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The Road to Precision Medicine for Acute Kidney Injury

Bethany C. Birkelo, DO, MSCI[1], **Jay L. Koyner, MD**[2], **Marlies Ostermann, MD, PhD**[3], **Pavan K. Bhatraju, MD, MSc**[4,5]

[1]Division of Nephrology, Department of Medicine, University of Minnesota, Minneapolis, MN.

[2]Section of Nephrology, Department of Medicine, University of Chicago, Chicago, IL.

[3]Department of Critical Care and Nephrology, King's College London, Guy's and St. Thomas' Hospital, London, United Kingdom.

[4]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, University of Washington, Seattle, WA.

[5]Kidney Research Institute, University of Washington, Seattle, WA.

Abstract

OBJECTIVES: Acute kidney injury (AKI) is a common form of organ dysfunction in the ICU. AKI is associated with adverse short- and long-term outcomes, including high mortality rates, which have not measurably improved over the past decade. This review summarizes the available literature examining the evidence of the need for precision medicine in AKI in critical illness, highlights the current evidence for heterogeneity in the field of AKI, discusses the progress made in advancing precision in AKI, and provides a roadmap for studying precision-guided care in AKI.

DATA SOURCES: Medical literature regarding topics relevant to precision medicine in AKI, including AKI definitions, epidemiology, and outcomes, novel AKI biomarkers, studies of electronic health records (EHRs), clinical trial design, and observational studies of kidney biopsies in patients with AKI.

STUDY SELECTION: English language observational studies, randomized clinical trials, reviews, professional society recommendations, and guidelines on areas related to precision medicine in AKI.

DATA EXTRACTION: Relevant study results, statements, and guidelines were qualitatively assessed and narratively synthesized.

DATA SYNTHESIS: We synthesized relevant study results, professional society recommendations, and guidelines in this discussion.

For information regarding this article, bbirkelo@umn.edu.

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CONCLUSIONS: AKI is a syndrome that encompasses a wide range of underlying pathologies, and this heterogeneity has hindered the development of novel therapeutics for AKI. Wide-ranging efforts to improve precision in AKI have included the validation of novel biomarkers of AKI, leveraging EHRs for disease classification, and phenotyping of tubular secretory clearance. Ongoing efforts such as the Kidney Precision Medicine Project, identifying subphenotypes in AKI, and optimizing clinical trials and endpoints all have great promise in advancing precision medicine in AKI.

Keywords

acute kidney injury; precision; subphenotypes

Acute kidney injury (AKI) is defined as an abrupt decline in kidney function and is a common form of organ dysfunction in critical illness (1, 2). AKI is associated with high mortality in the hospital (3, 4) and long term (5), and AKI survivors are at risk of adverse outcomes including incident and progressive chronic kidney disease (CKD) (5), cardiovascular disease (5, 6), and frailty (7). Unfortunately, little progress has been made in improving outcomes in these patients, with mortality rates remaining fairly stable over the past decade (8). AKI is not a distinct disease entity but rather a syndrome that encompasses a myriad of underlying pathophysiologies. This heterogeneity is not captured in the current AKI classification system, which is based solely on changes in functional markers of the kidneys, specifically the magnitude of elevations in serum creatinine (SCr) and decreases in urine output (UOP) (9).

Precision medicine, the concept of prevention and treatment strategies that take individual variability into account, is an important opportunity for the field of AKI with potential benefits throughout the life cycle of AKI (Fig. 1). Recent advances in identifying AKI subphenotypes, methods to leverage artificial intelligence and electronic health records (EHRs), understanding molecular pathways in human kidney tissue, optimizing clinical trials and selection of patient-centered endpoints all show promise in moving closer toward personalized AKI care.

EVIDENCE THAT PRECISION MEDICINE IS NEEDED

Limitations of Serum Creatinine and Urine Output

Much of the lack of precision in the field of AKI stems from the reliance on SCr and UOP as the primary biomarkers of AKI. Although the current Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI (9) have refined sensitivity compared with prior definitions (10), functional biomarkers of the kidney, SCr, and UOP, have limitations. Histopathologic data suggest that a substantial proportion of cases of AKI may be missed by the KDIGO criteria. A study that evaluated 303 kidney biopsies with histologic evidence of kidney damage found that only two-thirds met KDIGO criteria for AKI (11). Validation studies of novel AKI biomarkers have underscored this limitation with the recognition of “subclinical AKI,” a state of kidney injury that manifests only with elevations in kidney damage biomarkers without SCr elevation or oliguria (12). The label “subclinical” belies the significant adverse outcomes of this cohort compared with those who are negative for

both biomarkers and SCr or UOP (13-16), and mortality among patients with subclinical AKI approaches that of patients with KDIGO-defined AKI (13, 14). Additionally, fluid accumulation can artificially lower SCr concentrations, thereby delaying AKI diagnosis (17), whereas liver failure, muscle wasting, and sepsis can decrease creatinine generation (18-20). Further, reduced SCr concentrations can persist until hospital discharge and lead to overestimation of kidney recovery after AKI (21). Conversely, elevations in SCr do not always reflect a change in kidney function, such as those occurring with initiation of renin–angiotensin–aldosterone system (RAAS) inhibitors, sodium-glucose cotransporter-2 inhibitors, or drugs that inhibit tubular secretion of creatinine (22-24).

Limitations of Serum Creatinine and Urine Output for Differentiating AKI Subphenotypes

The heterogeneity of pathophysiologies underlying AKI has long been appreciated (Fig. 2), and clinicians have sought to use clinically available data (i.e., , blood urea nitrogen to creatinine ratio, fractional excretion of sodium) to differentiate “prerenal” vs. “intrinsic” AKI. More recently, creatinine trajectories (25-27) and AKI duration (28, 29) have been studied to identify distinct AKI subphenotypes. Within a given clinical setting, a wide range of kidney injury mechanisms are possible. For example, histopathologic case series in patients with COVID-19-associated AKI revealed an array of injuries including tubular injury, thrombotic microangiopathy, and glomerular injury (30-32). Other work has challenged prevailing understanding of the underlying mechanisms in some forms of AKI. For example, in sheep models of septic shock, elevations in SCr and oliguria occurred but renal blood flow remained preserved and minimal structural differences were observed in the kidney biopsies (33). Molecular approaches, including gene and protein expression analysis and gene transcript localization in mouse kidney tissue, have highlighted underlying heterogeneity even within acute tubular injury (ATI), with ATI from different injuries (e.g., hypotension, renal artery ligation, and lipopolysaccharide model) demonstrating less than 10% overlap in genetic expression (34). Conversely, challenges in diagnosis can arise with even the more classic “textbook” forms of AKI with relatively well-defined mechanisms of injury. In acute interstitial nephritis (AIN), for example, the classic triad of rash, fever, and eosinophilia is uncommon (35), long latent periods between drug exposure and AKI onset (36) can lead to low suspicion for the diagnosis, and urinalysis and urine eosinophils have questionable utility (37, 38).

A Lack of Effective Therapeutics for AKI

With a few exceptions (i.e., , immunosuppression for glomerulonephritis, corticosteroids for AIN, and terlipressin for hepatorenal syndrome), therapy for AKI is primarily supportive. The lack of effective therapeutics in clinical AKI is not, in our opinion, because of a lack of promising preclinical discoveries but due to the inability to identify the “right” patients at the right time for a given therapy (39, 40) and the limitations in applying findings from homogeneous preclinical models of injury (e.g., renal pedicle clamping, cisplatin exposure, cecal ligation, and puncture) to the heterogeneous syndrome that is clinical AKI. This heterogeneity has impeded the pairing of interventions with their therapeutic targets in randomized controlled trials (RCTs). The use of human kidney organoids, which can better recapitulate human kidney disease than animal models, may have potential in identifying

therapies for AKI in the future (41). At present, detecting a signal in RCTs remains problematic without more granular AKI phenotyping.

PROGRESS IN ADVANCING PRECISION IN AKI

Novel Biomarkers of AKI

One advance in precision has been the validation of novel biomarkers of AKI, which are more specific for parenchymal damage than SCr and UOP. The Acute Disease Quality Initiative has proposed AKI definitions that incorporate these kidney damage markers (12), a call that is well-supported in the literature around sepsis-associated AKI, with several markers demonstrating capacity for prognostic enrichment beyond SCr and UOP (Table 1).

Biomarkers have also demonstrated the potential to improve care and patient outcomes. For example, three separate RCTs that used elevated postoperative levels of tissue inhibitor of metalloproteinases 2 and insulin-like growth factor-binding protein 7 (TIMP-2*IGFBP7) to randomize patients to receive modified KDIGO guideline-based AKI care vs. usual care all demonstrated improved patient outcomes (49-51). Large-scale multicenter validation of these studies is underway (52). Similarly, a recent RCT demonstrated the feasibility of TIMP-2*IGFBP7 to risk stratify patients for enrollment in a kidney-sparing sepsis care bundle trial (53). Taken together, these data point to the utility of TIMP-2*IGFBP7 to guide clinical management, despite being measured at different timepoints (e.g., postoperatively, ICU arrival, after sepsis resuscitation) and in different AKI cohorts. However, it is important to note that AKI is a heterogeneous syndrome, and kidney damage markers that perform well in one population of AKI may be less well-suited for other AKI populations. For instance, neutrophil gelatinase-associated lipocalin, which has been shown to be predictive of outcomes in cardiac surgery and cardiac admissions (46), is released by activated neutrophils and elevated in the serum of patients with sepsis, limiting its usefulness as a marker of sepsis-associated AKI (54).

Biomarkers of AKI have also been used to define and refine AKI subphenotypes. Using a biorepository of blood and urine samples and kidney biopsies, investigators identified chemokine C-X-C-motif-ligand 9, an interferon-gamma-induced chemokine, as a urinary biomarker of AIN (55-58). Separately, in a series of post hoc analyses of patients with sepsis and acute respiratory distress syndrome, AKI subphenotypes were identified based on biomarkers of endothelial dysfunction (ratio of angiopoietin-I and II [Ang I/II] and soluble tumor necrosis factor receptor-1 levels [sTNFR-1]). Ang I/II and sTNFR-1 levels and genetic variation near the angiopoietin-2 gene were associated with a distinct AKI subphenotype which was more likely to benefit from treatment with vasopressin and norepinephrine (compared with norepinephrine alone) in septic shock (59, 60). These findings suggest the potential for the use of biomarkers in predictive enrichment during future investigations around AKI.

Finally, biomarkers can improve the prediction of AKI progression and non-recovery. Using samples from a prospective observational cohort of patients with sepsis or septic shock, levels of proenkephalin (an endogenous opioid protein) collected at the time of ICU arrival were associated with major adverse kidney events (MAKE) defined as a composite of

all-cause mortality, receipt of renal replacement therapy (RRT), and/or persistent AKI at day 7 (61). Separately, in an international prospective observational study of patients with established KDIGO stage 2 or higher AKI, urinary C–C motif chemokine ligand 14 (CCL-14) was predictive of persistent severe AKI, defined as stage 3 AKI lasting more than 72 h, need for RRT or death (62). Subsequently, in a cohort of 200 postoperative patients with stage 2 AKI, combining CCL-14 levels with low UOP after a furosemide stress test identified which patients would develop a clinical indication for RRT (63). This latter study is especially important as it demonstrates that whereas CCL-14 was "discovered" for its robust associations with changes in kidney function (SCr or UOP), it can be used for personalized care to identify patients destined to develop elevated potassium or severe acidosis that necessitate RRT. These data are an important step in moving away from sole reliance on SCr and UOP and using other tools to diagnose and prognosticate AKI and patient-centered adverse outcomes.

Leveraging the Electronic Health Record for Precision-Guided Disease Classification

An area of growing research is leveraging digital data stored within EHR to identify AKI subphenotypes (Fig. 2). The Medical Information Mart for Intensive Care (MIMIC) is a database of de-identified EHR data from patients who stayed in the ICU at Beth Israel Deaconess Medical Center in Boston, MA (64). Among 4001 ICU patients with sepsis-associated AKI, the application of artificial intelligence and K-means clustering to vital signs, laboratory results, and clinical data (188 total features) from MIMIC yielded identification of three sepsis-associated AKI subphenotypes, which had distinct differences in preadmission comorbidities and were associated with different risk of clinical outcomes (need for RRT and 28-d mortality) (65). Additional work remains in understanding the generalizability and reproducibility of these subphenotypes. Linking these AKI subphenotypes with genomic data or other data embedded in the EHR may improve our molecular understanding of AKI and identify potential therapeutic targets.

The EHR can also be leveraged to personalize care through improved AKI risk prediction. Several studies have estimated AKI risk in the ICU using structured and unstructured EHR data (66-70). In one study, investigators used a recurrent neural network to develop an AKI estimation model from 703,000 adult patients in the U.S. Department of Veteran Affairs Healthcare System using 620,000 features; the final model had a sensitivity of 55.8%, specificity of 82.7%, and lead time of up to 48h to predict AKI (71). Others have developed, internally validated, and externally validated a gradient-boosting machine learning model to predict the development of stage 2–3 AKI with C-statistics higher than 0.86 (72, 73). Although these examples of global models are generalizable to large hospital-based populations, prediction models may perform differently within AKI subgroups (e.g., those with sepsis) due to the underlying heterogeneity in AKI. This challenge was addressed in a proof-of-concept study in which personalized AKI risk estimation models were developed and validated and outperformed traditional models in high-risk subgroups (74). In the future, combining risk scores with novel biochemical biomarkers may be commonplace and a way to reduce reliance on SCr and UOP for AKI definition and diagnosis (75).

EHR data have also been used to improve AKI outcomes. A notable example is a program developed to recognize nephrotoxic AKI risk in children that entails systematic surveillance for nephrotoxic medication exposure with near real-time AKI risk alert and provision of decision support, which led to reductions in AKI rates (76, 77). This area of research provides a validated pragmatic and personalized bedside approach to AKI risk stratification and illustrates how risk models can be used in conjunction with existing tools to improve patient outcomes.

Tubular Secretory Clearance Phenotyping

Another advance in precision has been the phenotyping of tubular secretion, an important aspect of kidney function that is often overlooked. Secretory clearance occurs via transporters in the proximal tubules and is the primary means by which the kidney eliminates uremic toxins and many drugs (78). As the proximal tubules are the primary area of injury in most AKI in the ICU, it is possible that secretion may be impacted out of proportion to glomerular filtration in patients with common forms of AKI; however, secretory clearance is not routinely estimated or measured in clinical practice. A novel method has been developed to investigate secretory clearance and its associated outcomes. In this method, blood and urine concentrations of endogenous solutes cleared by tubular secretion are measured using liquid chromatography-tandem mass spectrometry; the urine-to-plasma ratios of these solutes provide an estimate of tubular secretory clearance (78, 79). In one prospective study, investigators found that compared with outpatients with normal kidney function, critically ill adults had impaired estimated secretory clearance even after adjustment for SCr, and this impairment was associated with MAKE-28 days (doubling of SCr, RRT, or death) (79). Further studies are needed before these methods can be implemented in clinical care, including validation in larger studies and correlation of urine-to-plasma ratios with secretory solute clearance as measured by timed urine collections.

THE PATH TO PRECISION

Molecular Determinants of AKI in Human Kidney Tissue

To improve the translation of preclinical discoveries to improvements inpatient outcomes, the NIDDK supported the development of the Kidney Precision Medicine Project (KPMP). The goals of the KPMP are to: 1) ethically and safely obtain kidney biopsies from participants with CKD or AKI, 2) create a reference kidney atlas, 3) characterize disease subgroups to stratify patients based on molecular mechanisms of disease and associated outcomes, and 4) identify critical cells, pathways, and targets for novel therapies (80). This initiative is well underway with over 60 kidney biopsies in hospitalized patients with AKI (personal communication). Early observations from kidney biopsies from patients with AKI have demonstrated findings not evident by histopathology alone. For example, in one patient with AKI presumed from non-steroidal anti-inflammatory drug use, the proteomic signature in kidney tissue demonstrated differences in kidney prostaglandin synthesis and signs of intrarenal inflammation and fibrosis that were not evident by histopathology alone (81). Future multimodal evaluation of kidney biopsies in AKI may provide greater insights into disease pathophysiology and improve the link between preclinical and clinical studies of AKI.

Leveraging human kidney biopsies to understand AKI pathophysiology presents several challenges. First, patients at highest risk of poor outcomes with critical illness and AKI are also at high risk for kidney biopsy complications. Second, each biopsy may present an $n = 1$ story, and identifying themes in the combined findings may be challenging. Third, in critical illness AKI is often a result of a systemic process that rarely is limited to the kidney, thus understanding the role of systemic processes in AKI development and recovery is essential. Fourth, critical illness is often a dynamic process, and linking the timing of the biopsy to the trajectory of kidney function is crucial. Despite these challenges, therapeutic discovery is likely to be accelerated by subphenotyping AKI according to mechanistic drivers that can be pharmacologically targeted. The KPMP initiative and others provide an exciting opportunity to gain a deeper understanding of AKI pathophysiology (82).

Improving Clinical Trials in AKI

There have been very few positive trials in AKI, which is at least in part a result of heterogenous patient cohorts, the type of trial design, and the selection of endpoints (83). Inclusion criteria are often defined by KDIGO stage, lumping together individuals with different underlying mechanisms of kidney injury, recovery patterns, and outcomes, which may conceal a positive treatment signal inpatient subgroups. RCTs in specific patient groups or in specific AKI subphenotypes may overcome some of these challenges but will take longer to complete. Alternative trial designs, such as pragmatic trials, adaptive trials, platform trials, and alternative methods of trial analysis have the potential to increase trial efficiency and improve the feasibility of RCTs (Fig. 2) (84). For instance, utilization of pragmatic studies can facilitate enrollment of larger numbers of patients, enabling the use of more complex analytic methods and analysis of different subgroups (83). Platform trial design allows multiple interventions to be tested simultaneously and offers another method of maximizing trial efficiency. However, it must be acknowledged that the exploration of specific biological processes and in-depth physiologic studies are usually not included in pragmatic or platform trials.

To increase a trial's chances of demonstrating the effectiveness of an intervention, enrichment strategies can be used to select patient cohorts in whom the effect is more likely to be detectable (83). In prognostic enrichment, patients who are more likely to develop the primary endpoint are selected (i.e., , prioritization of high-risk patients). In predictive enrichment, the aim is to improve the likelihood that the intervention will be beneficial, so specific clinical features or biomarkers are used to identify biologically distinct patient cohorts who are most likely to respond to the intervention. For instance, investigators identified two AKI subphenotypes with different clinical characteristics and biomarker profiles that also demonstrated heterogeneity in the response to vasopressin (60). Another potential avenue for increasing likelihood of positive trials in AKI is through the use of human organoids or kidney models on chip to test AKI therapeutics.

Choice of Trial Endpoints

Study endpoints for phase II and phase III trials must provide reliable signals for assessment of the efficacy of the intervention being investigated. When selecting an endpoint, an appropriate balance must be struck between specificity for the outcome and sensitivity

for detecting the effect of the intervention. Further, the choice depends on whether the aim of the study is prevention or treatment of AKI. Finding the right balance has been challenging in AKI trials and a variety of endpoints have been used, including mortality, new development of AKI, new use of RRT, kidney recovery, new CKD, progression to end-stage kidney disease, long-term dialysis dependence, and the composite endpoint of MAKE. Although these outcomes are measurable, patient-centered, and clinically relevant, they rely on SCr, a renal biomarker with the aforementioned limitations in critical illness. Further, the use of AKI as an endpoint raises additional important issues. First, the current AKI definition is insensitive to early phases of tubular cell stress and injury. In this situation, integration of specific tubular damage biomarkers might be in-sightful. Second, certain interventions might alter SCr concentrations without a change in renal function or overall prognosis. For instance, in patients with heart failure, increases in SCr of up to 20% can occur following RAAS blockade and are associated with a decrease in mortality (85). Alternative endpoints and strategies including the use of AKI biomarkers and subclinical AKI have been shown to enrich the patient population or to increase outcomes event rates (49, 51, 52). Continued progress in AKI subphenotyping will undoubtedly be crucial to improving the likelihood of positive trials.

Although much of the prior work has focused on AKI epidemiology and clinical outcomes, the importance of patient-centered endpoints has been widely recognized (84). To better reflect patient and family values, three fundamental questions could be asked when evaluating novel or existing interventions in patients at risk of AKI or with established AKI: 1) Will the intervention improve patient survival? 2) Will the intervention improve the chances that a patient will preserve (or improve) their function (e.g., physical function, activities of daily living)? and 3) Will the intervention improve the chances that a patient will feel better (e.g., mental health, cognitive function, health-related quality-of-life [HRQOL]) (86-89)? Although the need for long-term RRT is associated with impaired HRQOL, other endpoints that may also be very important to AKI survivors and their families (e.g., disability, social function, return to work, caregiver burden) have not been routinely explored in RCTs (90). An alternative approach would be to gain insight into states that patients perceive as worse than death, given that death has traditionally anchored the primary endpoint in most RCTs (91). States perceived as worse than death include perceived burden on family members and inability to maintain human connection (91), which could serve as patient-derived endpoints in future AKI trials. Finally, financial challenges are commonly experienced after AKI (e.g., medical bills, insurance coverage changes, and loss of employment) but have not been explored in AKI trials (92). In conclusion, new trial design, new tools to identify AKI phenotypes, and selection of important patient-centered endpoints offer opportunities to move closer to personalized AKI care.

CONCLUSIONS

Despite the substantial imprecision in the field of AKI, wide-ranging efforts to improve precision through more granular phenotyping of AKI, identification of molecular determinants of AKI, leveraging EHR data, and optimizing RCTs all show promise. Progress in these efforts will be crucial to impact outcomes for the countless ICU patients afflicted with this devastating complication.

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KEY POINTS

Question:

What has been done and what is still needed to advance precision medicine in kidney injury that occurs acutely in critically ill patients?

Findings:

Precision in acute kidney injury (AKI) is largely limited in that AKI is not a distinct disease entity but a syndrome with a wide array of causes, underlying pathophysiologic processes, recovery patterns, and outcomes in patients with different characteristics and comorbidities. Progress in precision medicine has been furthered through advances in AKI subphenotyping, facilitated by novel biomarkers of AKI and leveraging electronic health records. Ongoing and future efforts to further advance precision medicine include more comprehensive assessment of kidney function including the phenotyping of proximal tubular secretory function, identification of AKI subphenotypes, optimizing clinical trial design, including reconsidering trial endpoints and examining molecular determinants of AKI in human kidney tissue through the Kidney Precision Medicine Project.

Meaning:

Advancing precision medicine in AKI has the potential to improve outcomes for patients with AKI.

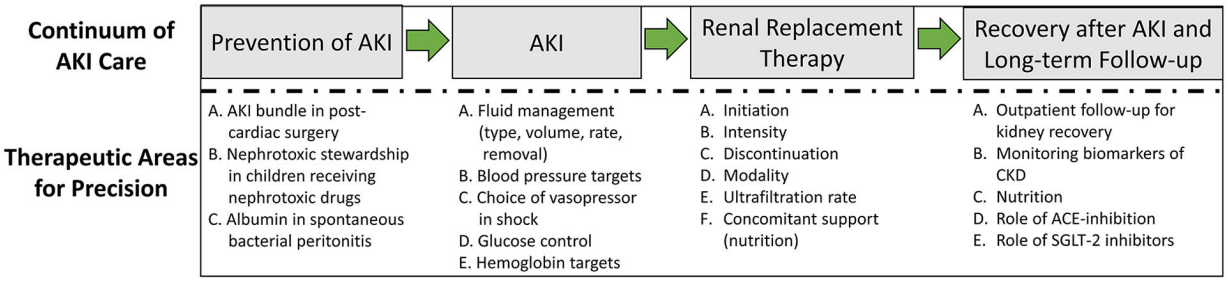

Figure 1.

Opportunities to improve precision across the kidney injury continuum. The *top panel* above the *dashed line* displays the continuum of acute kidney injury (AKI) care from prevention of AKI to development and progression of AKI to renal replacement therapy to recovery after AKI and long-term follow-up. Below the *dashed line* highlights examples of potential therapeutic areas of precision. ACE = angiotensin-converting enzyme, CKD = chronic kidney disease, SGLT-2 = sodium-glucose cotransporter-2.

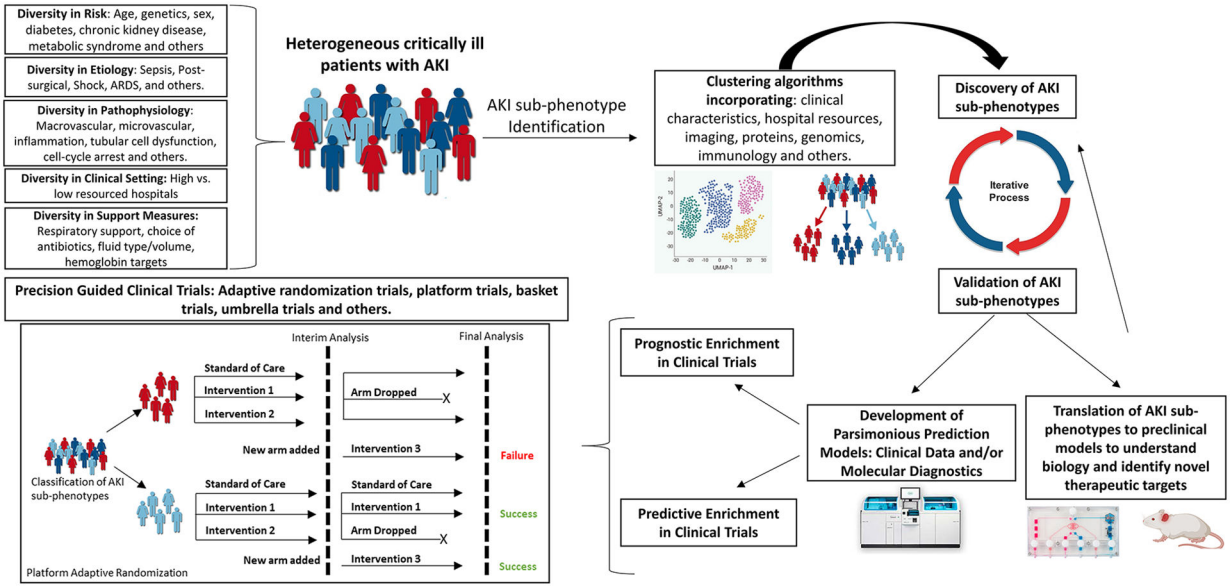

Figure 2.

The life cycle of discovery and validation of acute kidney injury (AKI) subphenotypes. The reader should move clockwise, starting in the *top left corner*, when viewing the figure. At the *top left* are diverse factors that influence development and severity of AKI in hospitalized patients. Clustering algorithms are one method to incorporate these various data to identify biologically similar AKI subgroups. Discovery and validation of AKI subphenotypes is an iterative process that can lead to translation of these AKI subphenotypes into preclinical experiments to understand biology or to develop prediction models for clinical trial enrollment. Prognostic and predictive enrichment are two strategies to select subgroups of patients that are more likely to respond to a given therapy in a clinical trial. Prognostic enrichment refers to the selection of patients with a higher likelihood of having a disease-related outcome of interest, such as renal replacement therapy. Predictive enrichment involves selecting patients who are more likely to respond to a given therapy based on a biological mechanism. An example of a platform adaptive randomization clinical trial leveraging AKI subphenotypes is provided. The platform trial design enables adding or dropping interventional arms during the trial based on interim analyses. ARDS = acute respiratory distress syndrome.

TABLE 1.

Biomarkers of Acute Kidney Injury That Are Elevated in the Absence of Elevations in Traditional Markers (Serum Creatinine and Urine Output)

Biomarker Name	Biomarker Properties	Enrichment Beyond Serum Creatinine and Urine Output
Urine DKK3	A secreted glycoprotein which modulates the Wnt signaling pathways	In post hoc analysis, preoperative DKK3 levels were able to detect the development of postoperative Kidney Disease Improving Global Outcomes for AKI. Require prospective validation (42).
Blood Proenkephalin	5kDa peptide derived from precursor enkephalins met- and leuenkephalin correlates with glomerular filtration rate	Levels measured at ICU admission in the setting of sepsis and in preoperative samples (in separate cohorts) before changes in SCr or UOP have been shown to be associated with the development of AKI, and AKI severity(43-45). Requires prospective validation.
Blood and urine NGAL	Protein with multiple dimer forms that play a role in iron sequestration and is released by renal epithelia in response to ischemia and stress	Pooled data analysis from over 2500 patients in the setting of cardiac surgery and cardiac admissions demonstrated an increased risk of RRT and inpatient mortality in those with elevated NGAL levels, even in the absence of changes in SCr or UOP, with event rates being even higher in those with elevated NGAL and traditional biomarkers of AKI (46).
Urine TIMP-2*IGFBP7	Two cell cycle arrest molecules that act as part of a checkpoint mechanism between G1 and S phase of the cell cycle	Accurately predict the development of stage 2 or higher AKI in those with No AKI or stage 1; but elevated TIMP-2*IGFBP7 values in the absence of changes in SCr and UOP increased the risk of stage 3 AKI, dialysis, or death events in mixed ICU patients (47, 48).

AKI = acute kidney injury, DKK3 = dickkopf-3, NGAL = neutrophil gelatinase-associated lipocalin, RRT = renal replacement therapy, SCr = serum creatinine, TIMP-2*IGFBP7 = tissue inhibitor of metalloproteinases 2 and insulin-like growth factor-binding protein 7, UOP = urine output.