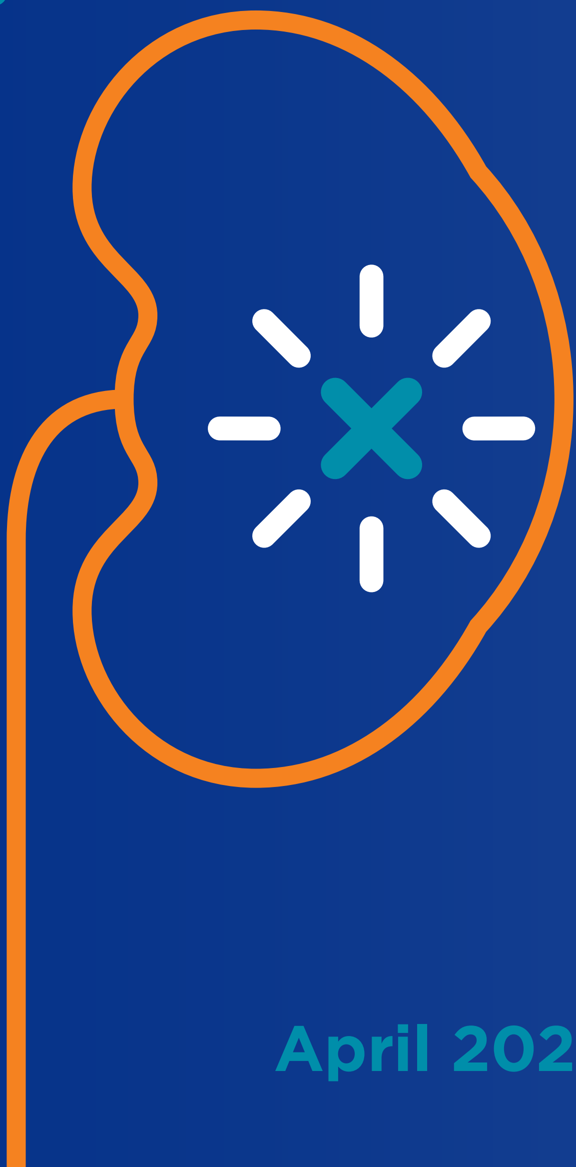
KHI KIDNEY HEALTH INITIATIVE

Roadmap for Accelerating the Development of Biomarkers for Acute Kidney Injury



Prepared by
NEXIGHT GROUP

April 2022

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Who Should Read this Roadmap

This roadmap is intended for stakeholders committed to improving kidney health, including:

- Patients, clinical trial participants, and care partners
- Basic, clinical, and translational researchers
- Industry professionals, such as drug developers and diagnostic companies
- Physicians and healthcare providers
- Government agencies, including regulators
- Payors

Collaboration across these groups will be crucial to achieve accelerated biomarker development and adoption.

About this Document

The Kidney Health Initiative (KHI) developed this roadmap in response to the significant unmet need for acute kidney injury (AKI) biomarkers to better inform patient care and therapeutic development. Established in 2012, KHI is a public-private partnership between the American Society of Nephrology (ASN) and the U.S. Food and Drug Administration (FDA) focused on catalyzing the innovation and development of safe and effective patient-centered therapies for people living with kidney diseases.

This roadmap is intended to guide community action during the next five years around key areas that could support accelerated biomarker development and adoption. These biomarkers can improve patient care and confidence in kidney safety during trials of therapeutics and support the development of candidate therapeutics for AKI. The widespread adoption, data collection, and interpretation of biomarkers also inform regulatory decisions around AKI biomarkers.

Roadmap Objective

The roadmap focuses on strategies for advancement of biomarkers that could provide greater insights into the timing, severity, reversibility, and underlying mechanisms of kidney injury when used in combination with traditional measures such as serum creatinine (sCr) and urine output.

For the purposes of establishing a roadmap for biomarker development, AKI is defined as rapid-onset damage to the kidney rather than the traditional definition based on sCr or urine output.

Key Roadmap Components

Vision for Accelerated Biomarker Development, including five key use cases for biomarkers and how they could benefit patients

- These use cases clearly articulate the use of AKI biomarkers in one or more of the categories defined by the FDA/National Institutes of Health (NIH) Biomarker Working Group in the BEST (Biomarkers, EndpointS, and other Tools) Resource

Major challenges slowing biomarker development and adoption

Activities to overcome these challenges recommended by experts in the community

The roadmap was informed by interviews with experts from industry, academia, and government, as well as by input received via two large virtual workshops and several focused sessions with selected subject matter experts in the working group (See Appendix B: Roadmap Contributors). KHI partnered with Nexight Group, a technical consulting company specializing in strategic roadmapping, to develop this document.

Current State

The community defines and evaluates acute kidney injury (AKI) based on **changes in functional biomarkers** (i.e., serum creatinine [sCr] or urine output) that do not always reflect true injury. Injury often occurs before measured changes in these functional biomarkers, and these biomarkers may change without true injury.

Conventional functional biomarkers alone are unable to reliably identify early injury to the kidney and provide little information relating to underlying mechanisms.

As a result, the community is using tools that are insufficient to:

- **Diagnose and monitor** kidney injury at an early stage
- **Predict** which patients are more susceptible to developing AKI in response to a therapeutic or procedure
- **Identify** AKI patients who are likely to progress to chronic kidney disease (CKD) and/or end-stage kidney disease (ESKD)
- **Measure response** to a therapeutic intervention for AKI
- **Predict** which patients will have a positive response to an intervention to prevent or treat AKI

Actions Encouraged by Roadmap

Answer key questions about biomarkers:

- How can we assess the utility of kidney injury biomarkers for diagnosis, monitoring, prediction of outcome and enhancement of drug safety?
- How can we interpret biomarker data to inform decision making?
- What are the impediments to broader biomarker usage?

Redefine AKI using a combination of traditional functional biomarkers and injury biomarkers that provide insights into the timing, severity, reversibility, consequences, and underlying mechanisms of kidney injury.

Desired Result

Facilitate therapeutic development and utilization by:

- Improving phase 2 success rate of trials for AKI treatment using biomarkers to quantitate target engagement, proof of mechanism, and efficacy
- Enabling patient stratification approaches using innovative biomarker-driven adaptive clinical trial designs for drugs to prevent or treat AKI
- Mitigating kidney safety concerns in trials for all therapeutic areas
- Providing reassurance that an increase in sCr, associated with a kidney protective drug, is due to hemodynamic effects or reduction of creatinine secretion and not kidney injury

Improve care of patients of all patient populations, regardless of age, sex, race, and ethnicity, by establishing biomarker tools to diagnose kidney injury early and improve risk assessment, monitoring of response to therapeutics, and other approaches to reduce short- and long-term consequences of kidney injury to patients.

Current methods for assessing acute kidney injury limit the ability to provide timely and effective interventions, worsening potential patient health outcomes.

Biomarkers can help.

Executive Summary

The Need for AKI Biomarkers

Biomarkers that reflect rapid-onset damage to the kidney and show meaningful changes earlier and with greater specificity than serum creatinine (sCr) would have a range of benefits when used in conjunction with traditional functional biomarkers. The use of traditional biomarkers in conjunction with injury biomarkers could:

- **Improve patient health** by increasing the likelihood that kidney injury will be predicted, detected, diagnosed, and addressed early. These biomarkers—coupled with clinical data—could improve risk assessment, identification of onset and severity, response, and prognosis, and inform kidney support and rehabilitation decisions.

- **Enable more accurate identification of therapeutics with potential nephrotoxic effects,** which would help protect trial participants and increase confidence in participant safety in clinical trials.

- **Facilitate the development of methodologies and treatments to predict, monitor, and manage acute kidney injury (AKI) and its consequences** by enabling improved trial designs, appropriately selected trial populations, and discovery of novel treatment pathways.

- **Enable identification of sub-phenotypes of AKI,** potentially transforming how AKI is described and how AKI patients are stratified, which will allow more targeted approaches to treat the multiple conditions that result in AKI.

- **Reduce the likelihood that trial participants receive unnecessary or ineffective interventions** for AKI by enabling earlier and more accurate AKI diagnoses.

- **Improve long-term health outcomes** by providing better insight into longer term consequences of kidney injury and how to mitigate them.

- **Help address challenges related to COVID-19, including early recognition and pathobiology of kidney injury** and its disproportionate impact on some racial and ethnic minority groups.

Vision for Accelerated Biomarker Development

VISION: Expedite development and widespread adoption of effective biomarkers that can...

- Help identify appropriate participants for trials.
- Enable more innovative biomarker-driven clinical trials for technologies and drugs to treat acute kidney injury.
- Better characterize kidney injury and functional changes:
  - For diagnosis, disease monitoring, prognosis, and response to various care and pharmacologic interventions
  - To redefine AKI
- Provide tools for assessment of efficacy and safety, which can be useful for advancing drugs through the development process and aid the clinician in the use of effective therapeutics where there is concern about possible toxicity.
- Increase understanding of disease, prevention, and/or treatment options for AKI.
- Identify opportunities for cross-collaboration to enhance biomarker utilization.
- Improve kidney safety in trials for all therapeutic areas.

Who will benefit:

- Basic, clinical, and translational researchers
- Government agencies, including regulators
- Industry professionals, such as drug developers and diagnostic companies
- Patients, clinical trial participants, and care partners
- Physicians and healthcare providers
- Payors

Roadmap for Accelerating Biomarker Development

Assess utility of kidney injury biomarkers

Interpret biomarker data to inform decision making

Overcome impediments to broader biomarker usage

Redefine AKI using biomarkers to provide insights into underlying mechanisms of kidney injury

UNDERTAKE THESE ACTIVITIES TO ACHIEVE ROADMAP GOALS:

Optimize Biomarker Testing and Integrate Appropriate Biomarker Use into New and Ongoing Studies

Study data can help answer critical questions about biomarkers to make them more actionable and further drive their development

Collaborate on Biobanking, Data Collection, and Data Sharing

Use existing resources such as biobanks and clinical trial datasets to support AKI biomarker studies and create a repository of AKI samples to support generation of data and validation of assays for AKI biomarker development

Use Biomarkers to Better Define and Predict AKI and its Phenotypes

An improved definition of AKI that maps closely with true kidney injury at a cellular level could support the development of clear AKI phenotypes and help enable efficient development of treatments for AKI

Support Coordinated Biomarker Development and Qualification

Organize a more systematic data collection effort that leverages the activities of different stakeholder groups and seeks to answer specific key questions and fill high-priority data gaps

Develop AKI Biomarker Guidance and Best Practices to Facilitate Adoption

The development of guidance and resources that target common questions and pain points for AKI biomarker use can help accelerate adoption by the community

Increase Awareness of Biomarker Benefits

Education campaigns targeted at clinicians, hospital administration, therapeutic developers, payors, and patients could help them to become active proponents of biomarkers and increase adoption of biomarkers as a standard part of risk evaluation, diagnosis, and care

Focus Community Efforts

Attention should be focused on 1–2 of the highest-priority use cases, with research focused on 5–10 biomarkers within each use case to prevent dilution of community effort

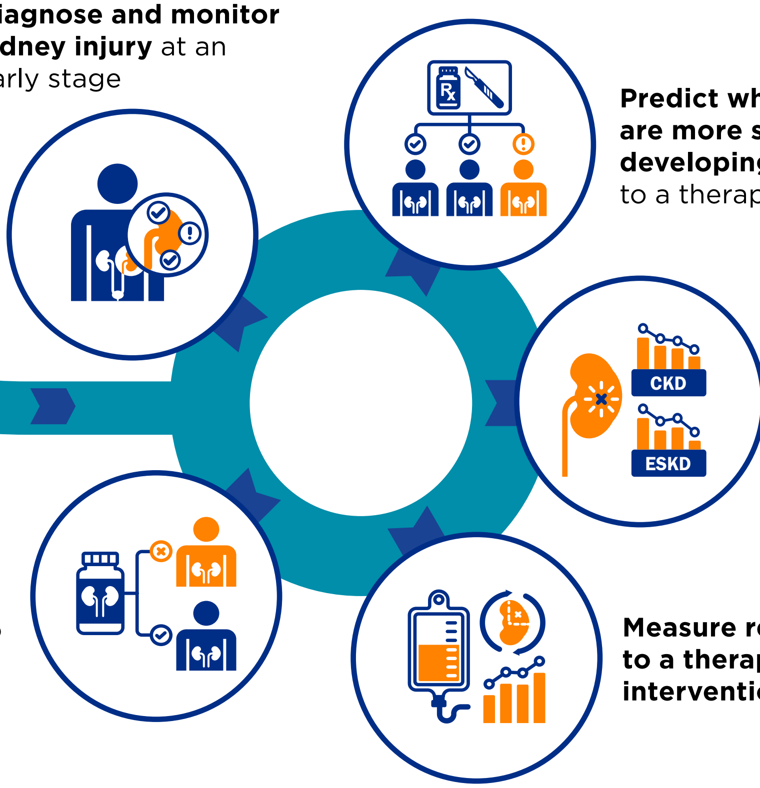
OVERCOME CHALLENGES:

Overarching Strategic Challenges
Challenges preventing effective collaborative action around shared goals such as a lack of community coordination and unclear measures of success

Technical Challenges
Challenges related to scientific understanding such as difficulty comparing and interpreting existing biomarker studies and gaps in the necessary data for biomarker development

Implementation Challenges
Challenges that impede biomarker adoption such as lack of market demand for biomarker tests and limited applications for biomarkers due to a lack of successful AKI therapies

ENHANCE DISCOVERY, BUILD EVIDENCE, AND ACCELERATE IMPLEMENTATION OF BIOMARKERS THAT:



Diagnose and monitor kidney injury at an early stage

Predict which patients are more susceptible to developing AKI in response to a therapeutic or procedure

Identify AKI patients who are likely to progress to CKD and/or ESKD

Measure response to a therapeutic intervention for AKI

Predict which patients will have a positive response to an intervention to prevent or treat AKI

Overview of AKI

Acute kidney injury (AKI) is traditionally defined as a rapid decline in kidney function over days, as measured through changes in serum creatinine (sCr) or urine output. However, this definition can be limiting because sCr and urine output are relatively non-sensitive and non-specific late measures of functional changes. In addition, while informative, these biomarkers are not necessarily markers of intrinsic injury to the kidney, and changes may not manifest until AKI has progressed (see Limitations of Current Kidney Injury Detection Methods). Furthermore, sCr and urine output do not provide any information regarding pathobiology or location of compromised function. This roadmap intends to build on existing efforts in the community to explore these challenges (see Recent AKI Biomarker Initiatives).

For the purposes of establishing a roadmap for biomarker development, **AKI refers to rapid-onset damage to the kidney,** where "damage" can refer to structural cell or tissue injury or cellular dysfunction.

AKI is associated with an increased likelihood of long-term care, hospitalization and long-term mortality, and high healthcare costs.[1,2] AKI can contribute to a loss of kidney function, including decreased glomerular filtration rate (GFR). An episode of AKI may **predispose an individual to development or progression of chronic kidney disease (CKD).** It can also put an individual at risk for **future episodes of AKI that can further exacerbate CKD,** which, in turn, can result in kidney failure and can contribute to other serious chronic health problems, such as cardiovascular diseases.[3]

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1 Pavkov, Meda E., Jessica L. Harding, and Nilka R. Burrows. "Trends in Hospitalizations for Acute Kidney Injury - United States, 2000–2014." Centers for Disease Control and Prevention, March 15, 2018. https://www.cdc.gov/mmwr/volumes/67/wr/mm6710a2.htm.

2 Lafrance, Jean-Philippe, and Donald R. Miller. "Acute Kidney Injury Associates with Increased Long-Term Mortality." Journal of the American Society of Nephrology 21, no. 2 (2009): 345–52. https://doi.org/10.1681/asn.2009060636.

3 Sykes, Lynne, Ozgur Asar, James Ritchie, Maharajan Raman, Diana Vassallo, Helen V. Alderson, Donal J. O'Donoghue, Darren Green, Peter J. Diggle, and Philip A. Kalra. "The Influence of Multiple Episodes of Acute Kidney Injury on Survival and Progression to End Stage Kidney Disease in Patients with Chronic Kidney Disease." PLOS ONE 14, no. 7 (2019). https://doi.org/10.1371/journal.pone.0219828.

The Impact of AKI

Many cases of AKI, as defined by the traditional indicators of sCr and urine output criteria, are associated with cellular and tissue injury. Using current criteria:

An estimated **13.3 million people are diagnosed with AKI** each year worldwide

In the United States alone, AKI is associated with an estimated **$5.4 –$24 billion increase in hospitalization costs**

AKI causes an estimated **1.7 million global deaths** per year

AKI can result in a nearly nine-fold risk increase for **development of chronic kidney disease (CKD)** and a three-fold risk of progression of CKD

SOURCES:
International Society of Nephrology: https://www.theisn.org
The Economic Consequences of Acute Kidney Injury: https://www.karger.com/Article/FullText/475607
The Role of Acute Kidney Injury in Chronic Kidney Disease:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4979984

Despite the potentially severe consequences of AKI, detection of AKI is delayed in up to 43 percent of hospitalized patients.[4] The effect of socioeconomic status and systemic inequality on AKI susceptibility, likelihood of recovery, and long-term consequences is a concern. AKI's impact varies by race and sex, with African Americans facing higher risk of AKI than Caucasians,[5] and men facing a higher risk than women.[6] The causes and extent of these disparities are not currently fully understood. AKI also occurs at an alarming frequency in hospitalized children and neonates.[7,8]

Biomarkers that show changes early in the course of injury and reflect true kidney injury could facilitate the development of therapeutics and diagnostics for AKI and help lower the risk of AKI and significant acute and chronic consequences to the patient in therapeutics trials for other conditions. In addition, more sensitive and informative safety biomarkers would be essential tools to improve kidney safety assessment of promising therapeutics.

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4 Rizvi, Mahrukh S, and Kianoush B Kashani. "Biomarkers for Early Detection of Acute Kidney Injury." The Journal of Applied Laboratory Medicine Volume 2, Issue 3 (November 2017): 386–99. https://doi.org/10.1373/jalm.2017.023325.

5 Grams, Morgan E., Kunihiro Matsushita, Yingying Sang, Michelle M. Estrella, Meredith C. Foster, Adrienne Tin, W.h. Linda Kao, and Josef Coresh. "Explaining the Racial Difference in AKI Incidence." Journal of the American Society of Nephrology 25, no. 8 (2014): 1834–41. https://doi.org/10.1681/asn.2013080867.

6 Neugarten, Joel, Ladan Golestaneh, and Nitin V. Kolhe. "Sex Differences in Acute Kidney Injury Requiring Dialysis." BMC Nephrology 19, no. 1 (2018). https://doi.org/10.1186/s12882-018-0937-y.

7 Selewski, D. T., Charlton, J. R., Jetton, J. G., Guillet, R., Mhanna, M. J., Askenazi, D. J., & Kent, A. L. (2015). Neonatal Acute Kidney Injury. Pediatrics, 136(2). https://doi.org/10.1542/peds.2014-3819.

8 Ciccia, E., & Devarajan, P. (2017). Pediatric acute kidney injury: Prevalence, impact and management challenges. International Journal of Nephrology and Renovascular Disease, Volume 10, 77–84. https://doi.org/10.2147/ijnrd.s103785.

AKI and COVID-19

Reports have shown a high incidence of AKI in COVID-19 patients, which appears to relate to the stresses of severe illness (e.g., inflammation, septic shock, microvascular disease) as well as possible direct infection of the kidney.

IMPACT

- Patients hospitalized with COVID-19 are approximately twice as likely to develop AKI compared with a historical cohort of non-COVID patients, and many develop kidney failure.
- AKI is often associated with severe illness and mortality in COVID-19 patients despite dialysis.
- COVID-19 patients diagnosed with AKI often experience ongoing kidney dysfunction after discharge from the hospital.

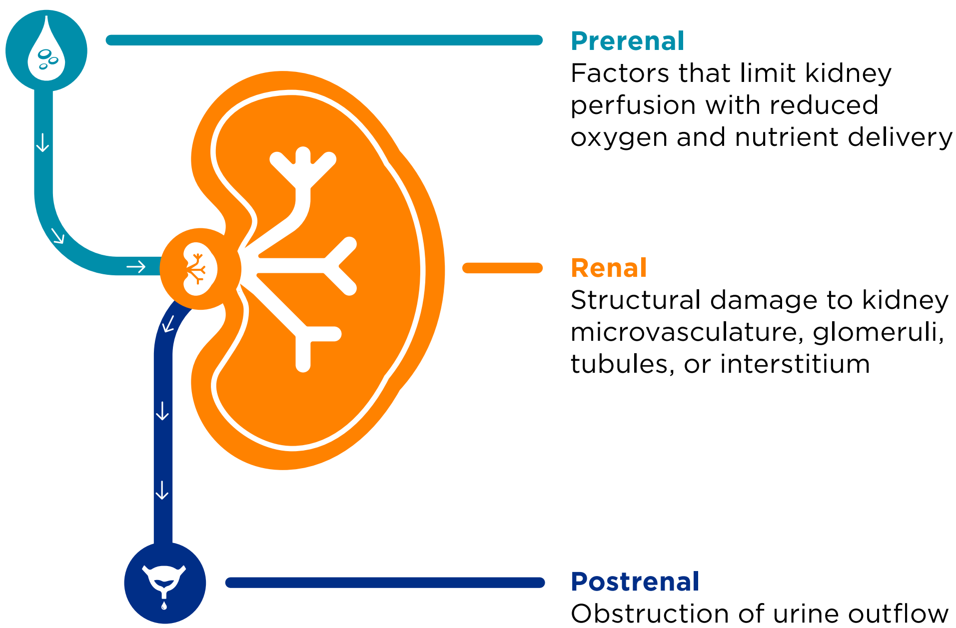
OPPORTUNITY FOR ACTION

COVID-19 reemphasized the critical need for tools that could be used to diagnose AKI, guide clinical decision making, and improve patient outcomes. Additional biomarkers will help clinicians better understand the incidence and causes of AKI and optimally care for patients with AKI during an urgent public healthcare crisis.

SOURCE:
National Kidney Foundation: https://www.kidney.org/
AKI in Hospitalized Patients with and without COVID-19: A Comparison Study: https://jasn.asnjournals.org/content/31/9/2145

A Simplified Overview of Sub-categories of Causes of AKI

The below diagram is a simplified overview that outlines the traditional understanding of potential causes of acute decreases in GFR. Not all acute decreases in GFR are associated with rapid-onset kidney damage. In the absence of a “personalized” mechanistically driven framework facilitated by cell type, kidney-segment-specific, and mechanistic injury biomarkers, the simplified concepts reflected below remain useful in communicating to patients and non-specialist medical caregivers.



In addition to these traditional categories, other ways of classifying AKI have also been proposed, including classifying AKI by injury mechanism, reversibility, affected kidney compartment, and clinical setting.

Limitations of Current Kidney Injury Detection Methods

Below are the current most commonly measured indicators for kidney injury detection in drug development and clinical practice. Although widely used and accepted, they have limitations and could be more informative if used in conjunction with injury biomarkers.

Measurable Indicator	Limitations
Serum creatinine (sCr)	• **May not show significant increases** until GFR has been reduced by more than 50% from normal,[9] resulting in delay in diagnosis as well as potential long-term kidney damage • **Does not provide insight into etiology or location of underlying subclinical cellular injury,** (e.g., site along the nephron or intrarenal compartment, such as tubule vs interstitium) making it more challenging to identify the cause(s) and target therapy • Increases are **not specific to kidney injury,** since sCr can vary within the same patient based on factors like diet, muscle mass, or medications, **meaning increases could have other causes** • **Drugs can affect the secretion of creatinine** by the nephron and hence result in a change in sCr without any damage to the kidney • **Normal levels vary from patient to patient** and can be affected by age, sex, race/ethnicity, and body habitus • **Requires stable values over time to accurately estimate GFR,** which is calculated based on sCr, whereas kidney injury typically results in changing values over short periods of time.[10] This makes GFR less reliable as an indicator of kidney injury and function
Urine output	• **Valuable as a diagnostic tool for AKI but difficult to collect reliable data in clinical settings,** particularly in non-intensive care unit (ICU) settings when patients are not catheterized[11] • **Reductions can be physiological** (e.g., dehydration and volume contraction) • There is **difficulty collecting urine output non-invasively in certain patient populations** (e.g., pediatric and disabled patients)

9 McIlroy, David R., Gebhard Wagener, and H. Thomas Lee. "Biomarkers of Acute Kidney Injury: An Evolving Domain." *Anesthesiology* Vol.112, no. 4 (2010). https://doi.org/10.1097/ALN.0b013e3181cded3f.

10 Liu, Kathleen D., Stuart L. Goldstein, Anitha Vijayan, Chirag R. Parikh, Kianoush Kashani, Mark D. Okusa, Anupam Agarwal, and Jorge Cerdá. "AKI!Now Initiative: Recommendations for Awareness, Recognition, and Management of AKI." *Clinical Journal of the American Society of Nephrology* 15, no. 12 (2020): 1838–47. https://doi.org/10.2215/cjn.15611219.

11 Rizvi, Mahrukh S, and Kianoush B Kashani. "Biomarkers for Early Detection of Acute Kidney Injury." *The Journal of Applied Laboratory Medicine* Volume 2, Issue 3 (November 2017): 386–99. https://doi.org/10.1373/jalm.2017.023325.

Measurable Indicator	Limitations
Blood urea nitrogen	• **Low sensitivity and specificity;** may be impacted by diet, nutrition, volume depletion, or non-AKI health issues such as gastrointestinal bleeding or chronic liver disease[12]
Fractional excretion of sodium, urine microscopy	• **Low sensitivity and specificity** limit their usefulness in reliably and accurately detecting kidney injury or determining its severity[13]

12 El-Khoury, Joe M., Melanie P. Hoenig, Graham R Jones, Edmund J. Lamb, Chirag R. Parikh, Nicole V. Tolan, and F. Perry Wilson. "AACC Guidance Document on Laboratory Investigation of Acute Kidney Injury." *The Journal of Applied Laboratory Medicine*, 2021. https://doi.org/10.1093/jalm/jfab020.

13 Ibid.

The Need for AKI Biomarkers

Biomarkers that reflect rapid-onset damage to the kidney and show meaningful changes earlier and with greater specificity than serum creatinine (sCr) would have a range of benefits when used in conjunction with traditional functional biomarkers. The use of traditional biomarkers in conjunction with injury biomarkers could:

Improve patient health by increasing the likelihood that kidney injury will be predicted, detected, diagnosed, and addressed early. These biomarkers—coupled with clinical data—could improve risk assessment, identification of onset and severity, response, and prognosis, and inform kidney support and rehabilitation decisions.

Enable more accurate identification of therapeutics with potential nephrotoxic effects, which would help protect trial participants and increase confidence in participant safety in clinical trials.

Facilitate the development of methodologies and treatments to predict, monitor, and manage acute kidney injury (AKI) and its consequences by enabling improved trial designs, appropriately selected trial populations, and discovery of novel treatment pathways.

Enable identification of sub-phenotypes of AKI, potentially transforming how AKI is described and how AKI patients are stratified, which will allow more targeted approaches to treat the multiple conditions that result in AKI.

Reduce the likelihood that trial participants receive unnecessary or ineffective interventions for AKI by enabling earlier and more accurate AKI diagnoses.

Improve long-term health outcomes by providing better insight into longer term consequences of kidney injury and how to mitigate them.

Help address challenges related to COVID-19, including early recognition and pathobiology of kidney injury and its disproportionate impact on some racial and ethnic minority groups.

What is a Biomarker?

The U.S. Food and Drug Administration (FDA)/ National Institutes of Health (NIH) Biomarker Working Group defines a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions."

Examples of biomarkers can include molecular, histologic, radiographic, or physiologic characteristics but do not include assessments of how an individual feels, functions, or how likely they are to survive.

The FDA/NIH Biomarker Working Group classifies biomarkers into seven major categories:

1 | **Diagnostic**
2 | **Monitoring**
3 | **Pharmacodynamic/Response**
4 | **Predictive**
5 | **Prognostic**
6 | **Safety**
7 | **Susceptibility/Risk**

SOURCE: BEST (Biomarkers, EndpointS, and other Tools) Resource: https://pubmed.ncbi.nlm.nih.gov/27010052/

Timeline of Community AKI Biomarker Efforts

Prior to 2006

Significant work by a number of laboratories and drug developers to develop more sensitive biomarkers

2006

Critical Path Institute (C-Path) launches **Predictive Safety Testing Consortium (PSTC)**

2008

PSTC obtains qualification of seven **rodent kidney safety biomarkers** by the FDA and the European Medicines Agency (EMA)

2010

PSTC preclinical safety biomarkers biomarkers are **qualified by Pharmaceuticals and Medical Devices Agency (PMDA)**

2013

Publication of the **10th Acute Dialysis Quality Initiative Consensus Conference Report**

2013

Liver-type fatty acid-binding protein (L-FABP) approved as a biomarker for AKI in Japan

2014

FDA approves NephroCheck® biomarker panel for assessing risk of AKI

2017 (ongoing)

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) launches **Kidney Precision Medicine Project**

2018

Innovative Medicines Initiative (IMI) /SAFE-T Drug-Induced Kidney Injury (DIKI) Consortium received EMA and FDA letters of support for 9 biomarkers

2018

FDA Biomarker Qualification Program qualifies composite measure of six biomarkers for DIKI clinical safety

2019

Heart-type fatty acid binding protein H-FABP-based test gains Conformitè Europëenne (CE) approval for use in the EU

2020

Neutrophil gelatinase-associated lipocalin (NGAL)- based test gains CE approval and becomes available for use in the EU, Canada, and Korea

Recent AKI Biomarker Initiatives

Recognizing the potential benefits of AKI biomarkers, various organizations have **highlighted the need to prioritize and facilitate their development.** Notable among these are the following:

- In 2005, the American Society of Nephrology proposed an increased focus on research to promote the identification, characterization, and development of new AKI biomarkers.[14]
- In 2014, an international group of experts at the 10th Acute Dialysis Quality Initiative released a consensus conference report that provided recommendations for clinicians to use in applying biomarkers to various AKI use cases.[15]
- More recently, in 2020, an expert panel organized by the Acute Dialysis Quality Initiative provided updated recommendations for the utilization of biomarkers to prevent and manage AKI.

Ongoing Initiatives

There are also a number of **ongoing initiatives** to increase understanding of the utility and effective implementation of biomarkers in AKI, including:

Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium (BC) and C-Path's Predictive Safety Testing Consortium (PSTC) Kidney Biomarker Project

This collaborative effort resulted in the FDA qualification of a panel of six clinical safety kidney biomarkers for safety monitoring in healthy volunteers participating in early-phase clinical trials; ongoing work is focused on understanding the utility of biomarkers, either alone or as a panel, to monitor kidney safety during clinical trials.

14 McIlroy, David R., Gebhard Wagener, and H. Thomas Lee. "Biomarkers of Acute Kidney Injury: An Evolving Domain." *Anesthesiology* 112, no. 4 (2010). https://doi.org/10.1097/ALN.0b013e3181cded3f.

15 Murray, Patrick T., Ravindra L. Mehta, Andrew Shaw, Claudio Ronco, Zoltan Endre, John A. Kellum, Lakhmir S. Chawla, Dinna Cruz, Can Ince, and Mark D. Okusa. "Potential Use of Biomarkers in Acute Kidney Injury: Report and Summary of Recommendations from the 10th Acute Dialysis Quality Initiative Consensus Conference." *Kidney International* 85, no. 3 (2014): 513–21. https://doi.org/10.1038/ki.2013.374.

ONGOING INITIATIVES

NIH-Sponsored Translational Research Networks

NIH-sponsored research networks are gathering data related to AKI biomarkers through multicenter studies:

- Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI)
- Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI)

Kidney Precision Medicine Project

This project aims to use human kidney biopsy specimens to improve understanding of the mechanisms of kidney injury, which would enable more tissue-based insight to be brought to biomarker studies.

C-Path's PSTC Biomarker Data Repository (BmDR)

This repository collects masked, de-identified data on novel translational safety biomarkers from drug development programs. The data are intended to support research for submission to regulatory agencies to qualify novel safety biomarkers. The repository is currently in a pilot phase focused on kidney safety biomarkers.

C-Path's AKI Working Group

This working group focuses primarily on the development of predictive tools for drug-induced kidney injury (DIKI). It is anticipated this initiative will also feed into, synergize with, and offer support for current and future efforts to develop tools to advance drug development for other causes of AKI and ultimately improve the care of AKI patients.

Use of Clinical Models and Artificial Intelligence to Predict Clinical Outcomes

There has been increasing exploration of the potential to use real-world data and clinical modeling to facilitate drug development and support clinical trials and clinical decision making. Some groups have developed AKI risk scores or identified patients who would benefit from guideline-based care bundles based on electronic medical record (EMR) data and other electronic data.[16] Kidney injury biomarkers, in combination with clinical risk profiles, have the potential to improve patient management. For example, the "renal angina" index—a composite of risk strata and clinical signs of kidney injury—has been used in combination with fluid overload and Neutrophil Gelatinase-Associated Lipocalin (NGAL) assessments in pediatric patients to inform decisions about dialysis.[17]

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16 Lieske, John C, Kianoush Kashani, John Kellum, Jay Koyner, Ravindra Mehta, and Chirag R Parikh. "Use of Biomarkers to Detect and Manage Acute Kidney Injury: Has Progress Stalled?" *Clinical Chemistry* 66, no. 2 (2020): 271–76. https://doi.org/10.1093/clinchem/hvz026.

17 Ibid.

ONGOING INITIATIVES

Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program

The mission of the CDER Biomarker Qualification Program is to work with external stakeholders to develop biomarkers as drug development tools. **Qualified biomarkers have the potential to advance public health by encouraging efficiencies and innovation in drug development**.[18] Under the program, FDA reviews biomarker data gathered by various organizations to determine if the data support qualification of the biomarkers for specific contexts of use that address specified drug development needs.

In 2008 and 2010, CDER qualified several urinary kidney biomarkers to be used with traditional indicators to indicate renal injury in preclinical studies in rats, based on data submitted by an external consortium. A decade later, FDA qualified a safety biomarker panel to be used in conjunction with traditional measures to aid in the detection of kidney tubular injury in phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause renal tubular injury in humans. This qualification was based on a joint submission of data by the FNIH BC and C-Path's PSTC.[19]

These qualifications provide an important foundation for further work that needs to be done to advance the development of biomarkers that can be used to aid in the detection of DIKI and thus better ensure the safety of clinical trial participants.

2008	FDA and EMA qualify 7 urinary markers as safety biomarkers to be used with traditional measures to indicate renal injury in rats	• Albumin • β2 macroglobulin • Cystatin C • Clusterin	• Kidney injury molecule-1 • Total Protein • Trefoil Factor-3
2010	FDA qualifies an additional safety biomarker to be used to indicate renal injury in rats; further support also provided for a previously qualified biomarker		• Renal Papillary Antigen (RPA-1) and Clusterin
2018	FDA qualifies a safety biomarker panel to aid in detection of kidney tubular injury in phase 1 trials in healthy volunteers	• Cystatin C • Clusterin • Kidney injury molecule-1	• N-acetyl-β-D-glucosaminidase • Neutrophil gelatinase associated lipocalin • Osteopontin

Center for Devices and Radiological Health (CDRH) Medical Device Development Tools (MDDT) program

The MDDT program supports the community in qualifying tools—including biomarker tests—that can be used to gather information to aid in the development and evaluation of medical devices. Through this program, FDA evaluates the tool and any supporting evidence provided by community stakeholders to determine whether it can provide scientifically plausible measurements within a specified context of use.

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18 U.S. Food and Drug Administration, "About FDA's Biomarker Qualification Program," YouTube video, 2:28, October 26, 2016, https://www.youtube.com/watch?v=vc-_C-5SSlo.

19 U.S. Food and Drug Administration, Center for Drug Evaluation and Research, "List of Qualified Biomarkers," updated July 7, 2021, https://www.fda.gov/drugs/cder-biomarker-qualification-program/list-qualified-biomarkers.

Vision for Accelerated Biomarker Development

VISION:
Expedite development and widespread adoption of effective biomarkers that can...

- Help identify appropriate participants for trials
- Enable more innovative biomarker-driven clinical trials for technologies and drugs to treat acute kidney injury
- Better characterize kidney injury and functional changes:
  - For diagnosis, disease monitoring, prognosis, and response to various care and pharmacologic interventions
  - To redefine AKI
- Provide tools for assessment of efficacy and safety, which can be useful for advancing drugs through the development process and aid the clinician in the use of effective therapeutics where there is concern about possible toxicity
- Increase understanding of disease, prevention, and/or treatment options for AKI
- Identify opportunities for cross-collaboration to enhance biomarker utilization
- Improve kidney safety in trials for all therapeutic areas

Who will benefit:

- Basic, clinical, and translational researchers
- Government agencies, including regulators
- Industry professionals, such as drug developers and diagnostic companies
- Patients, clinical trial participants, and care partners
- Physicians and healthcare providers
- Payors

While biomarkers that could potentially be used for risk stratification, prognosis, and early detection of AKI have already been discovered, the road from discovery of a biomarker to adoption by drug developers, clinicians, and regulators can take 10 or more years. **Accelerating the pace of biomarker development is vital.**

AKI Biomarker Use Cases

Biomarkers could address various critical unmet needs, not only for development of new therapies and clinical decision making for AKI, but also for improving kidney safety monitoring in preclinical and clinical drug, device, and biologic development across all therapeutic areas. For the purposes of this roadmap, application areas are divided into five major use cases. Each of the use cases is classified according to the biomarker categories defined by the U.S. Food and Drug Administration (FDA)/National Institutes of Health (NIH) Biomarker Working Group (see text box on Page 18).

The five use cases are presented in order of priority, as identified by a working group of experts from the nephrology community (see Appendix B: Roadmap Contributors).

1 Diagnose and monitor kidney injury at an early stage

Diagnostic | **Monitoring** | Pharmacodynamic/Response | Predictive | Prognostic | **Safety** | Susceptibility/Risk

Why it matters

AKI may be caused by toxicity from therapeutics or environmental contaminants, infection, or reduced blood flow to kidneys (due to low blood pressure, hemorrhage, small vessel disease, or other causes). Biomarkers are needed to **detect AKI during the subclinical phase, before elevation of serum creatinine (sCr), and to better understand the cause, severity, and cellular origin (e.g., glomerular vs. tubular vs. interstitial)** to guide diagnostic and therapeutic approaches or to alter the intervention that is causing the AKI.

Drug Development

Need

Drug trial participants who experience therapeutic-induced kidney injury need **more timely diagnosis and interventions** to allow for the safest possible progression of promising therapeutic candidates in clinical trials.

Participant Impact

✔ **Mitigate risk to clinical trial participants, including:**

- Acute morbidity and mortality due to kidney injury
- Health complications associated with chronic kidney disease (CKD) and long-term treatments that may be a consequence of therapeutic-induced kidney injury

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Clinical Care

Need

To **address AKI causes effectively in the clinic** (e.g., through volume resuscitation, eliminating toxins, adjusting drug dosing, or targeting therapies to other pathobiological processes), **biomarkers must enable detection of AKI as soon as possible after injury.**

Patient Impact

✔ Recognize and **treat patients who develop AKI earlier**

✔ If AKI is caught early, it might be possible to **prevent more severe injury and enable enhanced repair with consequent decreases** in morbidity and mortality

2 Predict which patients are more susceptible to developing AKI in response to a therapeutic or procedure

Diagnostic | Monitoring | Pharmacodynamic/Response | **Predictive** | Prognostic | Safety | **Susceptibility/Risk**

Why it matters

Current tools for assessing a patient's AKI risk are limited (e.g., screening for comorbidities).[20] Biomarkers are **needed for baseline risk assessment to better understand when a patient's kidneys may be under stress or more susceptible to injury, as well as the potential severity of injury.**

Drug Development

Need

Candidate therapeutics in development for conditions other than kidney disease (e.g., antibiotics or cancer drugs) may have the **potential to cause kidney injury.**

Participant Impact

- **More effectively tailor patient cohorts** of trials (e.g., **by excluding or more closely monitoring higher-risk** trial participants)
- Enable more efficient study of potentially nephrotoxic therapeutics **without exposing trial participants to unreasonable risks**

Clinical Care

Need

Clinicians want to avoid therapeutics, interventions, or procedures with potential nephrotoxic effects in patients at higher risk of toxicity.

Patient Impact

- **Enable clinicians to provide individualized care to high-risk patients** when considering therapeutic interventions, drugs, devices, or biologics (e.g., avoid recommending an intervention or take steps to mitigate its negative effects)
- Enhance **monitoring of high-risk patients** for earlier recognition of kidney injury and timely intervention

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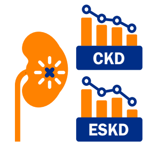
20 Rizo-Topete, Lilia Maria, Mitchell H. Rosner, and Claudio Ronco. "Acute Kidney Injury Risk Assessment and the Nephrology Rapid Response Team." *Blood Purification* 43, no. 1-3 (2016): 82–88. https://doi.org/10.1159/000452402.

3 Identify AKI patients who are likely to progress to CKD and/or ESKD



Diagnostic | Monitoring | Pharmacodynamic/Response | Predictive | **Prognostic** | Safety | **Susceptibility/Risk**

Why it matters

Though the kidney has the potential to repair itself after AKI, this repair is often incomplete or maladaptive. **Patients with AKI may progress to chronic loss of kidney function** with consequent increased cardiovascular complications, progression to end-stage-kidney disease (ESKD), and mortality.

Drug Development

Need

Biomarkers are needed to identify individuals who are most likely to develop a chronic loss of kidney function following an episode of AKI.

Participant Impact

- **Establish eligibility criteria** to focus clinical trials on people who are more likely to develop a chronic loss of kidney function following an episode of AKI
- **Increase the efficiency of drug development** by decreasing the size of trials

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Clinical Care

Need

Biomarkers predicting AKI progression could help clinicians better understand the causes of progression and enable them to **carry out close follow-up and surveillance after the use of procedures or agents that may trigger progression in a vulnerable group.**

Patient Impact

- Provide **increased monitoring and targeted interventions to patients at high risk of kidney disease**
- Offer **more accurate prognoses** for AKI patients
- **Reduce patient risks,** including reduction of renal and cardiovascular risk in AKI patients, post-AKI survivors, and those with CKD progression post-AKI
- Enable an **increase in the number of available donor kidneys** from deceased donors by identifying kidneys (pre-mortem) with a low likelihood of disease progression[21]

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21 Koyawala, Neel, and Chirag R. Parikh. "A Review of Donor Acute Kidney Injury and Posttransplant Outcomes." *Transplantation* 104, no. 8 (2020): 1553–59. https://doi.org/10.1097/tp.0000000000003144.

4 Measure response to a therapeutic intervention for AKI

Diagnostic | Monitoring | **Pharmacodynamic/Response** | Predictive | Prognostic | Safety | Susceptibility/Risk

Why it matters

The lack of early indicators of therapeutic efficacy is a major obstacle to identifying successful treatments for AKI.[22] Due to factors such as the time delay between measurable changes in sCr and reduced kidney function, **current methods of AKI detection often do not provide sufficiently clear and actionable information about a therapy's effect on kidney damage or recovery.** Efficacy biomarkers could potentially be therapeutic-specific for reduction in global or regional injury. Thus far, a lack of specific biomarkers of pathophysiological processes has impeded the development of therapeutics targeted to those mechanisms of injury.

Drug Development

Need

Therapeutic development programs need response biomarkers that could **provide early evidence that a treatment is effective in treating AKI** and/or to help select the dose of a drug or biologic that is most likely to be effective in treating AKI.

Participant Impact

- Enable **more efficient therapeutic development programs**
- **Expedite the development** of effective treatments for AKI

Clinical Care

Need

Because **traditional AKI biomarkers have a time delay in measuring reduced kidney function,** they provide an incomplete picture of whether an intervention is succeeding.

Patient Impact

- **Enable treatment to be more rapidly tailored to a patient's needs** by informing decisions to decrease, increase, continue, or stop an intervention
- Biomarkers indicating stabilization or recovery due to efficacy of a therapeutic or intervention may **enable earlier discharge from the hospital and render more efficient post-AKI clinical follow-up and management**

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22 Jo, Sang Kyung, Mitchell H. Rosner, and Mark D. Okusa. "Pharmacologic Treatment of Acute Kidney Injury: Why Drugs Haven't Worked and What Is on the Horizon." *Clinical Journal of the American Society of Nephrology* 2, no. 2 (2007): 356–65. https://doi.org/10.2215/cjn.03280906.

5 Predict which patients will have a positive response to an intervention to prevent or treat AKI

Diagnostic | Monitoring | Pharmacodynamic/Response | **Predictive** | Prognostic | Safety | Susceptibility/ Risk

Why it matters

The ability to predict which patients are more likely to have a positive response to an intervention (e.g., drug, biologic, fluid, or device) to prevent or treat AKI **will result in more personalized, patient-centered decision making.**

Drug Development

Need

A biomarker that **indicates underlying risk factors or pathophysiological pathways could be used to identify individuals with AKI** to enroll in trials of therapeutics that target that pathway. This could also increase the statistical power of the trial, enabling trials to be conducted more efficiently.

Participant Impact

- **Enable patient stratification approaches and biomarker-based adaptive clinical trial design strategies that allow targeting and dosing of therapeutics** to individuals who are more likely to experience the greatest response
- **Identify molecular or genomic targets** in a pathophysiological pathway that can be affected by therapeutics
- **Enhance benefit-risk profile** for trial participants

Clinical Care

Need

AKI intervention typically focuses on addressing the cause of the injury, balancing fluid and nutrient levels, and/or supplementing kidney function. In the future, it could involve administration of a drug, device, or biologic to prevent development and/or progression of AKI and avoid near-term morbidity and long-term CKD. Patients with AKI often experience multiple concurrent health issues, and **unnecessary interventions could increase their overall risk of negative health outcomes.**

Patient Impact

- Enable clinicians to use **precision medicine,** offering treatments and interventions to patients most likely to benefit
- Provide readouts on **whether the therapeutic successfully engages its target,** giving patients **more confidence that the care they receive for AKI will be successful** and minimizing health risks from unnecessary procedures

Characteristics of Effective AKI Biomarkers

There are various factors related to biomarker data and measurement that have an impact on how useful the biomarker will be in informing clinical decision making. The characteristics indicated below are the most critical for AKI biomarker applications. Note that the importance of individual characteristics varies by use case (e.g., correlation with timing, severity of disease, and regional specificity of cellular dysfunctions are more important for a diagnostic biomarker than for a biomarker used to predict response to an AKI treatment drug).

High sensitivity*	High sensitivity refers to the ability to identify positive cases and minimize false negatives. Sensitivity is a critical factor for AKI biomarkers because of the limited time window for effective AKI intervention. Failing to detect cases of AKI, heightened risk for AKI, or disease progression could **delay or prevent a necessary intervention and negatively impact patient outcomes.**
High specificity*	High specificity refers to a low rate of false positives (i.e., changes in a biomarker value caused by something other than AKI). Specificity is important to AKI because changes in biomarker values mistakenly attributed to AKI can result in **unneeded AKI interventions or unnecessary interruptions of critical medical interventions for other issues (e.g., antibiotics).**
Correlation with timing and severity of disease and regional specificity of cellular dysfunctions	Detecting injury early in its course is valuable in establishing a meaningful correlation to mild, moderate, and severe disease. In the case of AKI, more severe disease requires different interventions (e.g., drug dose modifications or renal replacement therapy [RRT]), so **the correlation of biomarker values with disease severity is crucial to avoid over- or under-treating patients.**[23] Biomarkers indicative of region-specific cellular dysfunctions (e.g., in glomeruli vs. tubules vs. interstitium) will enable precision medicine-based mechanistic interventions. In addition, easily collected and processed specimens abundant in the biomarker would also enable greater efficiency that could lead to faster detection of AKI.

* Sensitivity and specificity are often a trade-off. The diagnostic accuracy of a treatment is a value that takes into account sensitivity, specificity, and prevalence of disease to enable assessment of the overall predictive value of a biomarker.

23 McIlroy, David R., Gebhard Wagener, and H. Thomas Lee. "Biomarkers of Acute Kidney Injury: An Evolving Domain." *Anesthesiology* 112, no. 4 (2010). https://doi.org/10.1097/ALN.0b013e3181cded3f.

Assay standardization and robustness

For a biomarker to provide meaningful information, **it must also be possible to consistently measure and compare data from lab to lab,** which requires robust assays that are quality controlled and comparable across assay sites. Ideally, AKI biomarker assays should be able to provide rapid, consistent results despite variation among patients in blood parameters, drugs they are taking, urine pH and ionic strength, or freezing and storage of samples.[24] Quality control of assay workflow is also important to ensure that errors or inconsistent pre-analytical practices do not impact results. Additionally, clear guidance on assay interpretation is critical to ensure consistency.

Robust and reproducible change from baseline

Low normal biomarker variability will enable better understanding of signal versus noise in biomarker values. Biomarker changes would ideally demonstrate minimal diurnal patterns in both healthy and diseased populations, as well as minimal changes with fasting, exercise, menstruation, pregnancy, medications, and other factors under normal and abnormal physiological conditions. If there is baseline variability, then a consistent statistically robust change from baseline value will drive the interpretability and usage.

Minimal risk of adverse outcomes if incorrectly interpreted

Once adopted by clinicians, biomarkers will be used to guide clinical diagnostic and therapeutic decisions, guide participant selection for clinical trials, and measure the effects of drugs under development. Inaccurate interpretations of biomarker data (e.g., due to complexity of interpretation or clinical settings where there is no clear guidance on the clinical use of a biomarker-based measurement) could **put patients at risk of harm or lead to an erroneous conclusion about a drug's potential to cause kidney injury.** Regulatory decision making also depends on valid interpretations of biomarker data. The potential for harm varies depending on the use case but could include:

- Incorrectly identifying an individual who is at high risk of AKI as being "low risk"
- Falsely concluding there is injury when there is none and removing an effective therapeutic
- Failing to detect the presence of AKI and using a therapeutic that would be contraindicated if AKI was correctly ascertained

24 McIlroy, David R., Gebhard Wagener, and H. Thomas Lee. "Biomarkers of Acute Kidney Injury: An Evolving Domain." *Anesthesiology* 112, no. 4 (2010). https://doi.org/10.1097/ALN.0b013e3181cded3f..

Challenges to Accelerating AKI Biomarker Development

Newly discovered biomarkers must be investigated, proven valid for the use cases in the previous section, and found to be readily and reliably measurable before they can be widely adopted. **This development process is often complex and time consuming.** Progress in a biomarker's development is typically completed piecemeal through one-off studies, without a single process owner or centralized guidance to identify when a biomarker is mature enough to transition from one stage to the next. The process generally includes the following stages:

Discovery of a new biomarker

Analytical and Clinical Validation

- Analytical validation of biomarker clinical assays to demonstrate assay accuracy, precision, reproducibility in different labs (i.e., robustness), sensitivity, specificity, matrix effects, identification of interfering substances, stability at various temperatures, and other key biomarker characteristics
- Clinical validation of biomarker utility via successive studies across hundreds or thousands of trial participants to understand variability, identify thresholds, guide statistical interpretation of the data, and confirm the linkage to a health outcome

Implementation of a biomarker in therapeutics trials or clinical use, sometimes paired with a new intervention, with demonstration of utility in drug discovery and/or clinical use

The most common path to regulatory acceptance for a biomarker or panel of biomarkers involves submitting data demonstrating utility as part of the Investigational New Drug (IND), Biologics License Application (BLA), or New Drug Application (NDA) package. While this route can facilitate adoption, other stakeholders and pharmaceutical companies do not have access to the biomarker data submitted, leading to redundancy and/or underutilization of a valuable biomarker. It is therefore important to recognize the two other pathways through which regulatory acceptance can be attained for biomarkers as therapeutic development tools:

- Qualification using the U.S. Food and Drug Administration's (FDA) Biomarker Qualification Program or Medical Device Development Tools program
- Scientific/community consensus whereby peer-reviewed publications demonstrate general community agreement of a biomarker's analytical and clinical utility

Although acute kidney injury (AKI) biomarkers have been actively studied by the kidney community for many years, only a handful of AKI biomarker assays have been evaluated by regulatory agencies for use in the U.S., EU, and Asia. **Not only has the development process been slow, but these biomarkers have also seen limited adoption by the community to date.**[25]

This slow rate of progress is the result of various scientific and technical hurdles, including lack of effective interventions for AKI, absence of timely test availability, difficulty gaining access to unpublished data, and lack of organized collaborative efforts to bring together drug developers and academia to gather evidence and advocate for utilization in specific contexts of use. **With AKI increasing in incidence and increasingly recognized as leading to chronic kidney disease (CKD), patients cannot afford to wait decades for biomarkers that can improve diagnosis, care, and drug development for AKI.** The community must work together to overcome these challenges.

25 Ostermann, Marlies, Emma Karsten, and Nuttha Lumlertgul. "Biomarker-Based Management of Aki: Fact or Fantasy?" *Nephron* (2021): 1–7. https://doi.org/10.1159/000518365.

Overarching Strategic Challenges

All challenges are applicable to both **clinical care** and **therapeutic development.**

Limited Community Coordination on Biomarker Development and Regulatory Endorsement

Due to the de-centralized biomarker development process, **there is currently no broad consensus on which AKI biomarkers are equivalent or superior to traditional detection methods for specific use cases.** Biomarker studies are often performed in isolation, without communication between stakeholders or coordination of efforts toward the larger goal of filling gaps in data needed for the biomarker to justify its use.

Additionally, individual biases and preferences on biomarkers can slow progress, and there is a need to identify how certain biomarkers may map to specific disease processes or drug efficacy rather than expecting that a biomarker be universally applicable for all use cases relating to AKI. Greater cooperation by the community is needed to increase development, facilitate FDA qualification, and increase use of promising AKI biomarkers.

Large Number of Potential Biomarkers for Development

The sheer number of different biomarkers diffuses the efforts of the community. With attention spread across a wide field of potential biomarkers, biomarkers that initially showed promise frequently go years without additional study. Long lapses between studies result in a feedback loop where neglected biomarkers become less likely to receive attention or investment over time.

Community Reluctance to Share Data

In many cases, valuable data exist that could be used to advance the evaluation and use of biomarkers (e.g., patient samples or records from product development), but **organizations are often reluctant to share data, specimens, and samples.** They may be unaware of how data sharing could benefit the community, unable or unwilling to allocate resources or anonymize data, and/or concerned about the loss of intellectual property (IP), the risk of compromising patient privacy, or the possibility that data may be obtained that could compromise use of their drug. Clinical trial samples cannot be shared with a third party unless explicitly stated in the trial consent forms, so often these samples are not available for biomarker analyses unless a champion for biomarker studies is involved from the start of trial planning.

Unclear Measures to Quantify Biomarker Success

The community **lacks clearly defined metrics for quantifying the success of biomarkers.** True biomarker success must lead to facilitated drug development for AKI and/or improved patient outcomes if used in clinical care. For example, markers of success could include more therapeutic development programs advancing to later stages or researchers using biomarkers for earlier decision making, which would facilitate evaluation of therapeutic efficacy and safety. In clinical use, studies are necessary to link use of biomarkers to better patient outcomes.

Technical Challenges

All challenges are applicable to both **clinical care** and **therapeutic development.**

Limitations of the Definition of AKI

Varying definitions have been put forth for AKI, including the Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE); AKI Network (AKIN); and Kidney Disease Improving Global Outcomes (KDIGO) classifications. **These definitions rely on changes in serum creatinine (sCr) or urine output, metrics that provide limited information about kidney function and damage.** Furthermore, the relationship between sCr and glomerular filtration rate (GFR) is dependent on a steady state, which is often not present in patients with AKI. This limits the interpretation of AKI as an endpoint in studies, can slow the study of biomarkers, and can impede development of potential treatments for AKI.

One potential way to deal with the non-steady state evaluation of GFR is to use continuous monitoring methods using freely filterable markers in the blood that allow for direct measurement of GFR; however, these methods are currently in development. The use of varying definitions for AKI across different biomarker studies also makes data more difficult to compare. A recent ADQI report on the utilization of biomarkers for kidney injury proposed an approach to bridge these differing definitions by combining the use of sCr with biomarkers of injury.[26]

Dependency on Serum Creatinine and Urine Output as Benchmarks

It can be **challenging to design meaningful biomarker studies due to the reliance on sCr and urine output to diagnose AKI.** Members of the research community are searching for biomarkers to supplement sCr and urine output, but they often draw conclusions about the sensitivity or specificity of a novel biomarker based on its correlation with changes in sCr and urine output rather than with true injury. This has held back the field.[27]

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26 Ostermann, Marlies, Alexander Zarbock, Stuart Goldstein, Kianoush Kashani, Etienne Macedo, Raghavan Murugan, Max Bell, et al. "Recommendations on Acute Kidney Injury Biomarkers from the Acute Disease Quality Initiative Consensus Conference." *JAMA Network Open* 3, no. 10 (2020). https://doi.org/10.1001/jamanetworkopen.2020.19209.

27 Waikar, S. S., R. A. Betensky, and J. V. Bonventre. "Creatinine as the Gold Standard for Kidney Injury Biomarker Studies?" *Nephrology Dialysis Transplantation* 24, no. 11 (2009): 3263–65. https://doi.org/10.1093/ndt/gfp428.

All challenges are applicable to both **clinical care** and **therapeutic development.**

Complexity of Causes of AKI

Although AKI is often treated as one disease, **it can be caused by many different pathophysiological inputs (e.g., ischemia; sepsis; contrast agents; or drugs that affect the glomerulus, tubule, vasculature, and/or interstitium).** Studies that approach AKI as a single disease may fail to recognize biomarkers that are relevant for some specific causes of AKI but not for others. Additionally, effective AKI interventions often vary based on the cause of AKI (e.g., withdrawing a nephrotoxic drug and providing immunosuppressive therapy to treat acute interstitial nephritis).[28]

More work is needed to identify sub-phenotypes of AKI. Biomarkers can help drive this work by identifying the locations and mechanisms of kidney injury. There is also a need for a clearer understanding of molecular pathobiology and temporal patterns of kidney injury and repair to serve as a foundation for the advancement of biomarkers. Two recent reviews by Desanti De Oliveira et al.[29] and Scholz et al.[30] could serve as a starting point for this work.

Difficulty Evaluating Existing Biomarker Studies

Stakeholders within the medical community must make their own decisions on which biomarkers have sufficient supporting evidence for a given therapeutic development or clinical use case. Existing studies of AKI biomarkers have **widely variable study designs, diagnostic standards, test cut-off values, time frames, and clinical contexts (e.g., studies of trial participants with multiple comorbidities).**[31] This makes it difficult to compare studies, even if data on a biomarker have been included in published studies.

Need for More Robust Human Data

Because there has been little systematic study of biomarkers, **the data needed to validate the utility of biomarkers for use in larger-scale trials and in clinical settings are still lacking in many areas.** There is a need for increased data from different age ranges and across heterogeneous patient populations, more integration of human outcome data from longitudinal and interventional studies, adoption of context-driven testing, greater collaboration in personalized medicine, and increased use of highly annotated biopsies to assess AKI.

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28 Moledina, Dennis G., and Chirag R. Parikh. "Differentiating Acute Interstitial Nephritis from Acute Tubular Injury: A Challenge for Clinicians." *Nephron* 143, no. 3 (2019): 211–16. https://doi.org/10.1159/000501207.

29 Desanti De Oliveira, Beatriz, Katherine Xu, Tian H. Shen, Miriam Callahan, Krzysztof Kiryluk, Vivette D. D'Agati, Nicholas P. Tatonetti, Jonathan Barasch, and Prasad Devarajan. "Molecular Nephrology: Types of Acute Tubular Injury." *Nature Reviews Nephrology* 15, no. 10 (2019): 599–612. https://doi.org/10.1038/s41581-019-0184-x.

30 Scholz, Holger, Felix J. Boivin, Kai M. Schmidt-Ott, Sebastian Bachmann, Kai-Uwe Eckardt, Ute I. Scholl, and Pontus B. Persson. "Kidney Physiology and Susceptibility to Acute Kidney Injury: Implications for Renoprotection." *Nature Reviews Nephrology* 17, no. 5 (2021): 335–49. https://doi.org/10.1038/s41581-021-00394-7.

31 Rizvi, Mahrukh, and Kianoush Kashani. 2019. "Biomarkers For Early Detection Of Acute Kidney Injury". *The Journal Of Applied Laboratory Medicine* 2 (3): 386–399. https://doi.org/10.1373/jalm.2017.023325.

All challenges are applicable to both **clinical care** and **therapeutic development.**

Lab-to-Lab Measurement Variation

Many biomarkers are measured within non-commercial homebrew or research use only (RUO) assays. These assays often lack standardization across laboratories. This can potentially give **inconsistent measurements for the same assay from lab to lab.** Limited understanding of normal variation and how timing of sample collection impacts measurements could also lead to inconsistency in study data.

Lack of Baseline Biomarker Values

It is often not possible to obtain a baseline value for AKI biomarkers because patients are not evaluated until they are experiencing an adverse health condition and may not have a prior normal biomarker measurement. Establishing a well-characterized "normal" range for AKI biomarkers can enable clinical decision making even if a baseline value is unavailable. However, there has been little progress to date establishing normal ranges across diverse populations. This can lead to problems as biomarkers are used in larger studies with more diverse populations with potential comorbidities and varied demographics (e.g., age, sex, race/ethnicity). As one example, kidney function changes across the lifespan may affect normative biomarker values in pediatric patients compared to adult or geriatric patients.

Lack of Guidance on Sample Collection and Biobanking Needs

While it is recognized that timed urine collections are often better for consistency in biomarker data analysis as well as interpretation, there is currently an absence of **comprehensive guidance that details best practices for urine collection and biobanking needs** such as centrifugation, storage temperature, and stability over time. Such guidance would facilitate uniformity in research and clinical trials, thereby enabling biomarker data reproducibility.

Lack of Guidance on Interpreting Changes in Biomarker Values

Once a promising biomarker is identified, **researchers must assess how to interpret biomarker measurements as part of decision making.** Technical guidance on when and how to analyze biomarker values with respect to use of absolute values versus standard normalization practices to urine creatinine, urine volume, or urine protein will facilitate accurate biomarker data threshold calculations across studies and facilitate biomarker use. Key questions for this evaluation include how high or low levels need to be to indicate meaningful kidney injury, whether a small change is meaningful, and how to determine whether an increase or decrease indicates the need for a particular intervention (e.g., stopping use of a drug). These assessments often require a large amount of data from targeted studies. In a recent ADQI report on the utilization of biomarkers for kidney injury, the authors proposed several suggestions for decision making using AKI biomarkers.[32]

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32 Ostermann, Marlies, Alexander Zarbock, Stuart Goldstein, Kianoush Kashani, Etienne Macedo, Raghavan Murugan, Max Bell, et al. "Recommendations on Acute Kidney Injury Biomarkers from the Acute Disease Quality Initiative Consensus Conference." *JAMA Network Open* 3, no. 10 (2020). https://doi.org/10.1001/jamanetworkopen.2020.19209.

Implementation Challenges

All challenges are applicable to both **clinical care** and **therapeutic development.**

Risks of Premature Biomarker Adoption

Biomarkers require testing and validation in diverse populations prior to broad implementation. There are concerns within the nephrology community that **if biomarkers are used to guide decision making before they are well validated, their use could lead to worse clinical outcomes for patients.** For example, clinicians may respond to clinically insignificant or short-term changes in biomarker levels by unnecessarily delaying or suspending needed treatment (e.g., drugs or cardiac surgery) or by starting dialysis too soon. **In therapeutic trials, erroneous assumptions about biomarkers could lead to false conclusions about the risks or benefits of a therapeutic.**

Lack of Market Demand for Biomarker Tests

Driven by factors such as the belief that current AKI biomarkers are not actionable and the difficulty in convincing clinical labs to bring on new tests without a demonstrated clear benefit to patients, there has been low demand for existing biomarker tests, which limits the corporate incentive to create new or cheaper tests. In addition, **diagnostic companies perceive the AKI space to be limited and lacking in sufficient therapies to direct a biomarker-driven decision. This limits potential investment.** Without industry involvement to develop assay technologies and push for validation and regulatory approval of promising biomarkers, adoption of useful biomarkers is slowed. In addition, clinical trials or other data demonstrating that utilization of biomarkers can influence patient outcomes could drive further assay development, regulatory approval, and implementation by clinical laboratories.

Impact on Healthcare Disparities

As baseline biomarker data are generated at a population level, we will understand and interpret how race, ethnicity, and sex influence the biomarker level with or without disease or comorbid conditions. We must ensure that biomarker measurements and evaluation are made available from all populations and that existing **health disparities are not exacerbated** by the data generated at the population level. We must also ensure that the biomarker-based prognostic tests do not put patients at risk for predatory discrimination by insurance companies (e.g., health, life, disability).

Lack of Successful AKI Therapies Limits Biomarker Applications

Because there are few effective therapeutic options for AKI, clinicians often do not consider biomarkers to be actionable. Clinicians often follow the same precautions for all patients to minimize the risk of AKI and do not see a need for biomarkers unless they can be used to guide treatment decisions. This situation creates a cycle in which clinicians are unable to use biomarkers to identify successful therapies because of limited understanding of the insight biomarkers can provide. Without successful therapies, there is less incentive to study and increase understanding of biomarkers.

All challenges are applicable to both **clinical care** and **therapeutic development.**

Perceived Cost of Biomarkers

Laboratory-based clinical tests for biomarkers have a cost, which can be difficult to justify to payors when the impact of biomarker-based measurements on therapeutic decisions or patient outcomes is uncertain. There is also a disconnect between inpatient and outpatient care, which come from separate payor budgets, making it difficult to convince payors of the value of a biomarker-based test even if it has the potential to reduce costs over the long term. Additionally, clinicians and hospitals need buy-in from the Centers for Medicare & Medicaid Services (CMS) to provide payments for biomarker use to support adoption.

Resistance to Change Among Clinicians

Even for biomarkers with a strong body of relevant evidence supporting their application for a particular use case, **clinicians can be slow to adopt new methods.** It will be necessary to demonstrate the benefit to patient care and justify the cost of new tests by pointing to studies that demonstrate their cost effectiveness. Additionally, clinicians often already believe they are providing the highest possible standard of care and may be reluctant to be early adopters of new biomarkers.[33]

33 Lieske, John, Kianoush Kashani, John Kellum, Jay Koyner, Ravindra Mehta, and Chirag Parikh. 2020. "Use of Biomarkers to Detect and Manage Acute Kidney Injury: Has Progress Stalled?". *Clinical Chemistry* 66 (2): 271–276. https://doi.org/10.1093/clinchem/hvz026..

Action Items for Achieving Roadmap Strategy

Biomarker development challenges are complex and often interwoven, and no single organization has the resources to shepherd a biomarker fully through the process from discovery to adoption. To address the challenges to accelerated biomarker development and realize the many improvements that acute kidney injury (AKI) biomarkers could bring to therapeutic development and clinical care, **the community must take coordinated action on shared priorities.** This cooperation will be critical to ensuring that stakeholders can build on one another's activities and address challenges that cut across different stakeholder groups. **The recommendations outlined in this section chart a path for the next five years toward overcoming the challenges to accelerated biomarker advancement in a systematic, collaborative way.**

Key Activity Themes

This roadmap's recommendations are divided into seven key activity themes, which outline how the community can:

- **Align** around common goals
- **Increase incentives** for biomarker development and study
- **Create mechanisms** for coordination and collaboration among industry, clinicians, scientists, and regulatory agencies (e.g., NIH, FDA) to outline the steps required for biomarker development
- **Leverage** the National Evaluation System for Health Technology (NEST) and other coordinated databases to collect data
- **Enable more efficient** study of AKI by better defining AKI and its phenotypes using biomarkers
- **Support increased adoption** by using data to make biomarkers more actionable and demonstrate their benefits
- **Involve patients** in the process, as they will be the beneficiaries of biomarker development
- **Promote** international collaboration

Optimize Biomarker Testing and Integrate Appropriate Biomarker Use into New and Ongoing Studies

Data from new and ongoing studies **can be used to answer critical questions about biomarkers to make them more actionable and further drive their development** in coordination with the study of potential AKI treatments.

Collaborate on Biobanking, Data Collection, and Data Sharing

Biobanks and clinical trial datasets are valuable existing resources for evidence that could benefit AKI biomarker studies by 1) enabling computation of reference ranges and variability across demographics; 2) showing the correlation of biomarkers with kidney protective treatments or 3) answering other critical scientific questions. Developing partnerships and getting AKI biomarker champions involved in clinical trials early could help the community leverage these resources for biomarker studies. Additionally, there is the opportunity to create a dedicated, centralized repository of AKI samples to support generation of data and validation of assays for AKI biomarker development.

Use Biomarkers to Better Define AKI and its Phenotypes

AKI biomarkers can be used to **develop a more precise definition of AKI** that maps more closely with true injury at a cellular level than the current functional definitions based on serum creatinine (sCr) and urine output. An improved definition could also take into account the various potential causes of AKI and establish clear phenotypes. Such definitions can serve as the foundation for the use of biomarkers and help facilitate understanding of AKI as well as enable efficient development of treatments for AKI.

Support Coordinated Biomarker Development and Qualification

Current decentralized methods of data collection should be organized into a more systematic effort that leverages the activities of different stakeholder groups and seeks to answer specific key questions and fill high-priority data gaps. Additionally, **action is needed to spur increased research within academia, as well as investment by diagnostic companies** with the resources to drive validation of tests and help push biomarkers toward clinical adoption. This could be achieved through increased funding and initiatives to raise awareness of the opportunities within the AKI biomarker space.

Develop AKI Biomarker Guidance and Best Practices to Facilitate Adoption

Data collected by the nephrology community can be used to help researchers and clinicians interpret and use biomarkers. The **development of guidance and resources that target common questions and pain points** can help accelerate adoption by the community.

Increase Awareness of Biomarker Benefits

Clinicians, drug developers, payors, and patients all have limited awareness of the potential benefits of AKI biomarkers. **Patient education campaigns could help to drive enrollment in clinical trials** and build the foundation of demand for biomarkers, while also helping patients to better advocate for themselves and understand their health risks. **Successfully demonstrating the evidence of biomarker benefits for clinicians and payors will be important for increasing adoption of biomarkers** as a standard part of risk evaluation, diagnosis, and care.

Focus Community Efforts

Efforts within the nephrology community to study promising biomarkers are currently diluted across disparate candidates and are not sufficiently focused on answering specific questions or fulfilling specific data gaps to move biomarkers forward. **Attention should be focused on 1–2 of the highest-priority use cases, with research focused on 5–10 biomarkers within each use case.**

Timelines for Roadmap Activities

With concerted effort from the community around specific activities and adequate resources, **the vision of accelerated biomarker development could potentially be realized by 2028.** The table below describes action items that can help achieve meaningful progress in accelerating AKI biomarker development. Activities are divided by theme, use case, and whether they can be pursued over the near term (2022–2024), mid term (2025–2027), or long term (2028+).

Action Items and Proposed Timelinesto Accelerate AKI Biomarker Implementation

Optimize Biomarker Testing and Integrate Appropriate Biomarker Use into New and Ongoing Studies

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Demonstrate that use of biomarkers in clinical practice will result in positive net health impact, potentially by **conducting randomized controlled trials (RCTs).** These RCTs could evaluate a strategy in which the biomarkers are used to inform decision making against one in which the biomarkers are not used.	→		
Conduct simulation studies on clinical trial enrichment using biomarkers.	→		
Use available biomarkers to monitor for nephrotoxicity from known nephrotoxins in hospital and outpatient settings.	→		
Identify at-risk patients, using functional and/or kidney injury biomarkers, prior to initiation of a therapeutic drug or invasive intervention which has the potential for kidney injury.	→		
Aggregate data from clinical studies of therapeutics in development where there is well-defined information on time courses and dose dependency related to toxicity.	→		
Link with and leverage Foundation for the National Institutes of Health (FNIH) activity where safety biomarkers were evaluated and an algorithm established, including potentially identifying overlap between FNIH-identified markers and literature evidence for those markers as indicators of kidney injury when the cause is not an identified nephrotoxicant.	→		

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Identify clinical studies—either academic or pharma—where samples exist that can be used to validate biomarkers, and test patient samples.	→	→	
Quantify actual glomerular filtration rate (GFR) loss (total and baseline) and tubular function changes with measured GFR (mGFR) techniques prior to and following AKI in high-risk patients prior to initiation of a therapeutic drug or invasive intervention which has the potential for kidney injury.	→	→	
Establish cut-off values based on large, randomized, multi-site studies for AKI diagnosis, AKI severity, AKI resolution, and patient stratification for AKI prevention/ early treatment trials.	→	→	→

Collaborate on Biobanking, Data Collection, and Data Sharing

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Advocate for a presumptive availability of collected leftover study biological samples (an "opt-out" approach) to be used for biomarker research.	→		
Conduct coordinated advocacy efforts (e.g., between the American Society of Nephrology [ASN] and the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]) to establish **targeted Requests for Application (RFAs) related to AKI biomarker advancement,** similar to the acute respiratory distress syndrome (ARDS) network.	→		
Conduct a meta-analysis of existing biomarker data for therapeutic development, leveraging data that has not yet been analyzed in prior and current clinical trials where biomarkers are measured or samples collected.	→		
Leverage existing datasets across academia and industry, including prospective data if available, to try to get at the attributable risk (true etiologic contribution) of AKI for CKD and other important clinical outcomes.	→		
Establish a consortium to collect data from pharmaceutical companies, mining and making data available to the community in an anonymous, pre-competitive manner; a pilot under way by the Critical Path Institute (C-Path) related to drug-induced kidney injury could be leveraged or used as a model and broadened to include biomarkers to be used in clinical practice or as efficacy or safety biomarkers for AKI treatments.	→		

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Expand the role and participation of FDA in biomarker development and use, encouraging data sharing in the community by dissemination of "lessons learned" and facilitation of drug evaluation as a result of the use of biomarkers.	→		
Develop a central biomarker data repository using standardized data formatting that will leverage existing datasets and collect and share new data as they arise. This could potentially leverage existing data repositories from C-Path and NIDDK.	→		
Establish data sharing agreements between key stakeholders (e.g., pharmaceutical companies, industry, and academia) to help collectively analyze biomarker data, improve transparency, and facilitate adoption. Existing data sharing agreements (e.g., between C-Path, NIDDK, and pharmaceutical companies) could serve as a model.	→		
Develop a centralized biobank repository or more inclusive system of sample sharing for AKI samples with diverse subject demographics to support generation of robust and reproducible biomarker data and to help validate assays.	→	→	
Encourage existing biobanks to share samples to support biomarker research.	→	→	
Look for **opportunities to synergize and prevent duplication of effort** among activities across the AKI space (e.g., C-Path/FNIH, Kidney Precision Medicine Project, NIDDK).	→	→	

Use Biomarkers to Better Define AKI and its Phenotypes

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Use biomarker-based AKI phenotypes to help develop targeted therapies for AKI phenotypes.	→		
Identify financial resources to do **targeted biomarker analyses in well-phenotyped cohorts.**	→		

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Mine nonclinical data to understand relationships between biomarkers and physicochemical properties; absorption, distribution, metabolism, and excretion (ADME); transporter activity; therapeutic index; mechanism of action; or mechanism of toxicity.	→		
Define AKI sub-phenotypes more precisely (e.g., look at nephrotoxic, septic, and hypoperfusion related AKI). This effort could leverage trials from other disciplines (e.g., ARDS, heart failure), where there are banked samples and clinical data to combine with data science approaches and biomarker assessments.	→	→	
Link biomarker level quantitatively to severity of AKI to help identify patients with severe (e.g., stage 3) AKI, not simply AKI as a categorical event, to gather data for use in drug trials and to demonstrate value to payors and iterate this process as new data becomes available.	→	→	
Update the AKI definition to incorporate biomarkers, alongside or in place of sCr and urine output (once robust, reproducible data are generated clearly demonstrating AKI biomarker benefits). The new definition would enable understanding of dynamic changes based on how a combination of biomarkers changes over time, similar to how the indices for lung function (e.g., P/F ratio), blood gases, and oxygenation index (OI) can track ARDS.	→	→	→

Support Coordinated Biomarker Development and Qualification

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Work with FDA on strategy and requirements for qualification of biomarkers in narrow contexts of use and approval of devices involved in biomarker measurement (e.g., wearables or point of care testing systems) leveraging Predictive Safety Testing Consortium (PSTC)/FNIH work on safety biomarkers and the work of existing kidney consortia that have appropriate samples and clinical outcome data.	→		
Fund targeted research, with funding announcements (e.g., from NIH) using a systems-based approach to AKI biomarker research.	→		
Promote collaboration between translational research scientists, regulatory agencies, and industry to **validate a biomarker toolbox for use in AKI trials.**	→		

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Initiate a close collaboration with the **C-Path AKI initiative on drug-induced AKI.**	→		
Catalog biomarker publications for AKI by use case and evaluate conclusions and ambiguities.	→		
Establish biostatistical approaches to optimize analyses, including approaches to include multiple biomarkers and machine learning approaches.	→		
Conduct a metanalysis of existing data for clinical care, using newer statistical techniques to help identify which markers could be targeted for subsequent clinical assessment prospectively. Payors should be looped into this process to understand what they need to see.	→		
Conduct outreach to other relevant medical disciplines beyond nephrologists involved in biomarker development (e.g., pediatrics and neonatology, critical care, cardiology, anesthesiology, emergency medicine).	→		
Develop biomarker reference ranges that cover potential comorbidities and demographics (e.g., age, sex, race/ethnicity), as well as standardized approaches and methodologies for validating and establishing both the clinical utility and pathogenic significance of those reference ranges.	→	→	→
Develop panels of complementary biomarkers (e.g., combination of functional and damage biomarkers, or biomarkers for different injury pathways) to provide greater insight than specific biomarkers can provide in isolation.	→	→	→
Pursue additional approaches for biomarker discovery beyond urine and serum biomarkers (e.g., RNA sequencing, microscopy, ultrasound, CT scans, genomic biomarkers).	→	→	→

Develop AKI Biomarker Guidance and Best Practices to Facilitate Adoption

Activity	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Catalog laboratory validation status of assays.	→		
Identify point-of-care approaches to measurement in a clinical setting and demonstrate care management changes guided by AKI biomarkers.	→		
Recruit a subset of clinicians to act as early adopters of AKI biomarkers to promote their clinical use.	→	→	
Support the transition of promising AKI biomarkers from academia to the diagnostic/ biotech/pharma sector where there is the infrastructure and knowledge to gain FDA approval.	→	→	
Create uniform guidelines for biomarker data interpretation, compared to or in addition to the measurement of traditional markers and/or histology in non-clinical and clinical studies, for drug developers, clinicians, and regulators.	→	→	
Develop robust and reproducible assays for measuring qualified biomarkers in mice, rats, dogs, nonhuman primates, and humans on a standardized easily available platform.	→	→	

Increase Awareness of Biomarker Benefits

Action Items	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Educate patients on biomarker-based tests and their value and what the use cases mean to them to drive demand for biomarkers and enrollment in clinical trials (e.g., develop a patient information plan to advise them on their probability of developing AKI). Increase general knowledge of biomarkers (e.g., collection methods, associated cost, potential impact on insurance coverage), and their role in driving health predictions.	→		
Organize workshops to help raise awareness within the community of biomarker needs and opportunities for career growth in the space.	→		
Interview payors on what they need from biomarker studies/evidence.	→		

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Demonstrate a clinically actionable positive result to payors, clinicians, regulators, and patients to get buy-in and rapid forward movement. This could be achieved by designing a prospective study related to nephrotoxicity and showing the different outcomes from withdrawal or non-withdrawal of an agent.	→	→	
Continue to raise awareness in the kidney community on how AKI biomarkers have the potential to change medical practice.	→	→	→
Leverage artificial intelligence to conduct more sophisticated modeling to analyze the cost/benefit ratios of new AKI biomarkers, informed by input from payors about their needs, and draw conclusions based on historical trends in patient outcomes, helping to demonstrate long-term savings of AKI biomarker use to payors.	→	→	→

Focus Community Efforts

Action Item	Near Term (2022-2024)	Mid Term (2025-2027)	Long Term (2028+)
Select 1–2 specific use cases to focus on to better channel community resources.	→		
Choose a limited set of 5–10 biomarkers within the selected use cases to study more systematically.	→		
Interview clinicians and drug developers about their biomarker needs, including the types of biomarkers that would be most useful, the optimal number of biomarkers to include in a panel, and why they believe AKI biomarkers have not moved forward.	→		

By working together to achieve concrete objectives that address the barriers to AKI biomarker development and adoption, **the kidney community can close this persistent gap between the potential benefits of AKI biomarkers and the current reality of their slow advancement.**

Path Forward

The promise of acute kidney injury (AKI) biomarkers was identified by the community more than two decades ago, with efforts from the Predictive Safety Testing Consortium (PSTC) in 2006 building on many prior studies from various laboratories and drug developers. Since then, there has been a great deal of research in the AKI biomarker field but **limited overarching strategy or organization of community efforts.**

By working together to achieve concrete objectives that address the barriers to AKI biomarker development and adoption, **the kidney community can close this persistent gap between the potential benefits of AKI biomarkers and the current reality of their slow advancement.** This effort will require the participation of all stakeholder groups within the community, each of which touch on different aspects of the AKI biomarker development process and have specific roles to play:

- **Clinicians and healthcare providers** can be early adopters of validated biomarkers and advocate for their wider use, as well as contribute de-identified data on real-world patient outcomes and share knowledge to align work (e.g., among adult and pediatric nephrologists).
- **Government agencies** can play a key role in incentivizing cooperation and providing strategic leadership around biomarker development and can work with the community to identify opportunities to speed regulatory qualification and approval processes.
- **Industry professionals** can provide infrastructure and investment to develop commercial tests and help biomarkers achieve regulatory validation, as well as contribute de-identified data for common use.
- **Payors** can support the increased use of biomarkers by incorporating them into payment structures.
- **Researchers** drive the scientific investigation and development of biomarkers and can become key advocates for collaboration by identifying and leveraging mechanisms for the collection and sharing of data.

In addition to these specific roles, all stakeholders must work together through consortia and other trans-consortial data-sharing initiatives to ensure that their activities remain aligned and that verification of biomarker utility proceeds as efficiently as possible, without duplication of effort. **Through these actions, the community can accelerate biomarker development and begin to reap the benefits of these valuable tools for predicting, detecting, and informing treatment of AKI.**

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Roadmap for Accelerating the Development of Biomarkers for Acute Kidney Injury

KHI KIDNEY HEALTH INITIATIVE

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