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Nat Rev Nephrol. Author manuscript; available in PMC 2025 September 16.

Published in final edited form as:

Nat Rev Nephrol. 2025 October ; 21(10): 702–716. doi:10.1038/s41581-025-00988-5.

Microbiota and kidney disease: the road ahead

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Abstract

More than 850 million individuals worldwide, accounting for 10–15% of the adult population, are estimated to have chronic kidney disease. Each of these individuals is host to tens of trillions of microorganisms that are collectively referred to as microbiota — a dynamic ecosystem that both influences host health and is itself influenced by changes in the host. Available evidence supports the existence of functional connections between resident microorganisms and kidney health that are altered in the context of specific kidney diseases, including acute kidney injury, chronic kidney disease and renal stone disease. Moreover, promising data from preclinical studies suggest that targeting of gut microbial pathways may provide new therapeutic opportunities for the treatment of kidney disease. This Roadmap describes current understanding of the mechanisms by which microorganisms regulate host organ function, the effects of kidney disease on the gut microbiome, and how these insights may contribute to the development of microbe-targeted therapeutics. We highlight key knowledge gaps that remain to be addressed and strategies for addressing these, outlining both the promise and the potential pitfalls of leveraging our understanding of the gut microbiota to better understand and treat kidney disease.

Introduction

Current estimates suggest that 10–15% of the global population are affected by chronic kidney disease (CKD)[1]. Kidney replacement therapy — namely, dialysis or transplantation — is the only treatment option for patients who progress to kidney failure. Although life sustaining, dialysis takes a substantial toll on patient quality of life and is associated with high health care costs. Transplantation is generally associated with better outcomes than dialysis, but is limited by the number of donor organs. Neither option is universally available. Thus, novel perspectives that advance our understanding and treatment of CKD to slow progression to kidney failure are crucial.

Studies over the past decade have highlighted the existence of functional connections between resident microorganisms and kidney health that are altered in the context of CKD and acute kidney injury (AKI). These interactions are bidirectional in that the

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microorganisms can influence host health, and conversely, are themselves influenced by changes in host health (Fig. 1). Some of the effects of microorganisms on the host are mediated by microbial metabolites such as trimethylamine (TMA), short-chain fatty acids (SCFAs), and uraemic toxins. These metabolites are produced by microorganisms and interact with host signalling pathways to alter host function. These findings and others suggest that the microbiome could represent a therapeutic target to improve kidney health and slow the progression of disease in patients with CKD. To advance our understanding of this area and facilitate interactions across disciplines, the National Institutes of Health (NIH) sponsored a scientific workshop on 28 and 29 May 2024 entitled “Gut Microbiota and Kidney Disease” that was organized and hosted by the National Institute of Diabetes and Digestive and Kidney Diseases. This workshop involved attendees with expertise in diverse fields including nephrology, microbiology and bioengineering, and fostered robust discussions across a variety of topics including the bidirectional interactions between microorganisms and the kidney, microorganism–drug interactions in kidney disease, and the potential utility of microorganisms as prognostic tools or future therapeutics. This resultant Roadmap is aimed at documenting the current standing of the field and highlighting key challenges and opportunities for the future. We highlight studies that have uncovered insights into the functional interactions between microorganisms and kidney health. Specifically, we explore whether changes in gut microorganisms are a cause or consequence of kidney disease and the underlying mechanisms by which these changes occur; available evidence that supports the prognostic value of microorganisms and their metabolites; how gut microorganisms may interact with therapeutic agents; and the potential to leverage microorganisms as therapeutics. Although most studies in this area have focused on CKD, we also discuss other forms of kidney disease where data are available. In each section, we emphasize key gaps in knowledge and approaches that are needed to address these gaps and move the field forward. It is our hope that this Roadmap will serve as a blueprint that highlights key challenges and opportunities in the field as we strive to leverage this exciting new area to advance patient care.

Microbial changes in kidney disease

Studies to date strongly suggest a link between the gut microbiome and kidney health, although the directionality has not been clear. In fact, emerging data suggest that the relationship is bidirectional.

Influence of chronic kidney disease on the gut microbiome

A substantial body of evidence suggests that CKD influences the microbiome. CKD is associated with a shift in the composition of microbiota, the functions they carry out and the production of their metabolites. Such changes are often referred to as dysbiosis; however, the appropriateness of this terminology is questionable (Box 1). Microbial metabolites that are altered in the context of CKD include those produced by saccharolytic fermentation (SCFAs) and protein fermentation (aromatic amino-acid-derived uraemic toxins)[2,3]. A systematic review of adults with various kidney diseases reported a higher relative abundance of Pseudomonadota (previously known as Proteobacteria), unclassified Enterobacteriaceae, unclassified Enterococcaceae and *Streptococcus*, and a lower relative

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abundance of Bacillota (previously Firmicutes), unclassified Prevotellaceae and *Prevotella* than that of control individuals without kidney disease[4]. Interestingly, some of the microbial changes observed in adults have been validated in children with CKD, and seem to be largely independent of risk factors such as diabetes mellitus that are common in adults with CKD[5]. In addition, microbial changes that are typical of CKD can resolve after kidney transplantation; conversely, the (re-)appearance of CKD-typical microbiome changes can precede kidney transplant rejection[6]. However, we note that substantial interindividual variation exists in baseline microbiota composition between individuals, regardless of disease status. Indeed, CKD-associated microbiome changes are complex and dependent on environmental factors, such as individual diet and age, and intrinsic host factors that have not yet been fully elucidated. Thus, changes in the microbiota during disease might be influenced by the disease itself and by confounding factors, such as comorbid diseases or risk factors, as well as diet or medication exposure. With this point in mind, it is important to note that studies in animal models, in which diet and other factors can be controlled, have also demonstrated that CKD alters the gut microbiota[7–9].

A key early hypothesis to explain the shift in microbial composition and function in CKD suggested that the toxic effects of urea on the intestinal barrier and subsequent diffusion of urea into the intestinal lumen might favour the growth of urea-metabolizing microorganisms[10,11]. In support of this hypothesis, a secondary analysis of a study[7] that examined the gut microbiome in patients on haemodialysis reported that several of the enriched bacterial families possessed urease, uricase and other enzymes that promote the formation of the uraemic toxins, indole and *p*-cresol, whereas the depleted bacterial families included those that possessed the enzymes needed for SCFA production[12]. This shift in microbiome functional capacity was also observed in a subsequent, more comprehensive, assessment that involved shotgun metagenomics coupled with faecal and circulating metabolomics studies in individuals undergoing haemodialysis and healthy control individuals[13]. Specifically, that study found that the faecal microbiome of individuals with kidney failure was enriched in functions related to aromatic amino-acid degradation that correlated with higher concentrations of aromatic amino-acid precursors of uraemic toxins (that is, indole and *p*-cresol) and higher concentrations of aromatic amino-acid-derived uraemic toxins (that is, indoxyl sulfate and *p*-cresol sulfate)[13]. A 2025 study furthermore found that CKD severity correlated with a greater concentration of faecal uraemic toxins as well as greater enrichment of uraemic-toxinproducing bacteria[14]. Collectively, available evidence supports a direct effect of kidney disease on gut microbial composition and function. Although data are sparse, it is important to note that changes in the gut microbiome have also been reported in the context of AKI[15,16].

Influence of the gut microbiome on chronic kidney disease

Insights into the effects of the microbiome on CKD have primarily been gained from animal studies. For example, one study reported that mice with adenine-induced CKD raised under germ-free (GF) conditions had worse kidney-related outcomes than mice raised under specific pathogen-free (SPF) conditions[17]. In contrast to SPF mice, the GF mice had very low or non-detectable concentrations of harmful uraemic toxins, including indoxyl sulfate, *p*-cresol sulfate, and phenyl sulfate, and lower levels of potentially beneficial SCFAs[17].

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In a separate study, an absence of bacterial SCFA production was proposed to underlie the more extensive kidney damage observed in hypertensive GF mice than that of SPF controls[18]. These data suggest a potential key role of the microbiome in kidney disease, and indicate that the consequence of microbiome changes may depend on the concentration of microbe-derived metabolites, including the balance between beneficial metabolites such as SCFAs, and harmful uraemic toxins. Additional rodent studies have confirmed that the microbiota is a critical mediator of susceptibility and resistance to CKD[13,14]. Other data have shown that the microbiome influences the course of AKI[19] and kidney-stone disease[20]; of note, available data also indicate that the microbiome can modulate renal parameters in health, including glomerular filtration rate (GFR), renal gene expression and circulating aldosterone levels[21–23].

The effects of microbial metabolites on kidney function are supported by a study in which administration of the TMA-lyase inhibitor, iodomethylcholine, attenuated renal tubulointerstitial fibrosis and damage induced by dietary choline and its subsequent metabolism to TMA and trimethylamine-*N*-oxide (TMAO)[24]. In line with this finding, a community-based study reported an association between TMAO (generated from gut-derived TMA) and the risk of incident CKD and kidney function decline[25]. These findings are supported by an analysis of 1,741 adult Europeans with features of the metabolic syndrome in the MetaCardis cohort, which reported an inverse relationship between TMAO and kidney function, and by studies in mice with unilateral ureter obstruction-induced CKD, in which supplementation with choline or TMAO exacerbated kidney fibrosis[26]. Other studies have demonstrated an important and causal role for TMA and TMAO in mediating cardiovascular risk[27,28]. Overall, these data suggest that microbe-derived uraemic toxins exert detrimental effects on the kidney and other organs. Available evidence also suggests that this damage can be further exacerbated by an accumulation of toxins as a result of impaired renal clearance[29].

Challenges and opportunities

The processes that lead to an altered gut microbiome in CKD are insufficiently understood; assessing the timing and functional relevance of gut microbiome changes during the development and progression of CKD represents one of the most important challenges in the field. Although many studies continue to highlight the importance of the gut microbiome in kidney disease, several knowledge gaps must be addressed to move the field forward (Table 1).

First, studies often focus on one defined model or patient population of CKD, but it is unlikely that changes in the gut microbiome seen in one population are generalizable to all kidney diseases at all stages (Box 2). Thus, one must be careful not to overextend findings. On the other hand, and as described later, the disruption of microbial oxalate metabolism in the gut and its association with both renal-stone disease (RSD) and CKD is well established[30–33], implying that at least some changes may be common to more than one disease outcome. Nevertheless, a deeper understanding of the individual phenotypes of different diseases would facilitate improved studies that focus on both the specific type of pathology and the disease stage. Unfortunately, examination of individuals with later-stage

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kidney pathology may miss crucial early events that occur as the disease is established. Thus, future research should focus on earlier events to identify factors that influence the gut microbiome and could facilitate disease-modifying interventions.

Second, important confounding or effect-modifying variables must be considered in clinical studies. Numerous host and environmental characteristics such as diet[34–36], physical activity[37,38], medications[39,40], intestinal transit time[41] and comorbid cardiometabolic diseases[42,43] influence the gut microbiome and could mediate the effect of the microbiome on clinical outcomes; therefore, any investigation that does not consider these potential confounders or effect modifiers could yield misleading results. One strategy is to perform case–control studies, in which patients with kidney disease are compared with matched control individuals. For instance, several studies have reported that the gut microbiota composition of patients with advanced CKD is essentially the same as that of control individuals from the same household[44,45]. Similarly, the gut microbiota composition of patients with moderate CKD is reportedly similar to that of age-, sex- and race-matched control individuals who consume a similar diet[46]. One inherent challenge in selecting control groups is the lack of a consensus definition of a ‘normal’ range for gut microbial communities, although a 2024 study made some progress in this area[47]. Another strategy is to perform statistical adjustments for suspected confounding variables in cohort-study designs. Alternatively, prospective nested case–control studies could follow patients at risk of CKD, and compare the microbiomes of those who develop the disease (cases) with those who do not (controls), thus enabling cases and controls to be matched on important characteristics. In such studies, the gut microbiome will usually be the exposure variable and a key clinical event will be the outcome of interest.

Third, most studies to date have focused on gut bacteria, often ignoring the potential effects of other types of microorganisms. Understanding and leveraging the inter- and intraindividual variability in all gut microbiota constituents, including viruses and fungi, represent an opportunity for future targeted, personalized interventions. It will also be important to investigate the roles of microorganisms at sites beyond the colon; for example, microorganisms in the proximal gut host critical metabolic functions. Beyond the gut, bacteria that inhabit the urinary tract, termed the urobiome, represent an emerging field of research. Although the microbial density of the urobiome is far lower than that of the gut microbiota, these bacteria are in closer proximity to the kidneys and multiple studies have shown associations between the urobiome and CKD[48–50].

Fourth, new preclinical models are needed to determine the cause and effect of microbial perturbations on kidney disease. In animal models, diet and environment — key factors that influence gut microorganisms — can be controlled. Gnotobiotic mice associated with defined microbial communities could potentially be used to identify the ecological causes and consequences of CKD-associated microbiome changes. However, a general limitation of animal studies is that they often do not adequately model the complex environmental and genetic contributors that influence the development of human kidney disease. Indeed, no single animal model recapitulates all aspects of CKD, and each of the commonly used models has limitations that skew their representation of disease in humans[51]. Nonetheless, findings that are replicated in multiple models are more likely to be generalizable. Thus, the

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ability to dissect cellular and molecular mechanisms in animal models is invaluable, and the continued development of animal models that faithfully recapitulate key aspects of human disease remains an important task.

Fifth, one impediment to the interpretation of existing studies is the absence of critical metadata — for example, information about the sample, participant and site, including clinical information. However, new guidelines for the reporting of microbiome studies should address this issue[52]. Minimum data requirements, including cataloguing of critical dietary and behavioural factors, are needed to ensure interpretability of studies. Given the massive advances in personal technology and the increasing availability of personal electronics, one tool that may aid this form of research is the development of apps that track such information in study participants. On a similar note, improved data sharing between studies will facilitate greater discovery, as will computational modelling approaches. The collection of such data, if of high quality, could also enable future meta-analyses that may identify and/or confirm key themes across studies. Of note, currently available microbiome data are predominantly from high-income countries[53]; to support health equity and improve understanding of the regional effects of diets and other factors, it will be important to generate and use datasets from diverse global sites. Reporting of accurate metadata is also crucial for the interpretation and reproducibility of animal studies: key factors that affect gut microorganisms and often vary between studies include diet, bedding, suppliers, and how animals are caged. Adherence to guidelines that recommend best practices for these and other factors[54] is crucial to ensure that findings from animal models have maximum impact.

Sixth, most published studies that have investigated the gut microbiome in kidney disease have used 16S rRNA gene amplicon sequencing (16S), which has well-documented strengths and limitations compared with metagenomic sequencing[55]. In brief, 16S identifies bacterial taxa based on specific regions of the 16S rRNA gene, which often leads to genus-level taxon resolution. By contrast, metagenomic sequencing captures the gene content of the entire community and enables greater taxon resolution, often at the species and strain level. This increased resolution is important as many bacterial functions are strain specific; metagenomic sequencing therefore provides the ability to directly identify microbial functions. 16S is also constrained to bacterial sequences, whereas metagenomic sequencing can also identify fungi and viruses. Conversely, metagenomic sequencing is more prone to host contamination (more so in tissue samples than stool) and requires a far greater computational processing capacity. Moreover, a higher proportion of the data obtained with metagenomic sequencing cannot be accurately assigned owing to flaws in reference databases[56,57]. If only 16S data are available, the use of amplicon sequence variant (ASV; that is, sequences unique to the nucleotide level) instead of operational taxonomic units (OTUs; that is, clusters of similar sequences, often with 97% similarity threshold)-based clustering approaches may improve accuracy and reproducibility across studies[56,57]. Future studies should integrate multi-omics approaches (for example, metagenomics, metatranscriptomics, metaproteomics and metabolomics) to capture the comprehensive set of functions performed by the gut microbiome. Further validation of the effects of the identified bacterial species and associated metabolites on kidney function would considerably strengthen any conclusion that can be derived from the data.

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Finally, improved incorporation of our current understanding of microbial physiology into computational tools could enable the discovery of emergent properties of microbial communities and help the field to move beyond the concept of keystone species (for example, the identification of a particular fermenter species) to that of functional traits (for example, the function of fermentation). Iterative modelling and experimental validation are powerful strategies with which to gain a comprehensive understanding of host–microorganism interactions; however, the full potential of these approaches is yet to be realized. Future population-level multi-omics studies are needed to obtain further insight. In addition, analyses that incorporate the complexity and interdependencies of microbial communities, rather than focusing on individual species, may provide critical insights for novel intervention strategies.

Prognostic value of microbiome changes in kidney disease

Research to date has uncovered extensive effects of the gut microbiome on human health[58–60]. These studies have also led to a growing appreciation of the importance of interactions between diet, microbial metabolites and the gut microbiota in host well-being, including in kidney health[61–63]. Urea, phosphate, and uraemic toxins originate in the gut as a consequence of dietary intake and microbial metabolism of dietary components[64–66]. In patients with AKI or CKD, these toxins accumulate in the blood, and are recognized as major mediators of cardiovascular complications, cognitive dysfunction and risk of disease progression to kidney failure[67–69]. Of note, uraemic toxins are believed to be both a cause and a consequence of kidney disease: uraemic toxins accumulate in the blood as a consequence of kidney disease (owing to their decreased renal clearance), and as ‘toxins’ these compounds can also contribute to disease progression, at least in part by mediating changes in redox status[70–73].

The mechanistic links between gut microbiota, microbial metabolites and kidney disease suggest that these components could be used as biomarkers of CKD. An ideal biomarker would reflect disease activity and represent a therapeutic target. For example, an approach to remove or prevent the generation of toxins in the gut, thereby lowering their flux into the bloodstream and slowing kidney-disease progression, would represent an attractive alternative to dialysis[74].

Clear evidence supports a role for microbial metabolites as potential biomarkers to monitor a range of outputs, including the risk and/or rate of kidney-disease progression[75,76], potential adverse outcomes[75,76], proximal-tubule function[77], the effect of diet[77] and the response to therapeutic interventions such as sodium–glucose co-transporter 2 (SGLT2) inhibitors[78]. Some of these metabolites are produced by the gut microbiota from dietary substrates. For example, TMA is produced by specific bacteria in the gut from the dietary precursors, carnitine and choline, and is subsequently converted to TMAO by the host[75,79,80]. Similarly, the uraemic toxin *p*-cresol is produced via bacterial metabolism of the aromatic amino acid tyrosine[81]. However, the presence of such metabolites in the circulation often depends on more than one microorganism; in addition, circulating levels may be influenced by reduced renal clearance in the setting of CKD. Nevertheless, potential opportunities exist for the

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advancement of biomarker discovery and validation given the availability of several large and well-annotated CKD cohorts.

The potential of gut microbiota composition to be used as a biomarker in kidney diseases is less clear, in part because of our current inability to readily define a ‘normal’ range for various gut microorganisms. Initial efforts to use human gut microbiota data for prognostic value sought to identify differences in microbiome composition between cases and controls, for example, by assessing alpha diversity (that is, the number of different kinds of microorganisms or functions within a sample) or beta diversity (that is, the dissimilarity in community membership between samples)[82]. The introduction of machine-learning approaches such as random forests[83] provided a dramatic improvement in capability by enabling the construction of models that classify an individual as belonging to one group or another, along with statistics that determine the accuracy of such classifications[84]. Such models also provide feature importance measures that can reveal which specific taxa or functions are responsible for the classification into a healthy or diseased population. Of note, these variable importance scores must be treated with caution in instances where several variables are correlated, as often only one of the variables is used to build the classifier. Random-forest models have been used to associate the gut microbiome with hundreds of diseases, including various forms of kidney disease in adults[85–98] and children[99]. Intriguingly, the oral[100] and urine[101] microbiomes have also been associated with CKD and calcium oxalate stones, respectively, suggesting that such readily available specimens may yield useful biomarkers of diseases.

Challenges and opportunities

Despite the opportunities, several challenges exist in the field of microbial metabolomics of relevance to biomarker discovery for kidney diseases (Table 2). Untargeted metabolomic platforms that are generally used in biomarker discovery are only semi-quantitative. However, to have any clinical utility, a biomarker requires absolute quantification through the use of standards[102,103]. Currently, most analytes are mere spectral features that do not have a true identity, and thus may be described differently between different studies owing to a lack of consensus across databases; moreover, they may be prone to variation due to instrument settings and batch effects[104]. Of note, a disease biomarker does not necessarily need to be a bioactive compound — for example, a toxin — from a functional standpoint. However, a biomarker must have a meaningful association with the disease and exceed interindividual variability; if a biomarker varies by sex, age, ethnicity or other metadata, then this variation should be clearly documented. Finally, a useful biomarker should have greater utility and be more cost-effective than currently available biomarkers, such as creatinine for renal clearance. One way to increase the predictive efficacy of microbe-derived metabolites and reduce issues associated with interindividual variability is to focus on a set of metabolites that are highly prevalent for the phenotype of interest rather than individual metabolites[105].

The development of predictive models for microbial metabolite or microbiota-derived biomarkers requires the necessary data inputs to be available. The predictive ability of any model will be improved by the inclusion of data inputs from prospective longitudinal

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studies, intervention studies and more diverse cohorts. Prognostic models that predict responses to gut microbiome-related therapeutics are also needed. Computationally, newer artificial intelligence approaches, such as transformer models (neural networks that extract context and relationships from sequential data akin to reading a sentence, paragraph or manuscript) and related attention models (mechanisms that enhance deep-learning models, including transformer models, by prioritizing the most relevant inputs within a larger context similar to how humans scan visual fields until something attracts their attention)[106] may further improve classification and regression tasks, and their application in understanding the contributions of microorganisms to different kidney diseases holds considerable promise. However, caution must be exercised in the use of artificial intelligence technologies given the risks of overfitting, propagating bias and challenges in interpretability[107]. Improvements in technologies associated with data archiving would also improve accessibility to important data inputs. Predictive and prognostic biomarkers for kidney disease and health are lacking, and more consideration in this area is needed.

Gut microbiota–drug interactions

Interactions between medications and the gut microbiota have emerged as one of the most relevant and rapidly evolving topics in the microbiome field[108]. Early examples helped to define the roles of specific non-host factors in the efficacy and toxicity of a range of therapeutics, including cancer drugs[109] and heart medications[110]; subsequent research has extended these findings into other medical specialties, including nephrology.

Specific microbial gene products can affect the metabolism of certain drugs. In the context of reduced kidney function, it may be possible to block the activity of gut microbial proteins or use prebiotic or other dietary interventions to alter the composition of the microbiota to reduce microbial effects on, for example, nephrotoxic drugs. Beyond gene products, the protein factors expressed by the gut microbiome have important roles in medicating therapeutic outcomes. For example, differential activities of gut microbial beta-glucuronidases can modify the toxicity and efficacy of the immunosuppressant mycophenolate, which is widely used by kidney-transplant recipients[111]. Such microbial signatures may influence the response of individual patients to treatment and suggest that monitoring of the gut microbiome may provide an avenue to improve transplantation and other outcomes.

The role of the gut microbiome in mediating drug interactions in CKD is also highlighted by the fact that microbiota–drug interactions have been reported for both of the first-line drugs used in patients with CKD, namely angiotensin-converting-enzyme (ACE) inhibitors and SGLT2 inhibitors. For example, the anaerobic gut bacterium, *Coprococcus comes*, can catabolize ester ACE inhibitors, and was demonstrated to attenuate the antihypertensive effects of ester ACE inhibitors (such as quinapril and ramipril) but not nonester forms of the drug (such as lisinopril) in a rat model of hypertension[112]. Another study in rats found that depletion of gut microorganisms with antibiotics enhanced the blood-pressure-lowering effects of the ACE inhibitor, captopril[113]. SGLT2 inhibitors are associated with broad cardio-renal and metabolic benefits[114]. They act by inhibiting glucose uptake in the proximal tubule; however, they also affect organic anion and amino-acid transporters

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within the kidney tubules, and reconfigure the composition of the gut microbiota[115]. These alterations in gut and kidney components led to decreased levels of the uraemic toxin, *p*-cresol sulfate, in mice — even in the absence of SGLT2 transporters, and in patients treated with SGLT2 inhibitors. These studies emphasize the central role of the kidney proximal tubule in handling metabolic waste and coordinating other metabolic functions[116] but also demonstrate that communication exists between the kidney and gut microbial communities — probably even before effects on the heart are observed. Further research needs to address the identity of the microbial and renal off-target effects of SGLT2 inhibitors through direct binding and biochemical studies. Of note, the potential beneficial effects of the oral antidiabetic drug metformin — which is often used by patients with diabetic kidney disease — on cardiovascular comorbidities may also be dependent on the gut microbiome and SCFAs, further supporting the notion that microbial interactions with key drugs may affect the outcomes of patients with CKD[117].

Challenges and opportunities

Despite advances in our understanding of microbiota–drug interactions, critical knowledge gaps remain (Table 3). Challenges, particularly in human translation, include the various comorbidities associated with kidney disease and the lack of translatability of animal models. For human studies, use of controlled study designs with carefully defined diets and assessment of microbial communities and their function against defined molecular subtypes of kidney disease are essential to better define potential interactions between drugs and the microbiome. Improved translatability of animal models requires validation of findings across multiple models and the continued development of models that better represent human disease and drug metabolism.

A general knowledge gap relates to the mechanisms by which microbial metabolites are handled by the kidney — specifically the role of organic anion transporters and other drug transporters in this process[116,118] — as well as the mechanisms by which microbial and drug metabolites are handled by the microorganisms themselves. Modelling approaches have been used to predict how changes in the handling of an electrolyte in one part of the nephron (or a change in filtered load) might alter transport of the electrolyte elsewhere[119,120]. The development of similar models for the renal, intestinal and microbial handling of key drugs and drug metabolites could enhance our ability to predict how handling of these compounds could be altered under various conditions. However, a prerequisite for model development is high-quality training data, and this key information is largely lacking for both microbial and systemic drug handling.

Finally, advanced analytical tools such as activity-based proteome profiling[121], in vivo isotope labelling and tracing[122], and tools for the profiling of microbial communities that take into account community interactions rather than focusing on one or a few taxa, need to be further developed to gain insights into small molecule mechanisms and their handling.

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Therapeutic targeting of the gut microbiota

As described above, a growing body of evidence suggests that interactions between the gut microbiota and kidney are key contributors to several kidney diseases, including AKI, CKD and RSD, as well as outcomes following kidney transplantation.

Therapeutic interventions for acute kidney injury

Patients with AKI exhibit unique changes in their gut microbiome compared with patients with CKD and healthy control individuals[16]. Moreover, different aetiologies of AKI — for example, ischaemic and nephrotoxin-induced — also lead to distinct changes in the gut microbiome[15]. The microbiome, in turn, influences the course of AKI as demonstrated using germ-free mice and in faecal transfer studies[19]. Studies have also demonstrated important roles for gut-derived SCFAs, D-serine, antibiotics and probiotics in the prevention of AKI[123–126]. The kidney-protective effects of probiotics seem to be mediated by certain metabolites, including SCFAs, which improve gut-barrier function and reduce systemic inflammation[126,127]. A 2023 study in mice demonstrated that recovery from severe AKI was improved by amoxicillin treatment, by changing the composition of colonic bacteria and reducing numbers of $CD8^+$ (cytotoxic) T cells[128].

Therapeutic interventions in chronic kidney disease

As described earlier, shifts in the composition of gut microbiota have been observed in patients with CKD. These findings suggest that approaches to reverse these shifts could represent a therapeutic avenue for the treatment of CKD. This hypothesis is supported by findings from animal studies. For example, supplementation with *Faecalibacterium prausnitzii* reduced kidney dysfunction in a mouse model of CKD[129]. Available evidence also suggests that the gut microbial changes observed over the course of CKD contribute to disease progression through the induction of various metabolic changes, including the excessive production of uraemic toxins such as indoxyl sulfate, oxalate, phenyl acetate, *p*-cresol sulfate, TMA and TMAO[130–132]. Uraemic toxins induce the production of reactive oxygen species and can lead to insulin resistance, inflammation and fibrosis, all of which exacerbate CKD progression[133]. Indeed, clinical studies have revealed microbial metabolites that are associated with reductions in estimated GFR[134–137]. Future studies should investigate the gut microbiota composition at various stages of kidney disease, particularly in the early stages, and across CKD pathologies such as diabetic kidney disease, glomerulopathies, autoimmune-mediated diseases such as lupus nephritis, and ciliopathies such as polycystic kidney disease.

Preclinical studies that have used agents to target gut microbial enzymes have shown considerable promise in mitigating cardiac and kidney diseases and provide a potential path towards new therapeutics. For example, the development of oral agents that potently inhibit CutC/D enzymes — which are responsible for the production of TMA by microorganisms — reduced circulating TMAO levels and ameliorated thrombosis risk in a mouse model of carotid-artery thrombosis[138]. The therapeutic potential of these agents should also be explored in models of CKD, given the association of TMAO with incident CKD and CKD progression[25]. Similar approaches could also be used to inhibit the production of microbial

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uraemic toxins. Another such target is the uraemic toxin, indoxyl sulfate, which is poorly cleared by damaged kidneys and exacerbates kidney damage. Indoxyl sulfate is formed by the host from indole. However, indole is derived from the enzymatic processing of the essential dietary amino acid tryptophan by gut microbial tryptophanases (tryptophan-indole lyases). A 2023 study described the development of a pan-tryptophanase inhibitor that blocked the formation of indole in the mouse gut, and subsequently reduced indoxyl-sulfate levels in serum[139].

Uraemic toxin levels could alternatively be lowered by targeting their removal from the gut; however, such approaches are currently limited. Future studies might find inspiration from wastewater treatment science, which has used technologies such as hydrogel-encapsulated microorganisms to target the removal of nitrogen-, carbon- and phosphate-rich constituents from wastewater[140–146] Alternatively, future approaches could find inspiration from drugs such as AST-120, which adsorbs and eliminates enteric acidic and basic compounds, including some that are nephrotoxic[73].

The potential use of prebiotic and other dietary approaches to manipulate microbiota composition is also an active area of investigation[147–150]. Healthy diets, such as the DASH (Dietary Approaches to Stop Hypertension) diet, may lower the risk of developing CKD but may also benefit patients with established CKD, especially those with early-to-mid stage disease[151]. However, comprehensive data on which to base CKD stage-specific dietary recommendations that take the microbiota into account are currently lacking. A 2025 study that evaluated the effect of a diet high in plant diversity (defined as ≥30 unique plant foods weekly) in individuals with CKD stages 3–4 reported changes in gut microbiota, including a shift towards increased production of butyrate/isobutyrate, and achieved decreased levels of indoxyl sulfate and *p*-cresyl sulfate only in patients with more advanced CKD[152]. Clinical evidence indicates a reduction in faecal levels of SCFAs in patients with CKD, and preclinical studies have demonstrated the potential benefits of increasing SCFA levels in CKD[153–156]. Approaches to modulating dietary amino-acid composition have also been explored as a way of reducing uraemic toxins. For example, dietary methionine and cysteine might inactivate microbial enzymes that are critical for the generation of uraemic toxins such as indole. Specifically, these amino acids influence the production of hydrogen sulfide by gut microorganisms, which promotes s-sulfhydration and reduces the uraemic toxin-producing activity of microbial enzymes[157]. Although patient adherence to dietary regimens can be challenging, further studies in larger cohorts are needed to further investigate the extent to which the beneficial effects of a healthy diet can be attributed to effects on the gut microbiome. Additional studies are also needed to further examine the metabolic capacities of gut microorganisms and targeted strategies to decrease the production of uraemic toxins.

Of note, patients on dialysis and kidney-transplant recipients have extensive health care exposures that increase their risk of infection with multidrug-resistant bacteria, which can lead to deleterious clinical outcomes such as death or graft loss[158]. Observational research has identified an association between the relative abundance of enteric pathogens in the gut and the risk of bloodstream and urinary tract infections[159]. These data indicate that safe and effective treatments to reduce the relative abundance of gut pathogens may have meaningful health benefits, even for patients with low colonization levels[159–162]. For these reasons,

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patients with kidney diseases are an important group to prioritize for microbiome-based infection-prevention therapies[163].

Therapeutic interventions for hyperuricaemia

Hyperuricaemia is highly prevalent among patients with CKD, and CKD is an independent risk factor for the development of gout. Humans lack uricase — which in other mammals catalyses the oxidation of uric acid to allantoin — and therefore in humans, uric acid (or its conjugate base urate) is the end product of purine metabolism[164]. Hyperuricaemia causes gout, which affects ~5% of the US population; approximately 6.5 million US adults have gout and CKD[165]. Urate is excreted mainly through the kidneys and intestines via specific transporters. In patients with CKD, the intestines become the major route for uric-acid excretion[166]. The management of gout and hyperuricaemia in patients with CKD is challenging owing to the potential nephrotoxicity and drug interactions of currently approved medications. As a result, patients with CKD and gout have considerably worse outcomes than patients without CKD[167], highlighting a major unmet need for innovative, safe and effective urate-lowering therapies for patients with impaired renal clearance. Certain strains of the gut microbiota consume purines and purine derivatives, including uric acid, in the gut and can reduce serum urate levels[168,169]. These bacteria use a set of genes not previously known to be involved in purine metabolism that probably encode a novel pathway for anaerobic purine metabolism. These developments suggest that the regulation of uric acid levels through microbial therapeutics represents a promising approach to the creation of safe treatments for gout in patients with CKD.

Therapeutic interventions in renal stone disease

RSD is a common, increasingly prevalent and multifactorial condition that has diverse clinical phenotypes. Eighty-five per cent of cases are caused by calcium oxalate (CaOx) stones[170,171]. RSD is typically chronic, recurrent and is typically associated with multiple interventions, diagnostic procedures, medication use and reduced quality of life[172]. Available evidence suggests that gastrointestinal and urinary-tract microorganisms might influence stone development. Historically, the degradation of oxalate in the gut was attributed solely to obligate oxalotrophs, such as *Oxalobacter* species. Of note, in addition to its oxalate-degrading function, *Oxalobacter formigenes* also stimulates colonic oxalate secretion via an unknown secretagogue, and thereby reduces urinary oxalate excretion[173]. However, phase I–III trials of *O. formigenes* in patients with primary hyperoxaluria failed to lower urine or plasma oxalate levels, probably because of problems in patient selection (for example, the inclusion of patients whose RSD was unrelated to gut microbiome dysfunction) and dietary factors (for example, oxalate restriction, which limited microbial colonization)[174–182]. However, a number of studies have now shown that diverse oxalate-degrading bacteria maintain oxalate homeostasis. Specifically, gut oxalate metabolism is mediated by complex microbial communities that are defined by distinct selective pressures and often lack *O. formigenes*, providing an important potential source of variability in clinical trials with *O. formigenes*[20,31,183]. Oxalate is among the 20 most abundant uraemic toxins, and levels are substantially higher among patients with uraemia[184]. As a toxic end product with no known physiological function, elevated 24-h urinary oxalate excretion is an independent risk factor for CKD progression[185]. Plasma oxalate levels rise substantially

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(>30 μM) with declining estimated GFR, and is associated with an increased risk of CaOx supersaturation, inflammasome-induced inflammation and adverse cardiovascular outcomes, including sudden cardiac death in patients with kidney failure[186,187]. In addition, increased proximal tubular oxalate secretion promotes CaOx crystal-induced renal inflammation, which contributes to CKD progression[186,187]. Beyond oxalate degradation, RSD is also linked to deficient butyrate metabolism by gut microorganisms. In rats, oral supplementation with SCFAs upregulated the expression of intestinal oxalate transporters, enhanced caecal SCFA production and reduced urinary oxalate and renal CaOx crystals[188]. Of interest, one study reported that stone formation was more strongly associated with the composition of the urobiota as opposed to that of the gut microbiota[189]. This finding is in line with a study in animal models, which showed that antibiotics exposure induces metabolomic changes that result in a shift in the composition of the urobiota towards a more lithogenic environment, characterized by an increase in uropathogenic bacteria that promote CaOx mineralization and a decrease in uroprotective bacteria[190]. Future research in RSD should explore potential roles for gut–urinary microbiota interactions that may influence mineralization, strategies to enhance distal colonic oxalate excretion and oxalate-degrading capacity, and approaches to increasing SCFA production.

Challenges and opportunities

A number of challenges and opportunities should be considered in the context of approaches to therapeutically targeting the microbiome (Table 4). First, our understanding of the role of the gut microbiome across all stages of CKD is impeded by a lack of population-based cohorts with well-annotated metadata and deep microbiome profiling (that is, metagenomics, metatranscriptomics, metaproteomics and metabolomics data). Although extensive preclinical intervention studies in animal models are required to build a framework for the identification of mechanistic processes and therapeutic targets, large-scale human investigations are essential to enrich our understanding of microbiota populations in humans and how these relate to observed intraindividual and interindividual variation in disease progression and clinical responses.

Second, it will also be important to consider the effects of key biological factors — such as sex, age, diet, geographic region and genetic factors — that may influence the relationship between microbial therapies and outcomes. For example, sex differences in the aetiology and progression of CKD are well-documented[191], as are sex differences in gut microbiota composition and the metabolome[192].

Third, the identification of specific taxa and downstream signals (for example, metabolites and proteins) that drive host–microorganism communication is needed to stratify risk of disease progression under various conditions and translate findings into clinical applications. However, it should be noted that microorganisms live and function as a community, and future therapeutics could be designed from this perspective. For example, studies from the past few years have established defined consortia of common human gut bacteria as model communities; such insights may be useful for future mechanistic interrogations of gut microbiome function[193,194]. In addition, researchers should, where possible, avoid an over-reliance on faecal samples for analyses of gut microbiota composition, given that faecal

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samples may not be representative of the most relevant microbial communities that influence therapeutic responsiveness.

Fourth, as diet is one of the largest effectors of gut microbiome shifts, future studies will need to ensure that diet compositions are properly reported — a task that is tractable for basic science investigations but much more involved for clinical studies. Cultural and/or regional differences in food intake and potential interactions with existing medications are also relevant considerations for the implementation of microbe-based therapeutics in CKD and other diseases. Guidelines for the reporting of microbiome studies should be followed to ensure that studies adhere to best practices and report relevant metadata[52,54]. Although diet clearly affects the composition and function of the gut microbiome, it is important to note that most diet-induced microbiome changes are short-lived and revert when dietary perturbations are removed, which potentially limits the durability of this intervention type[34].

Fifth, gastrointestinal tract function and transit times differ between individuals, and compensatory changes in intestinal function can occur in CKD and may complicate the development of precision gut microbiome interventions and therapies. At a minimum, such differences must be considered as confounding variables in analyses. Ideally, transit time data from radio-tracing studies should be incorporated into models to control for this variable; however, substantial progress has been made in predicting transit time from the microbiology of the stool sample itself[41].

Sixth, microorganisms with selected or engineered activities are exciting therapeutic avenues in CKD[195,196]. For example, studies have reported that manipulation of the niche responsible for bile-acid 7α-dehydroxylation in defined complex human gut bacterial communities led to a massive, differential perturbation of phenylalanine metabolites, which are key metabolites associated with cardiorenal risk[196,197]. Engineered beneficial lactobacilli are also available and have been demonstrated to attenuate hypertension in rats[198]. Moreover, a growing number of tools are rendering gut anaerobes more amenable to genetic modification[199–202]. Investment in genetic platforms for the rapid manipulation of gut microorganism functions would help to advance research in this area towards clinical translation. However, again it is important to consider that microorganisms function in a community; thus, it may be useful to design interventions that focus on collective microbiota function rather than taxonomic composition. Faecal microbiota transplantation (FMT) is one of the most direct approaches to transferring microbial communities from healthy donors and achieving gut microbiome shifts in patients. Most data describing the use of FMTs in renal-transplant recipients are from retrospective analyses of patients with recurrent *Clostridioides difficile* or urinary tract infections[162,203,204]. Although limited in their scope, these studies did not identify increased risks of FMT in these groups. The FDA has approved two faecal microbiota products (faecal microbiota, live-jslm and faecal microbiota spores, live-brpk) to prevent recurrent *C. difficile* infection. As more safety data for these products are gathered, their use may be expanded, but clinical guidelines currently recommend conventional FMT (that is, stool from a healthy donor) for mild or moderately immunocompromised patients, such as solid-organ-transplant recipients[205].

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Despite the need to screen donors for potential opportunistic infections, FMTs may provide an approach to beneficially modify the composition and function of enteric microbiota in patients with kidney disease[206]. Although further work is needed to develop next-generation products that overcome safety and scalability limitations, initial FMT applications have shown promise. For example, in the PREMIX trial, 8 of 9 renal transplant recipients with enteric multidrug-resistant bacterial colonization had negative stool cultures after FMT treatment, and key taxonomic and metabolite dynamics were associated with response to treatment[207]. Additional translational studies of FMTs and consortia of bacteria associated with positive responses are needed to expand microbiota treatment options for patients with kidney disease.

Finally, like the vast majority of studies involving the gut microbiome, microbial associations with kidney diseases are mainly based on analyses of stool owing to difficulties in accessing and sampling the intestinal tract[208]. However, an important yet often overlooked aspect of the gut is the regional heterogeneity throughout the intestines and how it affects local physiology[209–211]. Stool samples reflect the microbiota composition of the colon and its associated waste products, within which regional variation is lost. The small intestine is where nutrients are absorbed and the interface for interactions between gut microorganisms and the mucosal immune system. Alterations in the microbiota of the small intestine have been linked to numerous serious conditions in humans[209]. The development of a passive sampling device[212] that collects fluid from multiple locations in the human intestines for ex vivo analysis has facilitated the discovery of large differences between the small intestine and stool in microbiota composition, abundance of gene classes such as carbohydrate active enzymes, and viromes, as well as gradients of metabolites such as microbially transformed bile acids[212,213]. Such devices could reveal biological factors that are inaccessible from stool or endoscopic sampling but have important connections with kidney disease. Moreover, the ability to culture microorganisms that have been obtained from the small intestine for use in animal models[214] may provide further mechanistic insights into host–microbiome interactions, enable the identification of potential probiotics that can specifically colonize the small intestine and improve the next generation of FMT therapies.

Conclusions

In this Roadmap, we have outlined current understanding of the relationship between the microbiome and kidney disease, highlighting the prognostic value of microorganisms and their metabolites, the clinical implications of microorganism–drug interactions and the concept of microorganisms as therapeutics. We have also attempted to outline solutions to help to drive this area forwards; however, we fully acknowledge that financial and other practical obstacles may constrain researchers from following every idealized recommendation in every study. Nevertheless, several key themes have emerged from these efforts that we believe are widely applicable. One is that kidney disease is not monolithic; at least some gut microbial interactions are likely to be specific to certain disease types and disease stages. In addition, it is clear that our concept of ‘normal’ or ‘healthy’ gut microorganisms is somewhat elusive and probably represents a broad spectrum; thus, it is crucial that comparator groups in clinical studies are carefully selected. Similarly, in certain

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contexts, specific microorganisms may be pathological whereas in other contexts those microorganisms may be neutral or even advantageous. This plasticity could be triggered by exposure to different gut-based environmental conditions, highlighting the need to focus on aggregate microbial functions rather than the effect of an individual species on human health. Indeed, and as stated earlier, microorganisms exist in a community, and therefore we must consider both individual taxa and community ecology. Furthermore, the relationship between host physiology and microorganisms is bidirectional, in that microorganisms influence host health and conversely, changes in host health influence microorganisms. Another key theme is the necessity for key metadata to be collected and routinely reported for both clinical and basic science studies. This practice will ensure that findings can be more fully leveraged by the scientific community and ultimately used to move the field forwards. A final theme is the concept that, for some urinary conditions, the urinary-tract microbiome (the urobiome) may have an important role in human health, highlighting the potential broader relevance of the microbiome beyond the gut.

In sum, although investigations of the gut microbiome and its metabolome constitute a rapidly advancing area of study, a substantial gap currently exists in our ability to interpret data and apply findings to clinical care. Broader scientific communication and additional funding for multidisciplinary microbiome-related translational science related to CKD is desperately needed. Although a number of challenges remain to be addressed in this emerging field, it is clear that these challenges represent exciting opportunities to accelerate our understanding of host–microbiome interactions in kidney disease and move towards clinical applications.

Acknowledgements

The authors would like to acknowledge the workshop sponsored by the National Institutes of Health (NIH) on 28 and 29 May 2024 entitled “Gut Microbiota and Kidney Disease” and hosted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The authors would specifically like to acknowledge D. Nihalani for helping to develop the workshop and bringing this expert panel together. They would also like to acknowledge other members of the NIDDK — P. Perrin, R. Lunsford, C. Maric-Bilkan, C. Mullins, C. J. Ketchum, and D. Gossett — who also helped to develop the workshop. The authors are grateful for funding that has supported their work: P.P.B. was supported by NIDDK grant K23 DK138239, and a research grant from Vedanta Biosciences, Inc.; K.L.P. was supported by NIH grant U24 DK127726; M.-K.H.W. was supported by NIH Katz Early Investigator Award R01 DK130815; S.L.H. was supported by NIH grants R01 HL172805, R01 HL103866 and P01 HL147823; J.A. was supported by the Urology Care Foundation grant UCF202-JA and ISAC award 22AU4279; A. Babiker was supported by an Antibacterial Resistance Leadership Group Early Faculty Seedling Award (NIAID) UM1 AI104681; D.D. was supported by NIH grants R35 GM142873 and R01 AT011396, the Stanford Microbiome Therapies Initiative and an OHF-ASN Foundation for Kidney Research Career Development Award; K.C.H. was supported by NIH grant RM1 GM135102; B.J. was supported by NHLBI grant R01 HL171401; A.W.M. was supported by NIDDK grant R01 DK121689; A.S. was supported by NIH grants R01 DK125256, U01 DK099914, and U01 DK099924; P.J.T. was supported by NIH grants R01 DK114034, R01 HL122593 and R01 CA255116; A.W.W. and the Rowett Institute were supported by core funding from the Scottish Government’s Rural and Environment Science and Analytical Services Division; N.W. was supported by the European Research Council grant 852796 under the European Union’s Horizon 2020 research and innovation programme, Corona-Stiftung grant S199/10080/2019, German Federal Ministry of Education and Research TAhRget grant 01EJ2202A and German Research Foundation (DFG) grant CRC 1470, 437531118; J.X. was supported by American Heart Association Career Development Award 23CDA1050485; T.Y. was supported by American Heart Association Career Development Award 852969, NIH grant R21 AG079357 and the University of Toledo Startup Fund; J.H. was supported by NIH grants UH3 TR003288, U2CTR004867, U01 DK133090, U24 DK114886, R01 DK133177 and R01 DK130815; M.R.R. is supported by NIH R35 GM152079; G.D.W. was supported by NIH grant R01 DK107566, the Center for Molecular Studies in Digestive and Liver Diseases under NIH grant P30 DK 050306, the PennCHOP MIcrobiome Program and the Penn Center for Nutritional Science and Medicine; H.R. was supported by NIDDK grants R01 DK123342 and R01 DK132278; M.H.W. was supported by NIAID grant K23 AI144036 and the US Centers for Disease Control and Prevention grant U54 CK000601; A.L.A. was supported by NIDDK

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grants K08 DK118176 and R01 DK138121, NCCIH grant R61 AT013008, DOD grant W81XWH2110644, the ISAC Award program, SUFU Foundation, Bristol Meyers Squibb Foundation, Cures Within Reach and the Urology Care Foundation; S.W. was supported by NIH grants R01 AI118807, R01 DK138912, R21 AI166263 and R21 AI171537 and Burroughs Wellcome Fund grant 1017880; M.M.R. was supported by DFG grants RI 2811/2-2 and SFB1192-project B10, Young Investigator Award NNF19OC0056043 from the Novo Nordisk Foundation, the Carlsberg Young Investigator fellowship and a grant by the Augustinusfonden, Denmark; A. Biruete was supported by NIH grant K12 TR004415 and the Showalter Trust Fund; A.H.A. was supported by NIH grants R01 DK107566, U24 DK060990, U24 DK137318 and UM1 TR004771; J.L.P. was supported by an American Heart Association Established Investigator Award and NIH grants R21 AG081683, R01 DK137762, R01 DK139021 and U54 DK137331.

Competing interests

P.P.B. has received research funding from Vedanta Biosciences and consults for Nexilico and Boehringer Ingelheim. W.S.G. has received research funding from Merck, Sharpe & Dohme, and Astellas Pharmaceuticals. and serves on the scientific advisory boards of Empress Therapeutics, Freya Biosciences, Sail Biosciences and Seres Therapeutics. S.L.H. is a co-inventor on patents relating to diagnostics and therapeutics with a right to receive royalty payments for inventions or discoveries related to diagnostics or therapeutics from Cleveland Heart Lab, a fully owned subsidiary of Quest Diagnostics, and is a consultant for and receives research funds from Zehna Therapeutics. A. Babiker has served on a clinical advisory board for Beckman Coulter. M.A.F. is a co-founder of Kelonia and Revolution Medicines, a co-founder and director of Azalea Therapeutics, a member of the scientific advisory boards of the Chan Zuckerberg Initiative, NGM Biopharmaceuticals and TCG Labs/Soleil Labs, and an innovation partner at The Column Group. C.H. serves on the scientific advisory committee for Seres Therapeutics and Empress Therapeutics. K.K.-Z. has received honoraria from Fresenius Kabi. R.K. is a scientific advisory board member and consultant for BiomeSense, Inc., through which he has equity and receives income, is a scientific advisory board member and has equity in GenCirq, is a consultant for and receives income from DayTwo, has equity in and acts as a consultant for Cybele, is a co-founder of and has equity in Biota, Inc., and is a cofounder and scientific advisory board member of and has equity in Micronoma; the terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies. A.W.M. has received funding from Coloplast and is a scientific advisory board member for the Oxalosis and Hyperoxaluria Foundation. H.R. is a scientific advisory board member for Renibus Therapeutics and Rapafusyn Pharmaceuticals. W.H.W.T. serves as consultant for Sequana Medical, Cardiol Therapeutics, Genomics plc, Zehna Therapeutics, WhiteSwell, Boston Scientific, CardiaTec Biosciences, Bristol Myers Squibb, Alleviant Medical, Alexion Pharmaceuticals, Salubris Biotherapeutics and BioCardia, and has received honoraria from Springer, Belvoir Media Group and the American Board of Internal Medicine. A.W.W. has a research grant from ZOE, Ltd. and consults for EnteroBiotix, Ltd. M.R.R. has received research funding from Merck and Lilly, and is a founder of Symberix, Inc. N.W. received speaker honoraria from Novartis and Bayer. G.D.W. is an advisory board member for Danone and BioCodex and receives research support from Intercept Pharmaceuticals. A.L.A. has received consulting fees from AbbVie, Inc., holds stock options in Watershed Medical and serves on advisory boards for GlaxoSmithKline and Desert Harvest. M.M.R. has received research funding from Novo Nordisk A/S, Copenhagen. H.A.H. is the co-founder, president and Chief Scientific Officer of Oxalo Therapeutics, and is a scientific advisory council member of Oxalosis and the Hyperoxaluria Foundation. A. Biruete has received honoraria from Ardelyx, FMC North America, Dialysis Clinic Inc. and the National Kidney Foundation, and is part of the NextGen Scientist Cohort of the National Dairy Council. All other authors declare that they have no competing interests.

References

1. Hill NR et al. Global prevalence of chronic kidney disease - a systematic review and meta-analysis. PLoS ONE 11, e0158765 (2016). [PubMed: 27383068]
2. Snelson M et al. A renal clinician’s guide to the gut microbiota. J. Ren. Nutr. 30, 384–395 (2020). [PubMed: 31928802]
3. Lambert K et al. Targeting the gut microbiota in kidney disease: the future in renal nutrition and metabolism. J. Ren. Nutr. 33, S30–S39 (2023). [PubMed: 37632511]
4. Stanford J et al. The gut microbiota profile of adults with kidney disease and kidney stones: a systematic review of the literature. BMC Nephrol. 21, 215 (2020). [PubMed: 32503496]
5. Holle J et al. Inflammation in children with CKD linked to gut dysbiosis and metabolite imbalance. J. Am. Soc. Nephrol. 33, 2259–2275 (2022). [PubMed: 35985814]
6. Holle J et al. Gut microbiome alterations precede graft rejection in kidney transplantation patients. Am. J. Transpl. 18, S1600–S6135 (2025).
7. Vaziri ND et al. Chronic kidney disease alters intestinal microbial flora. Kidney Int. 83, 308–315 (2013). [PubMed: 22992469]

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8. Nishiyama K et al. Chronic kidney disease after 5/6 nephrectomy disturbs the intestinal microbiota and alters intestinal motility. J. Cell Physiol. 234, 6667–6678 (2019). [PubMed: 30317589]
9. Mishima E et al. Canagliflozin reduces plasma uremic toxins and alters the intestinal microbiota composition in a chronic kidney disease mouse model. Am. J. Physiol. Renal Physiol 315, F824–F833 (2018). [PubMed: 29167170]
10. Vaziri ND, Yuan J & Norris K Role of urea in intestinal barrier dysfunction and disruption of epithelial tight junction in chronic kidney disease. Am. J. Nephrol. 37, 1–6 (2013). [PubMed: 23258127]
11. Chaves LD et al. Chronic kidney disease, uremic milieu, and its effects on gut bacterial microbiota dysbiosis. Am. J. Physiol. Renal Physiol 315, F487–F502 (2018). [PubMed: 29693447]
12. Wong J et al. Expansion of urease- and uricase-containing, indole- and p-cresol-forming and contraction of short-chain fatty acid-producing intestinal microbiota in ESRD. Am. J. Nephrol. 39, 230–237 (2014). [PubMed: 24643131]
13. Wang X et al. Aberrant gut microbiota alters host metabolome and impacts renal failure in humans and rodents. Gut 69, 2131–2142 (2020). [PubMed: 32241904]
14. Laiola M et al. Toxic microbiome and progression of chronic kidney disease: insights from a longitudinal CKD-Microbiome Study. Gut 10.1136/gutjnl-2024-334634 (2025).
15. Noel S et al. Gut microbiota-immune system interactions during acute kidney injury. Kidney360 2, 528–531 (2021). [PubMed: 35369013]
16. Noel S et al. Metagenomic sequencing reveals distinct gut microbiome profiles in patients with AKI compared to CKD and normals: KPMP project. Am. Soc. Neph. 10.1681/ASN.2024k2n81acd (2024).
17. Mishima E et al. Evaluation of the impact of gut microbiota on uremic solute accumulation by a CE-TOFMS-based metabolomics approach. Kidney Int. 92, 634–645 (2017). [PubMed: 28396122]
18. Avery EG et al. Quantifying the impact of gut microbiota on inflammation and hypertensive organ damage. Cardiovasc. Res. 119, 1441–1452 (2023). [PubMed: 35904261]
19. Jang HR et al. Early exposure to germs modifies kidney damage and inflammation after experimental ischemia-reperfusion injury. Am. J. Physiol. Renal Physiol 297, F1457–F1465 (2009). [PubMed: 19675178]
20. Al KF et al. Multi-site microbiota alteration is a hallmark of kidney stone formation. Microbiome 11, 263 (2023). [PubMed: 38007438]
21. Moore BN et al. Commensal microbiota regulate aldosterone. Am. J. Physiol. Renal Physiol. 326, F1032–F1038 (2024). [PubMed: 38634136]
22. Moore BN & Pluznick JL Commensal microbiota regulate renal gene expression in a sex-specific manner. Am. J. Physiol. Renal Physiol 324, F511–F520 (2023). [PubMed: 37053490]
23. Xu J et al. Microbes regulate glomerular filtration rate in health and chronic kidney disease in mice. Prerit at bioRxiv 10.1101/2025.04.08.647647 (2025).
24. Gupta N et al. Targeted inhibition of gut microbial trimethylamine N-oxide production reduces renal tubulointerstitial fibrosis and functional impairment in a murine model of chronic kidney disease. Arterioscler. Thromb. Vasc. Biol. 40, 1239–1255 (2020). [PubMed: 32212854]
25. Wang M et al. The gut microbial metabolite trimethylamine N -oxide, incident CKD, and kidney function decline. J. Am. Soc. Nephrol. 35, 749–760 (2024). [PubMed: 38593157]
26. Andrikopoulos P et al. Evidence of a causal and modifiable relationship between kidney function and circulating trimethylamine N-oxide. Nat. Commun. 14, 5843 (2023). [PubMed: 37730687]
27. Witkowski M, Weeks TL & Hazen SL Gut microbiota and cardiovascular disease. Circ. Res. 127, 553–570 (2020). [PubMed: 32762536]
28. Holle J et al. Gut dysbiosis contributes to TMAO accumulation in CKD. Nephrol. Dial. Transpl. 39, 1923–1926 (2024).
29. Gryp T et al. Gut microbiota generation of protein-bound uremic toxins and related metabolites is not altered at different stages of chronic kidney disease. Kidney Int. 97, 1230–1242 (2020). [PubMed: 32317112]
30. Agudelo J & Miller AW A perspective on the metabolic potential for microbial contributions to urolithiasis. Kidney360 2, 1170–1173 (2021). [PubMed: 35368346]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

31. Miller AW et al. Mechanisms of the intestinal and urinary microbiome in kidney stone disease. Nat. Rev. Urol 19, 695–707 (2022). [PubMed: 36127409]
32. Stepanova N Role of impaired oxalate homeostasis in cardiovascular disease in patients with end-stage renal disease: an opinion article. Front. Pharmacol. 12, 692429 (2021). [PubMed: 34122117]
33. Nazzal L, Puri S & Goldfarb DS Enteric hyperoxaluria: an important cause of end-stage kidney disease. Nephrol. Dialysis Transplant. 31, 375–382 (2015).
34. David LA et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 505, 559–563 (2014). [PubMed: 24336217]
35. Tang WHW & Hazen SL Unraveling the complex relationship between gut microbiome and cardiovascular diseases. Circulation 149, 1543–1545 (2024). [PubMed: 38739698]
36. Johnson AJ et al. Daily sampling reveals personalized diet-microbiome associations in humans. Cell Host Microbe 25, 789–802.e5 (2019). [PubMed: 31194939]
37. Mailing LJ et al. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. Exerc. Sport. Sci. Rev 47, 75–85 (2019). [PubMed: 30883471]
38. Vandecruys M et al. Revitalizing the gut microbiome in chronic kidney disease: a comprehensive exploration of the therapeutic potential of physical activity. Toxins 16, 242 (2024). [PubMed: 38922137]
39. Maier L et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature 555, 623–628 (2018). [PubMed: 29555994]
40. Biruete A et al. Phosphate binders and nonphosphate effects in the gastrointestinal tract. J. Ren. Nutr. 30, 4–10 (2020). [PubMed: 30846238]
41. Asnicar F et al. Blue poo: impact of gut transit time on the gut microbiome using a novel marker. Gut 70, 1665–1674 (2021). [PubMed: 33722860]
42. O'Donnell JA et al. The gut microbiome and hypertension. Nat. Rev. Nephrol. 19, 153–167 (2023). [PubMed: 36631562]
43. Byndloss M et al. The gut microbiota and diabetes: research, translation, and clinical applications-2023 diabetes, Diabetes Care, and Diabetologia Expert Forum. Diabetes Care 47, 1491–1508 (2024). [PubMed: 38996003]
44. Teixeira RR et al. Gut microbiota profile of patients on peritoneal dialysis: comparison with household contacts. Eur. J. Clin. Nutr. 77, 90–97 (2022). [PubMed: 35906334]
45. Poesen R et al. The influence of CKD on colonic microbial metabolism. J. Am. Soc. Nephrol. 27, 1389–1399 (2016). [PubMed: 26400570]
46. Wiese GN et al. Gut microbiota and uremic retention solutes in adults with moderate CKD: a 6-day controlled feeding study. J. Ren. Nutr 34, 26–34 (2023). [PubMed: 37468049]
47. Wu G et al. A core microbiome signature as an indicator of health. Cell 187, 6550–6565.e11 (2024). [PubMed: 39378879]
48. Liu F et al. Sex-specific dysbiotic bladder microbiome in CKD uncovered via high-throughput sequencing and culture. Preprint at *Research Square* 10.21203/rs.3.rs-3407275/v1 (2023).
49. Hrbacek J et al. Bladder microbiota are associated with clinical conditions that extend beyond the urinary tract. Microorganisms 10, 874 (2022). [PubMed: 35630319]
50. Kachroo N et al. Meta-analysis of clinical microbiome studies in urolithiasis reveal age, stone composition, and study location as the predominant factors in urolithiasis-associated microbiome composition. Mbio 12, e02007–21 (2021). [PubMed: 34372696]
51. Liang J & Liu Y Animal models of kidney disease: challenges and perspectives. Kidney360 4, 1479–1493 (2023). [PubMed: 37526653]
52. Mirzayi C et al. Reporting guidelines for human microbiome research: the STORMS checklist. Nat. Med. 27, 1885–1892 (2021). [PubMed: 34789871]
53. Abdill RJ, Adamowicz EM & Blekhman R Public human microbiome data are dominated by highly developed countries. PLoS Biol. 20, e3001536 (2022). [PubMed: 35167588]
54. Muralitharan RR et al. Guidelines for microbiome studies in renal physiology. Am. J. Physiol. Renal Physiol 325, F345–F362 (2023). [PubMed: 37440367]
55. Wensel CR et al. Next-generation sequencing: insights to advance clinical investigations of the microbiome. J. Clin. Invest. 132, e154944 (2022). [PubMed: 35362479]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

56. Nasko DJ et al. RefSeq database growth influences the accuracy of k-mer-based lowest common ancestor species identification. Genome Biol. 19, 165 (2018). [PubMed: 30373669]
57. Smith RH et al. Investigating the impact of database choice on the accuracy of metagenomic read classification for the rumen microbiome. Anim. Microbiome 4, 57 (2022). [PubMed: 36401288]
58. Mills S et al. Precision nutrition and the microbiome, part I: current state of the science. Nutrients 11, 1468 (2019). [PubMed: 31252674]
59. Sommer F & Bäckhed F The gut microbiota — masters of host development and physiology. Nat. Rev. Microbiol. 11, 227–238 (2013). [PubMed: 23435359]
60. Walter J & Ley R The human gut microbiome: ecology and recent evolutionary changes. Annu. Rev. Microbiol. 65, 411–429 (2011). [PubMed: 21682646]
61. Meijers B, Evenepoel P & Anders HJ Intestinal microbiome and fitness in kidney disease. Nat. Rev. Nephrol. 15, 531–545 (2019). [PubMed: 31243394]
62. Mulle JG, Sharp WG & Cubells JF The gut microbiome: a new frontier in autism research. Curr. Psychiatry Rep. 15, 337 (2013). [PubMed: 23307560]
63. Pluznick JL The gut microbiota in kidney disease. Science 369, 1426–1427 (2020). [PubMed: 32943509]
64. Harrison MA et al. Production of p-cresol by decarboxylation of p-HPA by all five lineages of *Clostridioides difficile* provides a growth advantage. Front. Cell. Infect. Microbiol. 11, 757599 (2021). [PubMed: 34778108]
65. Fishbane SN & Nigwekar S Phosphate absorption and hyperphosphatemia management in kidney disease: a physiology-based review. Kidney Med. 3, 1057–1064 (2021). [PubMed: 34939015]
66. Weiner ID, Mitch WE & Sands JM Urea and ammonia metabolism and the control of renal nitrogen excretion. Clin. J. Am. Soc. Nephrol 10, 1444–1458 (2015). [PubMed: 25078422]
67. Tonelli M, Karumanchi SA & Thadhani R Epidemiology and mechanisms of uremia-related cardiovascular disease. Circulation 133, 518–536 (2016). [PubMed: 26831434]
68. Chen Y et al. Kidney clearance of secretory solutes is associated with progression of CKD: the CRIC study. J. Am. Soc. Nephrol. 31, 817–827 (2020). [PubMed: 32205410]
69. Chen Y et al. Association of tubular solute clearances with the glomerular filtration rate and complications of chronic kidney disease: the chronic renal insufficiency cohort study. Nephrol. Dial. Transpl. 36, 1271–1281 (2020).
70. Lim YJ et al. Uremic toxins in the progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins 13, 142 (2021). [PubMed: 33668632]
71. Owada S et al. Indoxyl sulfate reduces superoxide scavenging activity in the kidneys of normal and uremic rats. Am. J. Nephrol. 28, 446–454 (2008). [PubMed: 18160814]
72. Niwa T Indoxyl sulfate is a nephro-vascular toxin. J. Ren. Nutr. 20, S2–S6 (2010). [PubMed: 20797565]
73. Liu WC, Tomino Y & Lu KC Impacts of indoxyl sulfate and p-cresol sulfate on chronic kidney disease and mitigating effects of AST-120. Toxins 10, 367 (2018). [PubMed: 30208594]
74. Al-mansouri A et al. Assessment of treatment burden and its impact on quality of life in dialysis-dependent and pre-dialysis chronic kidney disease patients. Res. Soc. Adm. Pharm. 17, 1937–1944 (2021).
75. Tang WH et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circ. Res. 116, 448–455 (2015). [PubMed: 25599331]
76. Meijers BK et al. p-Cresol and cardiovascular risk in mild-to-moderate kidney disease. Clin. J. Am. Soc. Nephrol. 5, 1182–1189 (2010).
77. Ren X et al. Plasma metabolomics of dietary intake of protein-rich foods and kidney disease progression in children. J. Ren. Nutr. 34, 95–104 (2024). [PubMed: 37944769]
78. Liu J et al. Effect of dapagliflozin on proteomics and metabolomics of serum from patients with type 2 diabetes. Diabetol. Metab. Syndr 15, 251 (2023). [PubMed: 38044448]
79. Koeth RA et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat. Med. 19, 576–585 (2013). [PubMed: 23563705]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

80. Tang WH et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N. Engl. J. Med. 368, 1575–1584 (2013). [PubMed: 23614584]
81. Saito Y et al. Identification of phenol- and p-cresol-producing intestinal bacteria by using media supplemented with tyrosine and its metabolites. FEMS Microbiol. Ecol. 94, fiy125 (2018).
82. Whittaker R Evolution and measurement of species diversity. Taxon 21, 213–251 (1972).
83. Breiman L Random forests. Mach. Learn. 45, 5–32 (2001).
84. Knights D et al. Human-associated microbial signatures: examining their predictive value. Cell Host Microbe 10, 292–296 (2011). [PubMed: 22018228]
85. Hu X et al. Characterizing the gut microbiota in patients with chronic kidney disease. Postgrad. Med. 132, 495–505 (2020). [PubMed: 32241215]
86. Ren Z et al. Alterations of the human gut microbiome in chronic kidney disease. Adv. Sci. 7, 2001936 (2020).
87. Yu W et al. The gut microbiome in differential diagnosis of diabetic kidney disease and membranous nephropathy. Ren. Fail. 42, 1100–1110 (2020). [PubMed: 33121301]
88. Khasnobish A et al. Dysbiosis in the salivary microbiome associated with IgA nephropathy — a Japanese cohort study. Microbes Env. 36, ME21006 (2021). [PubMed: 34078780]
89. Du X et al. Alteration of gut microbial profile in patients with diabetic nephropathy. Endocrine 73, 71–84 (2021). [PubMed: 33905112]
90. Yu B et al. The gut microbiome in microscopic polyangiitis with kidney involvement: common and unique alterations, clinical association and values for disease diagnosis and outcome prediction. Ann. Transl. Med 9, 1286 (2021). [PubMed: 34532423]
91. Xiang L et al. Prediction of the occurrence of calcium oxalate kidney stones based on clinical and gut microbiota characteristics. World J. Urol 40, 221–227 (2022). [PubMed: 34427737]
92. Shi X et al. Alterations of gut microbial pathways and virulence factors in hemodialysis patients. Front. Cell Infect. Microbiol. 12, 904284 (2022). [PubMed: 36093194]
93. Dong Y et al. Development and validation of diagnostic models for immunoglobulin A nephropathy based on gut microbes. Front. Cell Infect. Microbiol. 12, 1059692 (2022). [PubMed: 36569195]
94. Tang Y et al. Aberrant gut microbiome contributes to barrier dysfunction, inflammation, and local immune responses in IgA nephropathy. Kidney Blood Press. Res 48, 261–276 (2023). [PubMed: 36878203]
95. Chen TH et al. Exploring the relevance between gut microbiota-metabolites profile and chronic kidney disease with distinct pathogenic factor. Microbiol. Spectr. 11, e0280522 (2023). [PubMed: 36475922]
96. Cai F et al. Systematic microbiome dysbiosis is associated with IgA nephropathy. Microbiol. Spectr. 11, e0520222 (2023). [PubMed: 37227280]
97. Jiang Y et al. Combination of the gut microbiota and clinical indicators as a potential index for differentiating idiopathic membranous nephropathy and minimal change disease. Ren. Fail. 45, 2209392 (2023). [PubMed: 37199269]
98. Tang S et al. Guild-level signature of gut microbiome for diabetic kidney disease. mBio 15, e0073524 (2024). [PubMed: 38819146]
99. Lee AM et al. Using machine learning to identify metabolomic signatures of pediatric chronic kidney disease etiology. J. Am. Soc. Nephrol. 33, 375–386 (2022). [PubMed: 35017168]
100. Hu J et al. Location-specific oral microbiome possesses features associated with CKD. Kidney Int. Rep. 3, 193–204 (2017). [PubMed: 29340331]
101. Yang Y et al. The genetics of urinary microbiome, an exploration of the trigger in calcium oxalate stone. Front. Genet 14, 1260278 (2023). [PubMed: 37854058]
102. NIH/FDA. BEST (Biomarkers, EndpointS, and other Tools) Resource. ncbi.nlm.nih.gov https://www.ncbi.nlm.nih.gov/books/NBK326791/ (FDA, 2016).
103. Bennett M & Devarajan P in Biomarkers of Kidney Disease (ed. Edelstein C) 1–24 (Academic, 2011).
104. Yu Y et al. Assessing and mitigating batch effects in large-scale omics studies. Genome Biol. 25, 254 (2024). [PubMed: 39363244]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

105. Agudelo J et al. Delineating the role of the urinary metabolome in the lithogenesis of calcium-based kidney stones. Urology 167, 49–55 (2022). [PubMed: 35716870]
106. Vaswani A et al. Attention is all you need. In 31st Conference on Neural Information Processing Systems (NIPS) (eds. Guyon I et al.) https://papers.nips.cc/paper_files/paper/2017/hash/3f5ee243547dee91fbd053c1c4a845aa-Abstract.html (2017).
107. Theodosiou AA & Read RC Artificial intelligence, machine learning and deep learning: potential resources for the infection clinician. J. Infect 87, 287–294 (2023). [PubMed: 37468046]
108. Trepka KR et al. Pharma[e]cology: how the gut microbiome contributes to variations in drug response. Annu. Rev. Pharmacol. Toxicol. 65, 355–373 (2024). [PubMed: 39107044]
109. Wallace BD et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science 330, 831–835 (2010). [PubMed: 21051639]
110. Haiser HJ et al. Predicting and manipulating cardiac drug inactivation by the human gut bacterium *Eggerthella lenta*. Science 341, 295–298 (2013). [PubMed: 23869020]
111. Simpson JB et al. Metagenomics combined with activity-based proteomics point to gut bacterial enzymes that reactivate mycophenolate. Gut Microbes 14, 2107289 (2022). [PubMed: 35953888]
112. Yang T et al. Identification of a gut commensal that compromises the blood pressure-lowering effect of ester angiotensin-converting enzyme inhibitors. Hypertension 79, 1591–1601 (2022). [PubMed: 35538603]
113. Kyoung J & Yang T Depletion of the gut microbiota enhances the blood pressure-lowering effect of captopril: implication of the gut microbiota in resistant hypertension. Hypertens. Res. 45, 1505–1510 (2022). [PubMed: 35513487]
114. Vallon V & Verma S Effects of SGLT2 inhibitors on kidney and cardiovascular function. Annu. Rev. Physiol. 83, 503–528 (2021). [PubMed: 33197224]
115. Billing AM et al. Metabolic communication by SGLT2 inhibition. Circulation 149, 860–884 (2024). [PubMed: 38152989]
116. Chrysopoulou M & Rinschen MM Metabolic rewiring and communication: an integrative view of kidney proximal tubule function. Annu. Rev. Physiol. 86, 405–427 (2024). [PubMed: 38012048]
117. Szymczak-Pajor I et al. The gut microbiota-related antihyperglycemic effect of metformin. Pharmaceuticals 18, 55 (2025). [PubMed: 39861118]
118. Nigam SK The SLC22 transporter family: a paradigm for the impact of drug transporters on metabolic pathways, signaling, and disease. Annu. Rev. Pharmacol. Toxicol. 58, 663–687 (2018). [PubMed: 29309257]
119. Hakimi S, Dutta P & Layton AT Renal calcium and magnesium handling during pregnancy: modeling and analysis. Am. J. Physiol. Renal Physiol 327, F77–F90 (2024). [PubMed: 38721663]
120. Stadt MM & Layton AT A modeling analysis of whole body potassium regulation on a high-potassium diet: proximal tubule and tubuloglomerular feedback effects. Am. J. Physiol. Regul. Integr. Comp. Physiol. 326, R401–R415 (2024). [PubMed: 38465401]
121. Jariwala PB et al. Discovering the microbial enzymes driving drug toxicity with activity-based protein profiling. ACS Chem. Biol. 15, 217–225 (2020).
122. Rinschen MM et al. Accelerated lysine metabolism conveys kidney protection in salt-sensitive hypertension. Nat. Commun. 13, 4099 (2022). [PubMed: 35835746]
123. Andrade-Oliveira V et al. Gut bacteria products prevent AKI induced by ischemia-reperfusion. J. Am. Soc. Nephrol. 26, 1877–1888 (2015). [PubMed: 25589612]
124. Emal D et al. Depletion of gut microbiota protects against renal ischemia-reperfusion injury. J. Am. Soc. Nephrol. 28, 1450–1461 (2017). [PubMed: 27927779]
125. Nakade Y et al. Gut microbiota-derived D-serine protects against acute kidney injury. JCI Insight 3, e97957 (2018). [PubMed: 30333299]
126. Zhu H et al. The probiotic *L. casei Zhang* slows the progression of acute and chronic kidney disease. Cell Metab. 33, 1926–1942.e8 (2021). [PubMed: 34270930]
127. Yang Z et al. The prevention effect of *Limosilactobacillus reuteri* on acute kidney injury by regulating gut microbiota. Microbiol. Immunol. 68, 213–223 (2024). [PubMed: 38747013]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

128. Gharaie S et al. Microbiome modulation after severe acute kidney injury accelerates functional recovery and decreases kidney fibrosis. Kidney Int. 104, 470–491 (2023). [PubMed: 37011727]
129. Li H-B et al. *Faecalibacterium prausnitzii* attenuates CKD via butyrate-renal GPR43 axis. Circulation Res. 131, e120–e134 (2022). [PubMed: 36164984]
130. Shankaranarayanan D & Raj DS Gut microbiome and kidney disease: reconciling optimism and skepticism. Clin. J. Am. Soc. Nephrol. 17, 1694–1696 (2022).
131. He M et al. Gut microbial metabolites SCFAs and chronic kidney disease. J. Transl. Med. 22, 172 (2024). [PubMed: 38369469]
132. Tang Z, Yu S & Pan Y The gut microbiome tango in the progression of chronic kidney disease and potential therapeutic strategies. J. Transl. Med. 21, 689 (2023). [PubMed: 37789439]
133. Gao B et al. Butyrate producing microbiota are reduced in chronic kidney diseases. Sci. Rep. 11, 23530 (2021). [PubMed: 34876615]
134. Guo X et al. Novel metabolites to improve glomerular filtration rate estimation. Kidney Blood Press. Res. 48, 287–296 (2023). [PubMed: 37037191]
135. Yamaguchi Y et al. Plasma metabolites associated with chronic kidney disease and renal function in adults from the Baltimore longitudinal study of aging. Metabolomics 17, 1–11 (2021). [PubMed: 33387070]
136. Peng H et al. A metabolomics study of metabolites associated with the glomerular filtration rate. BMC Nephrol. 24, 105 (2023). [PubMed: 37085754]
137. Li T et al. Consistency of metabolite associations with measured glomerular filtration rate in children and adults. Clin. Kidney J 17, sfae108 (2024). [PubMed: 38859934]
138. Roberts AB et al. Development of a gut microbe-targeted nonlethal therapeutic to inhibit thrombosis potential. Nat. Med. 24, 1407–1417 (2018). [PubMed: 30082863]
139. Graboski AL et al. Mechanism-based inhibition of gut microbial tryptophanases reduces serum indoxyl sulfate. Cell Chem. Biol. 30, 1402–1413.e7 (2023).
140. Winkler MKH & van Loosdrecht MCM Intensifying existing urban wastewater. Science 375, 377–378 (2022). [PubMed: 35084964]
141. Candry P et al. Tailoring polyvinyl alcohol-sodium alginate (PVA-SA) hydrogel beads by controlling crosslinking pH and time. Sci. Rep. 12, 20822 (2022). [PubMed: 36460678]
142. Godfrey B et al. Co-immobilization of AOA strains with Anammox bacteria in three different synthetic bio-granules maintained under two substrate-level conditions. Chemosphere 342, 140192 (2023). [PubMed: 37722534]
143. Gottshall EY et al. Sustained nitrogen loss in a symbiotic association of comammox *Nitrospira* and anammox bacteria. Water Res. 202, 117426 (2021). [PubMed: 34274897]
144. Landreau M et al. Immobilization of active ammonia-oxidizing archaea in hydrogel beads. npj Clean Water 4, 43 (2021).
145. Li B et al. Mainstream nitrogen removal from low temperature and low ammonium strength municipal wastewater using hydrogel-encapsulated comammox and anammox. Water Res. 242, 120303 (2023). [PubMed: 37419028]
146. Saingam P et al. Towards an effective delivery system of a microbial sink of the uremic toxin, p-cresol; an *in vitro* study with *Thauera aminoaromatica* S2. Front. Microbiol 16, 1577556 (2025). [PubMed: 40469737]
147. Ogawa T et al. Oral administration of *Bifidobacterium longum* in a gastro-resistant seamless capsule decreases serum phosphate levels in patients receiving haemodialysis. Nephrol. Dialysis Transplant. 5, 373–374 (2012).
148. Wang I-K et al. The effect of probiotics on serum levels of cytokine and endotoxin in peritoneal dialysis patients: a randomised, double-blind, placebo-controlled trial. Benef. Microbes 6, 423–430 (2015). [PubMed: 25609654]
149. Soleimani A et al. Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects. Kidney Int. 91, 435–442 (2017). [PubMed: 27927601]
150. Taki K, Takayama F & Niwa T Beneficial effects of bifidobacteria in a gastroresistant seamless capsule on hyperhomocysteinemia in hemodialysis patients. J. Ren. Nutr. 15, 77–80 (2005). [PubMed: 15648012]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

151. Ikizler TA et al. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am. J. Kidney Dis. 76, S1–S107 (2020). [PubMed: 32829751]
152. Stanford J et al. High-diversity plant-based diet and gut microbiome, plasma metabolome, and symptoms in adults with CKD. Clin. J. Am. Soc. Nephrol 20, 619–631 (2025). [PubMed: 40094861]
153. Felizardo RJF et al. Gut microbial metabolite butyrate protects against proteinuric kidney disease through epigenetic- and GPR109a-mediated mechanisms. FASEB J. 33, 11894–11908 (2019). [PubMed: 31366236]
154. Li YJ et al. Dietary fiber protects against diabetic nephropathy through short-chain fatty acid-mediated activation of G protein-coupled receptors GPR43 and GPR109A. J. Am. Soc. Nephrol. 31, 1267–1281 (2020). [PubMed: 32358041]
155. Li YJ et al. Short-chain fatty acids directly exert anti-inflammatory responses in podocytes and tubular epithelial cells exposed to high glucose. Front. Cell Dev. Biol. 11, 1182570 (2023). [PubMed: 37215085]
156. Corte-Iglesias V et al. Propionate and butyrate counteract renal damage and progression to chronic kidney disease. Nephrol. Dial. Transpl. 40, 133–150 (2024).
157. Lobel L et al. Diet posttranslationally modifies the mouse gut microbial proteome to modulate renal function. Science 369, 1518–1524 (2020). [PubMed: 32943527]
158. Linares L et al. Epidemiology and outcomes of multiple antibiotic-resistant bacterial infection in renal transplantation. Transpl. Proc. 39, 2222–2224 (2007).
159. Magruder M et al. Gut uropathogen abundance is a risk factor for development of bacteriuria and urinary tract infection. Nat. Commun. 10, 5521 (2019). [PubMed: 31797927]
160. Shimasaki T et al. Increased relative abundance of *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae* within the gut microbiota is associated with risk of bloodstream infection in long-term acute care hospital patients. Clin. Infect. Dis. 68, 2053–2059 (2019). [PubMed: 30239622]
161. Taur Y et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin. Infect. Dis. 55, 905–914 (2012). [PubMed: 22718773]
162. Ghani R et al. Disease prevention not decolonization: a model for fecal microbiota transplantation in patients colonized with multidrug-resistant organisms. Clin. Infect. Dis. 72, 1444–1447 (2021). [PubMed: 32681643]
163. Mangalea MR et al. Decolonization and pathogen reduction approaches to prevent antimicrobial resistance and healthcare-associated infections. Emerg. Infect. Dis. 30, 1069 (2024). [PubMed: 38781679]
164. Roman YM The role of uric acid in human health: insights from the uricase gene. J. Pers. Med. 13, 1409 (2023). [PubMed: 37763176]
165. Krishnan E Reduced glomerular function and prevalence of gout: NHANES 2009-10. PLoS ONE 7, e50046 (2012). [PubMed: 23209642]
166. Sorensen LB Role of the intestinal tract in the elimination of uric acid. Arthritis Rheum. 8, 694–706 (1965). [PubMed: 5859543]
167. Vargas-Santos AB & Neogi T Management of gout and hyperuricemia in CKD. Am. J. Kidney Dis. 70, 422–439 (2017). [PubMed: 28456346]
168. Liu Y et al. A widely distributed gene cluster compensates for uricase loss in hominids. Cell 186, 3400–3413 e20 (2023). [PubMed: 37541197]
169. Kasahara K et al. Gut bacterial metabolism contributes to host global purine homeostasis. Cell Host Microbe 31, 1038–1053.e10 (2023). [PubMed: 37279756]
170. Moe OW Kidney stones: pathophysiology and medical management. Lancet 367, 333–344 (2006). [PubMed: 16443041]
171. Filler G et al. In focus: perplexing increase of urinary stone disease in children, adolescent and young adult women and its economic impact. Front. Med. 10, 1272900 (2023).
172. Vo AK et al. Measuring quality of life in patients with kidney stone disease: is it the future in endourology? Curr. Opin. Urol. 34, 91–97 (2024). [PubMed: 37889517]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

173. Hatch M et al. *Oxalobacter* sp. reduces urinary oxalate excretion by promoting enteric oxalate secretion. Kidney Int. 69, 691–698 (2006). [PubMed: 16518326]
174. Campieri C et al. Reduction of oxaluria after an oral course of lactic acid bacteria at high concentration. Kidney Int. 60, 1097–1105 (2001). [PubMed: 11532105]
175. Lieske JC et al. Use of a probiotic to decrease enteric hyperoxaluria. Kidney Int. 68, 1244–1249 (2005). [PubMed: 16105057]
176. Goldfarb DS, Modersitzki F & Asplin JR A randomized, controlled trial of lactic acid bacteria for idiopathic hyperoxaluria. Clin. J. Am. Soc. Nephrol 2, 745–749 (2007). [PubMed: 17699491]
177. Lieske JC et al. Diet, but not oral probiotics, effectively reduces urinary oxalate excretion and calcium oxalate supersaturation. Kidney Int. 78, 1178–1185 (2010). [PubMed: 20736987]
178. Siener R et al. Dietary hyperoxaluria is not reduced by treatment with lactic acid bacteria. J. Transl. Med. 11, 306 (2013). [PubMed: 24330782]
179. Tavasoli S et al. Effect of a probiotic supplement containing Lactobacillus acidophilus and Bifidobacterium animalis lactis on urine oxalate in calcium stone formers with hyperoxaluria: a randomized, placebo-controlled, double-blind and in-vitro trial. Urol. J 19, 179–188 (2021). [PubMed: 34129232]
180. Hoppe B et al. A randomised phase I/II trial to evaluate the efficacy and safety of orally administered *Oxalobacter formigenes* to treat primary hyperoxaluria. Pediatr. Nephrol. 32, 781–790 (2017). [PubMed: 27924398]
181. Hoppe B et al. Efficacy and safety of *Oxalobacter formigenes* to reduce urinary oxalate in primary hyperoxaluria. Nephrol. Dial. Transpl. 26, 3609–3615 (2011).
182. Milliner D, Hoppe B & Groothoff J A randomised phase II/III study to evaluate the efficacy and safety of orally administered *Oxalobacter formigenes* to treat primary hyperoxaluria. Urolithiasis 46, 313–323 (2018). [PubMed: 28718073]
183. Mukherjee SD et al. Complex system modeling reveals oxalate homeostasis is driven by diverse oxalate-degrading bacteria. eLife 14, RP104121 (2025). [PubMed: 40310467]
184. Duranton F et al. Normal and pathologic concentrations of uremic toxins. J. Am. Soc. Nephrol. 23, 1258–1270 (2012). [PubMed: 22626821]
185. Waikar SS et al. Association of urinary oxalate excretion with the risk of chronic kidney disease progression. JAMA Intern. Med 179, 542–551 (2019). [PubMed: 30830167]
186. Ermer T et al. Oxalate, inflammasome, and progression of kidney disease. Curr. Opin. Nephrol. Hypertens. 25, 363–371 (2016). [PubMed: 27191349]
187. Pfau A et al. High oxalate concentrations correlate with increased risk for sudden cardiac death in dialysis patients. J. Am. Soc. Nephrol. 32, 2375–2385 (2021). [PubMed: 34281958]
188. Choy WH et al. Deficient butyrate metabolism in the intestinal microbiome is a potential risk factor for recurrent kidney stone disease. Urolithiasis 52, 38 (2024). [PubMed: 38413462]
189. Zampini A et al. Defining dysbiosis in patients with urolithiasis. Sci. Rep. 9, 5425 (2019). [PubMed: 30932002]
190. Agudelo J et al. Cefazolin shifts the kidney microbiota to promote a lithogenic environment. Nat. Commun. 15, 10509 (2024). [PubMed: 39663374]
191. Chesnaye NC et al. Differences in the epidemiology, management and outcomes of kidney disease in men and women. Nat. Rev. Nephrol 20, 7–20 (2024). [PubMed: 37985869]
192. de la Cuesta-Zuluaga J et al. Age- and sex-dependent patterns of gut microbial diversity in human adults. mSystems 4, e00261–19 (2019).
193. Perez M et al. A synthetic consortium of 100 gut commensals modulates the composition and function in a colon model of the microbiome of elderly subjects. Gut Microbes 13, 1–19 (2021).
194. El Houari A et al. Development of an in vitro model of human gut microbiota for screening the reciprocal interactions with antibiotics, drugs, and xenobiotics. Front. Microbiol 13, 828359 (2022). [PubMed: 35495704]
195. Cheng AG et al. Design, construction, and in vivo augmentation of a complex gut microbiome. Cell 185, 3617–3636.e19 (2022). [PubMed: 36070752]
196. Wang M et al. Strain dropouts reveal interactions that govern the metabolic output of the gut microbiome. Cell 186, 2839–2852.e21 (2023). [PubMed: 37352836]

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197. Pascal Andreu V et al. gutSMASH predicts specialized primary metabolic pathways from the human gut microbiota. Nat. Biotechnol. 41, 1416–1423 (2023). [PubMed: 36782070]

198. Mei X et al. Genetically engineered *Lactobacillus paracasei* rescues colonic angiotensin converting enzyme 2 (ACE2) and attenuates hypertension in female *Ace2* knock out rats. Pharmacol. Res. 196, 106920 (2023). [PubMed: 37716548]

199. Guo CJ et al. Depletion of microbiome-derived molecules in the host using clostridium genetics. Science 366, eaav1282 (2019). [PubMed: 31831639]

200. Rubin BE et al. Species- and site-specific genome editing in complex bacterial communities. Nat. Microbiol. 7, 34–47 (2022). [PubMed: 34873292]

201. Brödel AK et al. In situ targeted base editing of bacteria in the mouse gut. Nature 632, 877–884 (2024). [PubMed: 38987595]

202. Ali N et al. Advances in CRISPR-Cas systems for gut microbiome. Prog. Mol. Biol. Transl. Sci. 208, 59–81 (2024). [PubMed: 39266188]

203. Kelly CR et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. Am. J. Gastroenterol. 109, 1065–1071 (2014). [PubMed: 24890442]

204. Cheng Y-W et al. Fecal microbiota transplantation for the treatment of recurrent and severe *Clostridium difficile* infection in solid organ transplant recipients: a multicenter experience. Am. J. Transplant. 19, 501–511 (2019). [PubMed: 30085388]

205. Peery AF et al. AGA clinical practice guideline on fecal microbiota–based therapies for select gastrointestinal diseases. Gastroenterology 166, 409–434 (2024). [PubMed: 38395525]

206. Carlson PE Regulatory considerations for fecal microbiota transplantation products. Cell Host Microbe 27, 173–175 (2020). [PubMed: 32053787]

207. Woodworth MH et al. Fecal microbiota transplantation promotes reduction of antimicrobial resistance by strain replacement. Sci. Transl. Med. 15, eabo2750 (2023). [PubMed: 37910603]

208. Tang Q et al. Current sampling methods for gut microbiota: a call for more precise devices. Front. Cell. Infect. Microbiol. 10, 151 (2020). [PubMed: 32328469]

209. Zhang X & Figeys D Perspective and guidelines for metaproteomics in microbiome studies. J. Proteome Res. 18, 2370–2380 (2019). [PubMed: 31009573]

210. James KR et al. Distinct microbial and immune niches of the human colon. Nat. Immunol. 21, 343–353 (2020). [PubMed: 32066951]

211. Anandakumar H et al. Segmental patterning of microbiota and immune cells in the murine intestinal tract. Gut Microbes 16, 2398126 (2024). [PubMed: 39254265]

212. Shalon D et al. Profiling the human intestinal environment under physiological conditions. Nature 617, 581–591 (2023). [PubMed: 37165188]

213. Folz J et al. Human metabolome variation along the upper intestinal tract. Nat. Metab. 5, 777–788 (2023). [PubMed: 37165176]

214. Culver RN et al. Improved mouse models of the small intestine microbiota using region-specific sampling from humans. Preprint at *bioRxiv* 10.1101/2024.04.24.590999 (2024).

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Box 1 |

Dysbiosis no more?

‘Dysbiosis’ is a term that is typically used to refer to an imbalance in gut microbiota. However, this term is highly misleading for two reasons. First, ‘dysbiosis’ implies that a normal, healthy standard exists. In reality, such a standard has not been clearly defined, and can vary drastically between individuals (based in part on age or diet), as well as over time in the same individual (owing to changes in age, diet or factors that we do not yet fully understand). Second, ‘dysbiosis’ implies that any change from the idealized value is detrimental (‘dys’ implying diseased or abnormal). However, some gut microbiome changes that occur in the setting of host disease may be adaptive and beneficial to the host. Thus, we propose simply noting ‘shifts’ or ‘changes’ in gut microbiota, rather than labelling these states as ‘normal’ versus ‘dysbiotic’.

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Box 2 |

Not all kidney diseases are alike

Kidney disease is extremely heterogenous, and it is important not to generalize findings from one type of disease to other disparate conditions. Although the differences between acute kidney injury and chronic kidney disease (CKD) are well appreciated, even within a subgroup such as CKD there is a huge variety of pathologies, each with their own (probably unique) relationship to the gut microbiome. Furthermore, the relationship of the host to gut microorganisms in the early stages of CKD are probably distinct from the relationships in patients with kidney failure. Thus, it is important to consider the context of the disease and staging for each host–microorganism interaction.

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Key points

- A bidirectional relationship exists between microorganisms and kidney disease: microorganisms can influence host health, and are themselves influenced by changes in host health.
- The relationship between microorganisms and renal disease is likely to be at least somewhat specific to each disease type.
- Further studies are needed to determine the prognostic value of gut microorganisms in kidney disease.
- Available evidence suggests that interactions occur between microorganisms and drugs used to treat kidney disease; further studies are needed to determine the nature and consequences of these interactions.
- There is also promise in the possibility of targeting gut microorganisms as a therapeutic strategy.

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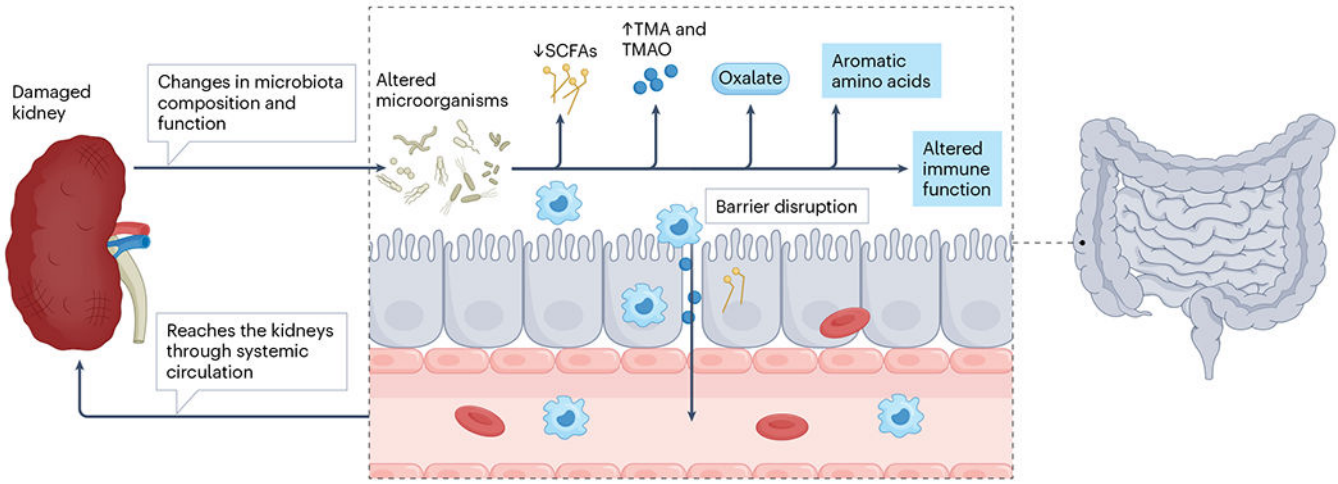


Fig. 1 |. Interactions between the kidney and gut microbiota.

Changes in kidney function can induce changes in gut microbial composition and conversely, gut microbial changes can influence kidney function. Of note, the microbiome changes that occur in the context of chronic kidney disease are complex and are also probably influenced by environmental factors, such as diet and age, and intrinsic host factors that are not yet fully understood. Altered microbial metabolites in chronic kidney disease include those produced by saccharolytic fermentation, such as short-chain fatty acids (SCFAs), and protein fermentation, such as aromatic amino-acid-derived uraemic toxins including oxalate, trimethylamine (TMA) and trimethylamine oxide (TMAO). In turn, alterations in microbial composition and function have been linked to several downstream effects, including alterations in immune cell function and impaired barrier function. TMAO has been linked to adverse cardiovascular outcomes and oxalate is a risk factor for renal stone disease.

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Table 1 |

Approaches to determining the causality of microbiome–disease associations

Experimental challenge	Potential solutions
Individuals with kidney failure constitute a readily accessible population for study, but focusing on this late stage may miss microbiome changes that occur earlier in disease development	Powering clinical studies to be able to effectively evaluate and compare kidney disease sub-types and stages; early diagnosis of CKD is a prerequisite for such studies. Of note, early diagnosis is more tractable for some aetiologies (for example, inherited genetic conditions) than others
	Animal models represent an invaluable opportunity to examine early microbiome changes, as the precise time of disease onset or insult is known. Thus, models can be examined even before the development of overt pathology that would typically be required for diagnosis in a patient
Well-matched control groups are needed to appropriately compare control and kidney-disease populations	Future studies require more homogeneous and matched CKD subgroups and well-matched controls, to enable better comparisons
	Use modern statistical techniques to control for confounders
	Longitudinal studies to identify consistent microbial signatures associated with disease
	Well-matched control groups are a major advantage of animal studies as common confounders such as diet composition can be controlled
No single animal model recapitulates all aspects of human kidney disease	Findings that are replicated in more than one model may be more generalizable
	Novel preclinical models should be developed and explored
Most studies lack sufficient metadata for interpretation, including subsequent meta-analysis	Follow recommendations for best practices such as the STORMS checklist for human studies[52], as well as guidelines for animal studies[54]
	Use smart-device applications to assist participants in collecting dietary and physical activity, and other important metadata
Gut bacteria have been the main focus of much research, ignoring other important facets of the microbiota	Future research should cover viruses, fungi and other components of the gut microbiota
	Other microbial sources, such as the urinary tract, should be evaluated
The faecal microbiome has been the focus of much research, whereas the proximal gut hosts critical metabolic and other microbial functions	Use endoscopy or other devices that enable small-bowel sampling
Most studies rely on 16S rRNA gene amplicon sequencing	If only 16S sequencing is available, the use of ASV- instead of OTU-based clustering approaches may improve accuracy and reproducibility across studies
	Future studies should be aimed at integrating multi-omics approaches (metagenomics, metatranscriptomics and metabolomics) to capture the comprehensive functional capacity of the gut microbiome; to ensure that such studies are not merely descriptive, key findings should be confirmed by functional validation in vivo
	In addition to studying omic changes, it will be important to also pursue mechanistic studies to shed light on functional host–microbiota interactions

ASV, amplicon sequence variant; CKD, chronic kidney disease; OTU, operational taxonomic unit; STORMS, Strengthening The Organization and Reporting of Microbiome Studies.

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Table 2 |

Approaches to assessing the prognostic value of gut microbiota and metabolites in kidney disease

Experimental challenge	Potential solutions
Many metabolic biomarkers identified in studies to date are not suitable for clinical use	Focus on a set of biomarkers as opposed to a single biomarker
	Use biomarkers that can be absolutely quantified
	Clearly document whether a biomarker varies by clinical characteristics (for example, sex, age)
Most studies lack sufficient metadata for interpretation	Follow recommendations for best practices such as the STORMS checklist for human studies[52], and guidelines for animal studies[54]
	Use smart-device applications to assist participants in collecting dietary and physical activity and other important metadata
The predictive abilities of current biomarkers are limited	Future studies should be longitudinal to identify consistent microbial signatures associated with disease
	Use more diverse cohorts
	Use artificial intelligence approaches, such as transformer models and related attention models[106] to improve on classification and regression tasks

STORMS, Strengthening The Organization and Reporting of Microbiome Studies.

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Table 3 |

Approaches to determining gut microbiota–drug interactions

Experimental challenge	Potential solutions
Comorbidities of human disease, which may influence the microbiome and the microbiome–kidney relationship and thus introduce experimental and analytical challenges	Use study designs that control for comorbid conditions
	Consider prescribing consistent or defined diets in clinical studies to increase uniformity across different groups
Lack of translatability of animal models	Findings replicated in more than one model may be more generalizable
	Novel preclinical models should be developed and explored with the aim of yielding better human translation
Lack of general knowledge regarding metabolite handling	Within the kidney, there is a need for studies to improve understanding of how metabolites are handled along the nephron (in terms of their filtration, reabsorption and secretion), and an understanding of how changes in metabolite handling at one site influences their handling elsewhere
	A focus on organic anion transporters and drug transporters would be particularly useful
	Beyond the kidney, studies should be aimed at improving understanding of metabolite handling by microorganisms within the intestine and in other organs or sites
	High-quality training data are a key prerequisite for the development of any model that explains metabolite handling
Need for more sophisticated analytical tools	Development of microbial analyses with a community focus (taking into account community interactions rather than focusing on one or a few taxa)
	Development of activity-based proteome profiling

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Table 4 |

Challenges in the therapeutic targeting of gastrointestinal microbiota

Experimental challenge	Potential solutions
Lack of population-based cohorts with well-annotated metadata and microbiome profiling	Preclinical animal studies that examine metagenomics, metatranscriptomics and metaproteomics will help to build a framework of understanding
	Large-scale human studies with well-annotated metadata and deep-microbiome profiling (metagenomics, metatranscriptomics, metaproteomics and metabolomics)
Need to consider other biological factors that may mitigate the relationship between microbial therapies and outcomes	Clinical studies: include assessment of the potential effects of sex, age, diet and genetic factors
	Basic science studies: include assessment of the potential effects of sex, age and diet
Need to consider the microbial community, instead of individual taxa	Experiments that use a defined consortium of microorganisms rather than studying individual taxa separately
	Development of microbial analyses with a community focus (taking into account community interactions, instead of focusing on individual taxa)
Most studies lack sufficient metadata for interpretation, especially diet	Follow recommendations for best practices such as the STORMS checklist for human studies[52], and guidelines for animal studies[54]
	Potential interactions between diet and medications should be taken into account
Differing GI transit times between individuals, especially in patients with CKD	Radio tracers can be used to document transit times, and data incorporated into models
Barriers to genetic manipulation of gut microorganisms	Genetic platforms for rapid manipulation of microbial function
	Additional focus on microbial function, rather than taxonomy alone
Overreliance on faecal samples	Researchers should be cognizant of the heterogeneity of gut microorganisms
	Where possible, use endoscopy or other devices that enable small-bowel sampling

CKD, chronic kidney disease; GI, gastrointestinal; STORMS, Strengthening The Organization and Reporting of Microbiome Studies.