difficulties associated with collection of the information. In addition, the frequent use of diuretics in hospitals and ICUs has made it more unreliable.

John Kellum: I believe there are. We have the most data on NGAL and KIM-1, and I think both are major advances over clinical evaluation alone. They are far from perfect, but I think both offer value. TIMP-2 and IGFBP-7 are new markers and look very good for risk stratification. They are linked to G_1 cell cycle arrest, which is the cell's own alarm system. These markers may be allowing us to hear that alarm even before the cells are injured.

Jay Koyner: There are several biomarkers that have been approved for clinical use throughout Europe and Asia. Continued investigation will further clarify the strengths and weaknesses of these assays and will have them ready for real-time patient application in the US in the immediate future.

Ravindra Mehta: While several markers have been studied, I don't think any are ready to replace serum creatinine. However, several biomarkers are being tested in different situations to establish their utility for different purposes. The FDA and the European Medicines Agency (EMEA) have qualified a panel of 7 urinary kidney-damage biomarkers for the identification of nephrotoxicity, and clinical studies have been initiated by a collaboration among several large pharmaceutical companies participating in the Predictive Safety Testing Consortium and the Foundation for the NIH to evaluate their performance. Several other studies in cardiac surgery, contrast nephropathy, and heart failure also under way will provide more data for developing standardized approaches for the future use of biomarkers.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: J.C. Lieske, IDEXX Laboratories; L. Chawla, Alere, Astute Medical, Abbott Laboratories, NxStage Medical, and Gambro; J.A. Kellum, Alere, Abbott Laboratories, Astute Medical, and Roche; R.L. Mehta, Astute Medical.
Stock Ownership: R.L. Mehta, Astute Medical.
Honoraria: R. Mehta, Abbott Laboratories and Alere.
Research Funding: J.C. Lieske, Bioporto and Gentian; K. Kashani, Astute Medical and Alere; J.A. Kellum, Astute Medical and Alere; J.L. Koyner, Astute Medical and Abbott Laboratories.
Expert Testimony: J.L. Koyner, Smith Amundsen LLC, for case involving acute kidney injury after cardiac surgery.
Patents: None declared.

Previously published online at DOI: 10.1373/clinchem.2012.201988