International 2022 Drug-induced Kidney Injury Biomarker Workshop Proceedings

Facilitating Progress in Evaluation and Utility of Drug-induced Kidney Injury Biomarkers

Introduction

Drugs contribute to severe acute kidney injury (AKI) in large numbers of patients (ASN KHI, 2022; Bendjama et al., 2014). Early diagnosis of drug-induced kidney injury (DIKI) is a significant challenge in clinical care and during drug development. On May 23 and 24, 2022, the Critical Path Institute's (C-Path's) Predictive Safety Testing Consortium (PSTC) held the *International 2022 Drug-induced Kidney Injury Biomarker Workshop* for stakeholders to assess the state of the field and align on a plan for developing improved tools to detect and monitor DIKI. C-Path is a non-profit organization that creates private-public consortia to facilitate the drug development process. Workshop participants and presenters included people with chronic kidney disease (CKD), those who experienced past DIKI events, clinicians, academics, U.S. Food and Drug Administration (FDA) staff, and representatives from the pharmaceutical and biotechnology industry. The workshop addressed the following DIKI-related topics: challenges and unmet needs, patient personal perspectives, the power of collaboration, and proposed solutions and innovative drug development tools (DDTs).

Addressing the Unmet Need through Biomarkers

Biomarkers can provide information relating to the risk of developing acute kidney injury (AKI), diagnosis of AKI, monitoring of disease status, and the site of injury in the kidney. The mechanisms underlying DIKI are varied and multifactorial. Drugs can cause injury via different mechanistic pathways, resulting in vasoconstriction, glomerular injury with impaired filtration and proteinuria, capillary loss or enhanced permeability, and/or tubular damage with secretory and reabsorption dysfunction and/or tubular obstruction. These processes can involve multiple kidney regions. Workshop participants agreed that biomarkers are needed to identify both site and mechanism of kidney injury. Different mechanisms of injury to the same nephron region may result in different biomarker profiles. To characterize biomarker responses to different types of injury, a wide range of data are needed from diverse drugs with different modes of nephrotoxicity. In addition to the type of kidney injury, it is important to obtain biomarker data in various demographic groups, defined by gender, ethnicity, race, and age, including children and the elderly. Patients with a range of background kidney diseases and comorbidities receiving various concomitant medications should be included.

While severe kidney injury can lead to dialysis dependence or death, even mild kidney injury takes on a high level of importance when we recognize that DIKI can lead to long-term kidney damage with tissue fibrosis and contribute to the growing population prevalence of CKD. Given the prevalence and unfavorable consequences of DIKI, we need better diagnostic tools since current biochemical standards, blood urea nitrogen (BUN) and serum creatinine (SCr), are neither sufficiently sensitive nor specific. Renal reserve can result in SCr and estimated glomerular filtration rate (eGFR) remaining within normal ranges

even when there is significant kidney injury and parenchymal replacement by fibrosis. Also, SCr and eGFR changes are delayed upon loss of renal function due to the need to accumulate creatinine in the blood before a significant change can be detected and can result in a false sense of security when the SCr is in the "normal" range. Finally, drugs interfering with the extraglomerular clearance of creatinine can lead to false positive safety signals.

In addition to supporting the diagnosis of drug-induced AKI, DIKI biomarkers can identify which patients are more susceptible to nephrotoxicity when exposed to certain drug classes and help to identify patients who are at higher risk to progress to CKD after DIKI. New DIKI biomarkers will enhance safer clinical trial designs and monitor efficacy of novel treatments in the future. Informing participants of their changing trends in standard and novel biomarkers of injury can be considered a critical component of the informed consent between drug developers, investigators, and study participants. Technically and clinically validated biomarker assessments can protect clinical trial participants by enabling earlier detection of potential adverse effects of study drugs or procedures on their kidneys. As more novel biomarker data accrue, decision-making can improve for patients, clinicians, drug developers, and health authorities.

An example of subsets of patients that are often subjected to nephrotoxic drugs are individuals with cancer. This greater susceptibility is in part due to the intrinsic nephrotoxicity of many cancer therapies, frequent concurrent medication usage, unrecognized prior kidney injury, and other prevailing comorbid conditions such as liver abnormalities in these patients (Salahudeen and Bonventre, 2013). The effectiveness of these drugs in transforming many patients with cancer into cancer survivors with chronic diseases has led to a growing prevalence of AKI and CKD.

Addressing Patient Perspectives and Involvement

At the workshop, eleven people with demographically diverse backgrounds shared their DIKI experiences (**Appendix 2**). Stories, such as the one below, highlighted the importance of ensuring that people who may be at greatest risk of DIKI, such as people with CKD or those who have received a kidney transplant, are educated about the risks of DIKI, and are empowered to advocate for themselves. One individual's personal experience below is representative of informed workshop participants. Unfortunately, it is not typical of what most patients know or experience. Typically, patients aren't aware of DIKI risks. Sharing the results of this workshop will assist in increasing patient knowledge and ability to advocate for themselves and other patients.

"After receiving a kidney transplant, while most patients are warned against taking ibuprofen and too much aspirin, I never received patient education on the risks of DIKI. Patients are advised to notify their transplant centers before they add or change medications, but that's a far cry from educating them about the potential for DIKI. I gained my knowledge when I was hospitalized several times due to infections. During hospital admissions, I did my own research on the DIKI risks created by antibiotic use and hospitalization itself. This is one example that stands out to me: After my radical prostatectomy, I had a post-operative infection that resulted in hospitalization. Upon admission, the infectious disease physician wanted to initiate vancomycin antibiotic treatment. I told the attending physician that I was aware of the kidney health risk and that I preferred an antibiotic with a better kidney safety profile. To the attending's credit, he found a safer option that resolved the infection."

Patients are uniquely positioned to provide "individual insider perspective" on potential life enhancements expected from novel kidney disease drug treatments. Active patient engagement committees (PECs), convened by drug developers, facilitate the inclusion of patient insight and experiences, as well as desires and preferences, into all stages of clinical trial design (Patrick-Lake, 2018).

As described in the oncology example above, the higher risk-to-benefit ratio in vulnerable patient populations, amplified by the rigors of daily life responsibilities, may disincentivize patient anticipation and enrollment in clinical trials of new investigational drugs, and can negatively impact retention in long-term extension trials. When study participants are fully informed – using patient-friendly language – about how standard and novel biomarkers can provide early signs of potential kidney toxicity, they may better understand how their participation in a clinical trial could prevent further kidney damage and benefit both themselves and other patients.

The informed consent process provides an opportunity to level-set study participants' understanding of safety and tolerability, as well as the potential benefits and risks of any investigational product. When presenting a clinical trial participation opportunity to patients, extensive medical/legal/regulatory experts' inputs should optimally be consolidated into the Informed Consent Document (ICD) and conveyed in patient-friendly language.

There are several opportunities to proactively inform patients about safety information to increase clinical trial participation, as summarized below:

- Augment standard safety biomarker data by sharing **novel** kidney safety and efficacy biomarker information to provide fair and balanced information immediately relevant to the study participant.

- When trial results are known, convey the relationship of biomarkers to patient-reported outcomes of efficacy and safety allowing an ongoing dialogue with study participants with how they feel, and relate these results to function and survival.

- When trial results are known, inform patients of individual or aggregate "snapshots" of efficacy and safety of standard and novel biomarkers to further motivate retention in clinical trials.

The potential use of kidney safety biomarkers as efficacy biomarkers in kidney disease trials could facilitate new drug development programs. Better patient understanding of the role of biomarkers in monitoring efficacy, as well as safety, would further encourage more informed participation in clinical trials.

In summary, individual patient and PEC awareness of standard and novel biomarkers of kidney safety and efficacy in kidney diseases will provide feedback to study participants considering clinical trial "high risk to attain high reward" participation. Our recognition of patient faith and courage to accept benefit/risk tradeoffs may foster robust and diverse exploration of treatment options for kidney diseases. Involvement of patients and empowering them as equal partners in clinical research and design will ultimately inform the wider patient community.

Enhancing Drug Development Tools (DDTs) by Standardizing Approaches & Integrating Data

There are several important efforts underway to obtain data that could inform our understanding of potential biomarkers of DIKI. These efforts represent an important opportunity to obtain impactful data in the near term. Large biomarker datasets can also facilitate FDA qualification of biomarker(s) and ultimate clinical utility. There is an opportunity to integrate disparate biomarker datasets from large sample sizes across a wide range of demographics, different types of kidney injury, and from a mix of clinical trials, observational studies, and possibly real-world data. The pooling of rich data obtained from heterogeneous sources will allow detailed sub-group analyses that is not possible with individual datasets. Once data are collected into a large, curated database, FAIR (Findability, Accessibility, Interoperability, and Reusability) principles allow for simpler interrogation of the data by multiple researchers. Workshop consensus confirmed the importance of combining data from different sources: public-private consortia, pharmaceutical and academic clinical trials, and cohort studies. Effective collaboration among academia, industry, and the patient community is crucial to advance detailed analyses that lead to expanded or novel use cases for the kidney injury biomarkers to detect the presence and site of injury, predict who is more susceptible to injury, predict the likely outcome of injury, or establish surrogate endpoints. There will be challenges, however, in integrating data from multiple sources, combining retrospective, prospective, and real-world datasets, such as:

- Data may not have been collected consistently across types, with certain data being incomplete or lacking elements that other data contain. Vastly different data formats and structures can require a need for robust standardization. Data handling and storage conditions can also vary causing challenges to standardization.
- Different data may have been attained using different assays. Variability may exist between assays due to variable quality control. There may also be differences in characterization of the kidney injury and data recorded across studies. This can result in residual ambiguity despite using standardized case report forms for data extraction and transfer. The importance of collecting metadata (e.g., how samples were collected, precise clinical phenotype, assays used) was highlighted at the workshop.
- Consent or de-identification may not be adequate to allow for sharing data across organizations.

A Biomarker Data Repository, Collaboration

Drug development tools (DDTs) that help predict or mitigate safety issues, diagnose AKI early, and evaluate treatment efficacy can improve patient management by enabling early drug withdrawal, guiding selection of safter therapies, and preventing progression to CKD. Also, the engagement of the FDA will potentially encourage the *in vitro* diagnostic (IVD) industry, biotechnology companies and laboratories to develop supporting assays and diagnostic tests.

Sharing data is critical for all stakeholders, as no single organization has the resources to collect adequate evidence for biomarker qualification. As such, public-private partnerships should be leveraged. There are many examples of successful collaborations wherein complete de-identified medical history and demographic data, as well as technical validation plans and analytics quantifying correlations and insights, are routinely available for analyses. These collaborations include the Kidney Precision Medicine Project (KPMP) (Hansen et al.,2022), the Predictive Safety Testing Consortium (PSTC) (Bonventre et al., 2010;

Burch et al., 2015; Mikaelian et al., 2014; Sistare et al., 2010; US FDA, 2018), the Innovative Medicines Initiative (IMI) consortia SAFE-T, and TransBioLine (Bendjama et al., 2014; Church et al., 2018).

By using accepted data standards and clinical consensus for kidney disease endpoints to streamline clinical data submissions, it becomes more feasible to robustly assess meaningful clinical correlations between novel biomarkers and clinical outcomes. The multifaceted complexity of data needed is summarized in the supplemental materials (**Appendix 3**).

A new real-time opportunity exists to contribute data and advance new qualifications through sharing data with the C-Path Biomarker Data Repository (BmDR). During the workshop, as initial examples, Pfizer presented three projects involving new renal biomarker datasets that the company plans to share with C-Path's BmDR after publication. These data are intended to provide an opportunity to understand the thresholds and variability of renal biomarkers from healthy volunteers (HV) and different disease backgrounds.

Conclusions

This workshop brought together the breadth of stakeholders involved in development, implementation, and interpretation of DIKI biomarkers. Presenters, panelists and other participants provided their perspective and concluded:

- Patient input is critically important to embody the importance of biomarkers for kidney health and welcome their participation as proactive allies in demographically diverse clinical studies whose conclusions will ultimately serve all populations who are at risk of kidney injury.
- Advancement and implementation of emerging DIKI biomarkers will require contributions and participation from all stakeholders.
- Sharing clinical trial data on use of the qualified DIKI biomarkers is needed for broad implementation and for the understanding of baseline and thresholds of concerns across all demographics and diseases.

Public-private partnerships such as the BmDR, KPMP, and the TransBioLine project, and enhanced utilization in clinical trials with input from regulatory agencies, will enable the accumulation of evidence for the utility of biomarkers in various contexts of use. Biomarkers will help identify individuals at higher risk for kidney injury, identify kidney injury at an early stage, monitor efficacy of therapeutic agents, and identify subpopulations of individuals who are particularly prone to long term consequences of kidney injury. As biomarker data accrue, they will also be incorporated into clinical use to improve decision-making for patients, clinicians, drug developers, and health authorities.

After the workshop, a core team, with representation of all stakeholders, continued to meet to establish the strategy, structure and governance for the BmDR (https://c-path.org/programs/bmdr/). Their work identified initial demographic and disease populations to target for data collection, and began outreach to obtain data sets. BmDR established a Data and Analytics Platform (DAP), where the collected datasets can be viewed, requested, and analyzed by qualified researchers. A goal is to have the BmDR lead to active participation of the community in contributing relevant data sets and helping in the analyses and evidence generation to justify regulatory agency qualification efforts.

The path forward for DIKI biomarker qualification will build on a successful qualification process of pre-clinical safety biomarkers in 2008 by the FDA that has had significant impact on pre-clinical drug

development (Chen Ru et al., 2018; EMA, 2009; Sistare and Degeorge, 2011; Troth et al., 2019; US FDA, 2008). After the 2008 qualification, clinical qualification projects of DIKI biomarkers were launched by PSTC and the SAFE-T Consortium. From this research, PSTC and the Foundation for the National Institute of Health (FNIH) brought data that resulted in the first clinical safety biomarker qualification in 2018 (US FDA, 2018). Prior to the workshop, the Kidney Health Initiative (KHI) Roadmap outlined the priorities to focus on to advance emerging DIKI biomarkers for broader clinical use (ASN KHI, 2022). The C-Path PSTC DIKI workshop demonstrated the necessity to engage across all stakeholders to ensure all perspectives are considered for successful implementation of emerging DIKI biomarkers in drug development and clinical practice.

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Appendices:

1. Workshop agenda and recordings: https://c-path.org/register-now-international-2022-drug-induced-kidney-injury-biomarker-workshop/
2. Patient Experience Videos: https://www.youtube.com/playlist?list=PLk_lN1eQBlnlx7qPRtklBLIO18BZeEg3n
3. Resource List
    a. Supplement to LBDomain for Assay Validation
    b. FDA-BIH Biomarker Working Group: BEST (Biomarkers, EndpointS, and other Tools) Resource
    c. FDA Biomarker Qualification Program
    d. *International 2022 Drug-induced Kidney Injury Biomarker Workshop* Participants
        i. Planning Committee
            1. U.S. FDA
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                b. Michael Pacanowski, PharmD, MPH (OTS)
                c. Ameeta Parekh, PhD (OTS)
                d. Rodney Rouse, PhD, DVM, MBA (OTS)
                e. Aliza Thompson, MD, MS (OND)
            2. NIDDK
                a. Deepak Nihalani, PhD
                b. Ivonne Schulman, MD
                c. Robert Star, MD
            3. Academia
                a. Joe Bonventre, MD, PhD (Harvard)
                b. Ray Harris, MD (Vanderbilt University)
                c. Jonathan Himmelfarb, MD (Univ of Washington)
                d. Matthias Kretzler, MD (Univ of Michigan)
                e. Chirag Parikh, PhD, MBBS (Johns Hopkins)
            4. Patient Community
                a. Richard Knight (American Assoc of Kidney Patients)
                b. Marla Levy
                c. Glenda Roberts
            5. Industry
                a. Frank Dieterle, PhD
                b. Gary Friedman, MD, MS (Pfizer)
                c. Stefan Sultana, MD (AstraZeneca)
            6. American Society of Nephrology
                a. Mark Lim, PhD, PMP (Alliance for Kidney Health)

7. C-Path
    a. Nick King, MS
    b. Tina Fortin
    c. Michelle Morgan
    d. Katrina Peron, MS
    e. Wendy Vanasco

ii. Workshop Speakers and Panelists (with titles/organizations at the time of the workshop)

1. Nicholas King, MS: Associate Director, Translational and Safety Sciences Program, Critical Path Institute
2. Rebecca Cheung: Director for Corporate and Foundation Relations, University of Washington
3. Marla Levy: Medical Industry Motivational and Inspirational Conference Speaker
4. Aliza Thompson, Deputy Director, Division of Cardiology and Nephrology, US FDA
5. Frank Dieterle, Leader in Life Sciences, Novartis
6. Matthias Kretzler, Professor of Medicine/Nephrology, University of Michigan
7. Jonathan Himmelfarb, Professor, Division of Nephrology | Director, Kidney Precision Medicine Project
8. Joseph Bonventre, Chief, Renal Division, Brigham and Women's Hospital, Harvard Medical School
9. James Dear, Professor of Clinical Pharmacology, University of Edinburgh
10. Vishal Vaidya, Global Bioanalytical Lab Lead, Pfizer, Inc.
11. Gary Friedman, Director, Pfizer, Inc.
12. Stefan Sultana, Renal Toxicity Expert, AstraZeneca
13. Steve Piccoli, Head Clinical Biomarkers, SPARC
14. Glenda Roberts, MS: Director, External Relations & Patient Engagement – Center for Dialysis Innovation, University of Washington
15. Ameeta Parekh, PhD: U.S. Food and Drug Administration
16. Richard Knight, MBA: President, AAKP
17. Kevin Fowler: Principal, The Voice of The Patient
18. Chirag Parikh, Director, Division of Nephrology, John Hopkins Medicine
19. Jiri Aubrecht, Vice President, Sarepta Therapeutics, Inc.
20. Yemi Adedeji, Principal Scientist-Pathologist, Genentech
21. Amanda Borens, MS: Executive Director of Data Science, Critical Path Institute
22. Christine Garnett, Cardiac Safety | Clinical Pharmacology | Pharmacometrics, US FDA
23. Shashi Ramaiah, Executive Director-Global Biomarker Head, Pfizer, Inc.
24. Ray Harris, MD: Professor and Chief, Division of Nephrology, Vanderbilt University Medical Center
25. Mike Pacanowski, PharmD, MPH: Director, Division of Translational and Precision Medicine, US FDA
26. Robert Star, MD: Director, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

27. Norman Stockbridge, MD, PhD: Medical Officer, US FDA - CDER

iii. AKI Working Group Sub Teams: Patient Engagement, Industry, and Landscape & Connectivity

1. Jiri Aubrecht
2. Piyush Bajaj
3. Joe Bonaventure
4. Nicholas Buckley
5. Rebecca Cheung
6. James Dear
7. Frank Dieterle
8. Gary Friedman
9. Tina Fortin
10. Kevin Fowler
11. Rebecca Gerstein
12. Warren Glaab
13. Daniel Gossett
14. Ray Harris
15. Jonathan Himmelfarb
16. Rekha Kambhampati
17. Matthias Kretzler
18. Nick King
19. Richard Knight
20. Madhu La-Nag
21. Marla Levy
22. Lauren Lewis
23. Dennis Moledina
24. Michelle Morgan
25. Patrick Murray
26. Deepak Nihalani
27. Leslie Obert
28. Mike Pacanowski
29. Ameeta Parekh
30. Katrina Peron
31. Laura Riley
32. Glenda Roberts
33. Rodney Rouse
34. John-Michael Sauer
35. Ivonne Schulman
36. Laura Song
37. Bob Stafford
38. Rob Star
39. Stefan Sultana
40. Danilo Tagle
41. Aliza Thompson
42. Wendy Vanasco
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44. Jenna Wood
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46. Tanja Zabka

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