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Urinary Microbiome and Genetic Determinants in an Obstetric Disease, Kidney Stone Disease : A Review Article

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Abstract

Background: Kidney stone disease (KSD) is a significant health burden globally and its prevalence rate has been rising in developed and developing nations. Conventionally viewed as a mere physicochemical process, current developments have shown that it has a more complicated etiology due to the involvement of host genetics, metabolic factors, and the urinary microbiome. The fact that the urinary tract is not sterile has redefined the knowledge in stone pathogenesis, which is the interaction of microbial community and genetic determinant affecting crystal formation, urinary pH and oxalate metabolism.

Objective: The purpose of this review is to conduct a synthesis of existing evidence that connections urinary microbiota composition and host genetic architecture with the development, recurrence and phenotypic differences of kidney stones. It also addresses the concept of incorporating genome and microbial information in order to improve diagnosis, risk assessment and individualized preventive measures.

Recent Findings: Certain bacterial taxa, such as Enterococcus, Escherichia and Corynebacterium, to be linked with calcium oxalate and strauvite stones, whilst the loss of Lactobacillus and Prevotella species is linked with lower urinary citrate and higher indices of supersaturation. At the same time, genome-wide association studies (GWAS) have identified over 50 loci that are associated with susceptibility to stones, including the genes, which regulate calcium reabsorption (CLDN14, CASR), oxalate metabolism (AGXT, GRHPR) and uric acid processing (SLC2A9, SLC22A12). The genetic variants tend to interplay with the microbiome-dependent metabolic pathways and this gives an effect on the urinary composition and inflammation. Multi-omics systems that are integrative are now starting to uncover the role of gene-microbiome crosstalk in lithogenic environments and recurrence dynamics.

Conclusion: Knowledge of the urinary microbiome-genetic axis offers a novel paradigm to kidney stones research. Recent data indicate that, there is collaborative contribution of both host and microbial genomes in lithogenesis via metabolic, inflammatory, and immunomodulatory respondences. The combination of metagenomics, transcriptomics, and polygenic risk modelling in future translational studies can potentially set the basis of kidney stone disease prevention and management based on microbiome guidance and genotype specificity.

Keywords: Kidney stone disease. Urinary microbiome. Urobiome. GWAS. Genetic susceptibility. Oxalate metabolism. Customized nephrology.

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Introduction

Kidney stone disease (KSD) is now one of the most common and frequent urological conditions, with almost 12 percent of the world population experiencing it at some point in their life (Siener, 2023). It can be explained by lifestyle changes, food intake, metabolic syndromes, and climatic factors, however, recent findings reveal that the genetic predisposition and urinary microbiota composition are the main factors in the lithogenesis (Geraghty *et al*., 2024). Traditionally, the urinary tract is thought to be sterile, but recent innovations in next-generation sequencing (NGS) have shown the presence of a complex urinary microbiome (urobiome) whose changes can cause changes in crystal formation and recurrence (Pei *et al*., 2025).

Recent investigations have shown that the bacterial communities within the urinary tract are not just the contaminants, but active regulators of the urinary biochemistry and immune homeostasis (Koudonas *et al*., 2025). *Corynebacterium*, *Enterococcus faecalis*, and *Escherichia coli* are only some of the taxa that are linked to the presence of calcium oxalate and struvite stones, implying that they cause them, which is mediated by the formation of biofilms, urease enzyme activity, and urinary urethra pH modulation (Lu *et al*., 2025). Conversely, a reduction in the protective genera of *Lactobacillus* and *Prevotella* is associated with a drop in the urinary citrate and an increase in lithogenic capacity (Zhang *et al*., 2023).

Along with these microbial findings, genetic studies have revealed that there are powerful heritable elements in KSD. More than 50 loci of risks in metabolism of calcium and oxalates, renal tubular transport, and crystallization pathways have been determined by genome-wide association studies (GWAS) and exome sequencing (Cao *et al*., 2025). Casr variant CLDN14, CASR, AGXT, and SLC2A9 as well have been shown to have main variants associated with particular biochemical phenotype including hypercalciuria, hyperoxaluria and uric acid supersaturation (Spasiano *et al*., 2025). In addition, now it is possible to predict stone recurrence and onset at younger ages using the polygenic risk scores (PRS) generated using multi-ethnic GWAS datasets (Chen *et al*., 2024).

The cross-over between dysbiosis of microbiomes and host genomic architecture is an untapped but promising field of research in nephrolithiasis. The microbial metabolites, oxalate-degrading enzymes and short-chain fatty acids can interact with the host transporters and immune genes, which form a pro- or anti-lithogenic urinary environment (Cheng *et al*., 2024). Combination of metagenomics, transcriptomics and genomics. The integrative multi-omics paradigms of stone disease are thus re-defining the pathophysiology of stone disease beyond metabolic paradigms (Wang *et al*., 2025).

This two-way cross-talk of host genetics and the urinary microbiome would change the clinical care of KSD. It can support the early detection of high-risk persons, microbiome-specific therapies, and genotype-directed prevention. This review therefore summarizes the latest developments with the urinary microbiome research and genetic determinants of stone disease highlighting their interaction and translational applications in individual nephrology.

1. Kidney Stone Disease Genetic Determinants

Kidney stone disease (KSD) is a pathology that has a central contribution by genetic predisposition. Twin and family designs suggest a range of heritability, 40-60% of which means that host genomic architecture plays a major role in determining urinary chemistry, mineral metabolism and risk of crystallization (Geraghty *et al*., 2024). The recent genome-wide association studies (GWAS) have widened the scope of monogenic causes and identified a polygenic scenery that constitutes loci that are linked to calcium homeostasis, oxalate metabolism, and renal tubular transportation.

1.1 Monogenic Variants

In the case of monogenic types of KSD, the proportion is around 10 percent, mostly in patients with early-onset or recurrent nephrolithiasis. Types I, II, and III of primary hyperoxaluria are caused by mutations in such genes as AGXT, GRHPR, and HOGA1 that result in surplus production of oxalate in the liver and frequent calcium oxalate stones (Cao *et al*., 2025). Cystinuria, the disease caused by biallelic mutations in SLC3A1 or SLC7A9, is an inability to absorb cystine in the proximal tubule and the appearance of cystine calculi (Spasiano *et al*., 2025). Also, tight junction defects in the thick ascending limb result caused by mutations in CLDN16 and CLDN19 lead to familial hypomagnesemia with hypercalciuria and nephrocalcinosis (Kawamura *et al*., 2023).

Most recent efforts in whole-exome sequencing have implicated new rare variants in SLC34A1, SLC26A1 and UMOD in the process of phosphate management and crystal retention (Cheng *et al*., 2024). These observations have demonstrated the role of genes associated with renal tubular transport as the main control mechanism of mineral balance and risk of stones.

1.2 Polygenic Risk and GWAS Discoveries.

The introduction of large-scale GWAS consortia has made possible the discovery of more than 50 kidney stone formation loci in several ancestries (Chen *et al*., 2024). Marked risk alleles are the variants of CASR, CLDN14, DGKH, TRPV5, SLC22A12, and SLC2A9, which involve the calcium sensing, ion transport, and urate metabolism pathways (Cao *et al.*, 2025). The polymorphism of CASR affects the serum calcium and parathyroid hormone and alter urinary calcium excretion and induce supersaturation. Equally, CLDN14 variants decrease the calcium reabsorption in the thick ascending limb, which predisposes to hypercalciuria (Spasiano *et al.*, 2025).

These GWAS datasets have been developed into emerging polygenic risk scores (PRS) that have been shown to be clinically useful. Patients with the highest PRS decile are at the risk of nephrolithiasis and earlier onset up to fourfold and at a younger age than the lowest PRS decile (Chen *et al*., 2024). The multi-ancestry studies of East Asian, European and Middle Eastern cohort also showed that shared and ancestry specific loci were present, underlining the heterogeneity of KSD genetically (Wang *et al.*, 2025).

1.3 Gene Environment and Epigenetic Interactions

Interindividual variations in stone formation cannot be entirely attributed to genetic susceptibility only. DNA methylation and histone modification are instances of epigenetic processes that have been suggested in the control of renal oxalate metabolism and inflammation (Zhou *et al*., 2023). Indicatively, oxalate detoxification can be down-regulated by hypermethylation of AGXT promoter regions that increase the lithogenic impact of dietary oxalate. On the same note, the presence of microRNAs (miR-23a, miR-155, miR-223) also regulates the reaction of renal epithelial injury and oxidative stress, connecting inflammation with crystal retention (Nayak *et al*., 2024).

Dietary, hydration, and microorganism-derived metabolite environmental exposures can alter gene expression by epigenetic reprogramming. Such a bidirectional interaction highlights the necessity to use integrative models of risk of stones by combining genes, the environment, and microbiomes (Pei *et al*., 2025).

The implications of this study on a clinical context include the following:

Clinical nephrology is transforming the manner in which patients are handled due to the integration of genetic testing. Genetic screening panels have now made it possible to detect the pathogenic variants of the underlying recurrent or early occurrence stones and inform individualized dietary and pharmacological treatment (Geraghty *et al.*, 2024). Indicatively, CASR variant carriers might be more likely to respond to thiazide therapy, and SLC3A1 mutated patients can be treated with specific thiol-binding cystines drugs. Besides, PRS combined with biochemical profiling has a positive effect on risk stratification and early preventive counseling (Cao *et al*., 2025).

In the end, genetic knowledge can be used to establish a more accurate nephrolithiasis care, which can be used to anticipate more personalized prevention approaches and treaties with urinary microbiome data to get a clearer picture of the multi-factorial effect of stone formation.

2. Kidney Stone Disease: Urinary Microbiome.

The identification of resident urinary microbiome (urobiome) has transformed the conceptualization of kidney stone disease (KSD). The urinary tract was traditionally thought to be sterile, although the rise of the next-generation sequencing (NGS) and 16S rRNA metagenomics has demonstrated the existence of complex microbial ecosystems even in an asymptomatic person (Thomas-White *et al*., 2022). These microbiomes are involved in complex functions of regulating urinary chemical, immune stability, and crystal growth. Microbial composition changes, which are known as dysbiosis, have been implicated in the development and reoccurrence of nephrolithiasis (Pei *et al*., 2025).

The composition of the Urinary Microbiome in Health and in Stone Disease will be studied.

Lactobacillus, *Corynebacterium*, *Streptococcus*, and *Gardnerella*, are of the healthy urinary microbiome and play a role in keeping the urinary pH stable and preventing pathogenic colonization (Koudonas *et al*., 2025). On the contrary, KSD patients exhibit urease-producing and pro-inflammatory taxa enrichment, such as *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Escherichia coli* (Lu *et al.*, 2025).

Recent metagenomic studies have shown that people that have calcium oxalate and struvite stones have a lower microbial diversity and a greater relative abundance of ureolytic bacteria (Zhang *et al*., 2023). These changes cause an increase in urinary ammonia and pH and an increase in the level of precipitation of struvite and apatite crystals (Bordier *et al*., 2024). Also, the loss of *Lactobacillus* and *Prevotella* species is associated with reduced urinary citrate -a significant inhibitor of calcium stone development- thus, exposing them to high risk of crystallization (Cheng *et al*., 2024).

2.2 Mechanisms of interconnection between Microbiome and Stone Formation

Lithogenesis via microbiomes can be considered to consist of a number of interconnected processes:

1. Urease Activity: Urease-producing bacteria (*Proteus*, *Klebsiella*, *Corynebacterium*) break urea down into ammonia and carbon dioxide, raising the urinary alkalinity and facilitating the formation of struvite (Xu *et al*., 2024).
2. Oxalate Metabolism: Oxalate is degraded by some intestinal and urinary microorganisms *oxalobacter* formigenes and *bifidobacterium*, and this lowers urinary oxalate excretion (Pei *et al*., 2025). The hyperoxaluria and frequent stones of calcium oxalate are associated with the loss of these taxa (He *et al*., 2023).
3. Biofilm Formation: Crystals Bacterial biofilms on stone or renal epithelium surfaces promote nucleation, retention and growth of crystals. The biofilms of *Escherichia col*i and *Enterococcus faecalis* have been visualized on reclaimed calculi and they serve as organic matrices stabilizing the deposition of the mineral (Lu *et al.*, 2025).

4. Inflammatory Modulation: Dysbiotic microbiota have the capacity to stimulate Toll-like receptors (TLRs) and release cytokines (IL-6, IL-8, TNF- 0) leading to damage of the epithelium, oxidative stress, and adhesion of calcium crystals (Kumar *et al*., 2024).

Altogether, these processes depict that the urinary microbiome is not a mere spectator but a player in the lithogenesis process via metabolic, inflammatory and immunological mechanisms.

2.3 Gut Kidney Axis and Urobiome Cross-Talk

According to accumulating evidence, there is a two-way communication between the gut and urinary microbiota- the gut-kidney axis. Metabolites that are produced in the gut such as short-chain fatty acids (SCFA) and secondary bile acids have an effect on renal inflammatory processes and oxalate translocation (Li *et al*., 2024). Besides, it has been demonstrated that the presence of *Oxalobacter formigenes* in the gut can decrease urinary oxalate release and recurrence (He *et al*., 2023). As recently revealed, the gut-urinary niche microbial translocation in dysbiotic conditions can be possible, leading to the introduction of pro-lithogenic species in the urinary tract (Wang *et al*., 2025). These results emphasize the necessity to consider the urinary microbiome as a component of a larger host -microbe network, and not an isolated organism.

2.4 Clinical- Translational Implications

There are important diagnostics and treatment implications with the characterization of the urinary microbiome. The microbial signature can identify stone formers and controls with a high sensitivity in metagenomic profiling of urine samples, which is a potential biomarker of microbial signatures (Koudonas *et al*., 2025). In addition, the specific modulation of microbiota, whether by using probiotics, prebiotics, or diet can be a new preventive strategy. Indicatively, the administration of *Lactobacillus plantarum* and *Bifidobacterium* breve has demonstrated potential in decreasing the urinary oxalate concentration and metabolic homeostasis (Bordier *et al.*, 2024).

Nevertheless, clinical translation is associated with multiple issues, such as contamination of the samples, low biomass in the urine, and non-standardized sequencing procedures. These methodological problems will be critical to causal relationship determination and construction of microbiome-based treatments in KSD.

3. Communication between the Urinary Microbiome and Genetic Determinants.

An emerging amount of literature suggests that host genetics and urinary microbiome (urobiome) meet on overlapping biochemical and epithelial pathways controlling lithogenesis. Genetic variants provide an innate predisposition towards lithogenic risk, and microbial communities increase or decrease the risk by modifying the pH, the oxalate metabolism and biofilm formation (Pei *et al*., 2025; Cao *et al*., 2025). As a result, kidney stone disease (KSD) is now considered to be a gene-microbe co-phenotype as opposed to a more metabolic disease (Pastuszka *et al.*, 2025).

The pathway involves converging actions between calcium and pH homeostasis via a common set of intricate and interconnected effects.

3.1 Convergent Pathways: Calcium and pH Homeostasis

The pathway comprises overlapping effects between calcium and pH homeostasis through a set of complex and mutual effects.

Various loci that impact calcium sensing and tubular reabsorption (especially, the CASR and CLDN14) have been discovered to affect the urinary calcium levels, using genome-wide association studies (GWAS) (Cao *et al.*, 2025; Luo *et al*., 2024). At the same time, urease-positive bacteria like *Proteus*, *Klebsiella*, and *Corynebacterium* increase the alkalinity of the urine and precondition the formation of struvite or apatite (Razi *et al*., 2024). The quintessential effects of these factors, when combined, are a boost in the crystal nucleation and supersaturation (Hao *et al*., 2023). The experimental models also

support the fact that microbial metabolites cause epithelial injury that overlaps with calcium-sensing receptor (CaSR) signaling, which confirms the dual genetic-microbial impact on the formation of the stone (Luo *et al*., 2024).

3.2 Flux Oxalate: Genes to Microbes

Monogenic disorders of AGXT and GRHPR impair the hepatic process of oxalate detoxification and raise urinary levels of oxalate (Cao *et al*., 2025). In the meantime, the loss of oxalate-degrading microorganisms, like *Oxalobacter formigenes* or *Bifidobacterium breve*, increases the hyperoxaluria and risk of its recurrence (He *et al*., 2023). Genetic predisposition to the overproduction of oxalate also explains studies of mendelian randomization confirming that genetic influences on oxalate production interacts with the microbiome composition to determine the degree of overproduction of oxalate (Liu *et al*., 2023). The two-way control is an example of a feedback mechanism between host transporters and the metabolic ability of microbes (Pei *et al*., 2025).

3.3 Biofilm-Epithelium interface and innate Immunity

In part, genetic differences in epithelial integrity and inflammatory processes contribute to renal epithelial micro-injury that forms niches to epithelial microbes (Li *et al*., 2025). The biofilm-forming bacteria like *E. coli* and *Enterococcus faecalis* attach to these locations to stabilize the retention of crystals and safeguard the bacteria against destruction by the immune system (Razi *et al*., 2024). Dense biofilms of calculi retrieved have been visualised using ex vivo imaging, and it confirms the microbial colonisation of stone matrices (Association between Urinary Flora and Urinary Stones, 2024). This contact between the host cell epithelial genes and the bacterial virulence factors thus serves as a trigger to recurrent lithogenesis (Hao *et al*., 2023).

A multi-omics integration and predictive model are provided into the field of multi-omics integration and prediction in scenarios demanding rapid responses to novel conditions and challenges in considerate health status, behavior, and disease mechanisms (Kim *et al.*, 2016).

The most recent integrative techniques are multi-omics, which use PRS and urinary metagenomic data to narrow predictive models in KSD (Kachroo *et al*., 2021; Wang *et al*., 2025). Those who have the high-polygenic risk pattern and the dysbiotic pattern of urobiome have significantly higher recurrence rates (Cao *et al*., 2025). The implications of these results are that combined genomic-microbiome risk stratification could be used to detect and prevent the disease in its early stages (Pastuszka *et al*., 2025). Nonetheless, the methodological variability, especially the contamination and the sequencing inconsistency, is also a major limitation (Kachroo *et al*., 2021).

3.4 Translational Outlook

Genetic testing and urinary microbiome profiling have the potential to be clinically combined as a means to identify high-risk individuals and offer personalized preventive therapy early before the disease occurs. Patients with CASR or CLDN14 variants might be placed on thiazide therapy with dietary control being supplemented by the restoration of oxalate-degrading microbes in genetically vulnerable patients (Li *et al*., 2025). The longitudinal multi-ethnic cohort studies should be used in the future to determine causality and characterize the actionable gene-microbiome signatures (Pei *et al*., 2025; Liu *et al*., 2023).

4. Kidney Stone Disease Clinical Translation and Personalized Prevention

Genetic and microbiome considerate applications in clinical nephrology are transforming the path of kidney stone disease (KSD) management. The conventional methods which are based on dietary changes and the use of fluids though necessary do not help in solving interpersonal differences in the risk of stones. Now, precision medicine intends to be applied to prevent and treat diseases according to the genetic background and the microbial profile of the urine of every patient (Cao *et al*., 2025; Geraghty *et al*., 2024).

Genetic-guided risk stratification represents an important approach to addressing the issue at hand

(Lomenie and Elgin, 2010).

4.1 Genetic-Guided Risk Stratification

Genetic data offer a platform of risk forecasting and personalized treatment. Even before clinical manifestations, polygenic risk scores (PRS) obtained with large-scale GWAS are capable of identifying people who are as much as four times more susceptible to KSD (Chen *et al*., 2024). As a case in point, individuals with carriers of risk alleles in genes of the CLDN14 or CASR gene families are characterized by an increased urinary calcium excretion, and thiazide diuretics could be helpful to decrease hypercalciuria (Luo *et al*., 2024). Likewise, patients with SLC3A1 or SLC7A9 mutations leading to cystinuria must also take alkali treatments throughout their life as well as take thiol-binding agents to help cystine dissolve (Spasiano *et al*., 2025).

Additionally, the specific sequencing can be used to differentiate the monogenic and the idiopathic, which enhances the accuracy of diagnosis and can be used to implement an early intervention, particularly in recurrent or pediatric cases (Geraghty *et al*., 2024).

4.2 Therapeutic Modulation of microbiomes

Interventions based on microbiome are promising adjunctive options in the prevention of KSD. The beneficial taxa, including *Oxalobacter formigenes*, *Lactobacillus plantarum*, and *Bifidobacterium breve*, could be restored to reduce the level of urinary oxalate and stabilise the urinary pH (Pei *et al*., 2025). Urinary oxalate excretion and recurrence rates in calcium oxalate stone formers have been demonstrated to reduce significantly with the help of experimental probiotic therapies (Koudonas *et al*., 2025).

Also, the analysis of microbiomes provides diagnostic biomarkers: dysbiotic patterns that are either dominated by *Enterococcus, Corynebacterium*, or *Proteus forecast* more recurrence and risk of infection (Lu *et al*., 2025). The adjunction of these microbial signatures into clinical algorithms will allow timely detection of a patient who is prone to one or the other intervention of probiotic or antibiotic stewardship (Li *et al*., 2024).

4.3 Predictive Model with Gene-Microbiome Data

Integration of genomics, transcriptomics, metabolomics and microbial multi-omics has provided new possibilities in predictive modeling of nephrolithiasis. Wang *et al*., (2025) showed that PRS with urinary microbiome diversity indices could increase the accuracy of the prediction of stone recurrence by 28 points in combination with PRS. On the same note, machine-learning models built on gene-microbe interactions have been demonstrated to classify the subtypes of KSD according to metabolic phenotype, which allows targeted prevention approaches to be used (Hao *et al*., 2023).

This acquisition is consistent with the rising idea of systems nephrology, that sees the kidney as a non-equilibrium connection between genetics and microbial metabolism (Pastuszka *et al.*, 2025).

4.4 Personalized Prevention Strategies

KSD will need tailored interventions based on the risk profile of every individual. In patients with a genetic predisposition, dietary counseling must be supported by genotype-based pharmacotherapy - thiazides in the case of CASR variants or vitamin B6 in the case of AGXT mutations leading to hyperoxaluria (Geraghty *et al*., 2024). At the same time, the urinary microbiome can be modulated by using probiotic supplements, prebiotic fiber, and controlled antibiotic intake and result in the restoration of microbial equilibrium and stone prevention (Bordier *et al*., 2024).

Lifestyle interventions such as proper hydration, low sodium, and moderate consumption of animal protein are applicable to everyone, but they are more effective in case the genetic and microbiome risk data will be implemented (Cao *et al*., 2025).

4.5 difficulties and Future Outlooks

Although the advances are fast, multiple barriers exist in the application of the findings of genetic and microbiome research into clinical practice. Small cohort sizes, absence of longitudinal follow-up, and the inconsistency in sampling and sequencing techniques are the limitations of current evidence (Kachroo *et al*., 2021). The problem of ethical and economic considerations also arises when the genetic testing and microbiome profiling is widespread. Universally accepted guidelines and multinational data sharing systems are required to increase the reproducibility and clinical interest (Wang *et al*., 2025).

The future studies must be randomized trials of microbiome modification in genetically characterized groups, integrative analysis of polygenic and microbial data, and investigation of gene-microbiome interactions in different ancestries (Li *et al*., 2025). The end product is to build an accurate urolithiasis paradigm - prevention, diagnosis and treatment being personalized to genomic and microbial signature of a specific patient.

5. Genomic and Microbiome Profiling Technological advances

The current technological advances have revolutionized the capability of exploring kidney stone disease (KSD) on a molecular level. The observation of the next-generation sequencing (NGS), metagenomics, and multi-omics integration in parallel has availed a never-before oversight of the interactions between genes and microbes applicable in lithogenesis (Wang *et al*., 2025).

5.1 Genomic Sequencing, Polygenic Risk Modeling

The monogenic and polygenic determinants of KSD can now be identified with the use of whole-exome and whole-genome sequencing platforms (Cao *et al*., 2025). Pipelines based on quality control, imputation and ancestry adjusted GWAS include on-cloud computing, which has increased the discovery of low-frequency variants, and machine-learning-based polygenic risk scores (PRS) enhance prediction accuracy across groups of people (Chen *et al.*, 2024). DeepVariant and EVE-Score are the example of artificial intelligence (AI)-based variant annotation tools, which allows prioritizing pathogenic alleles quickly and translate them to clinical use (Zhou *et al*., 2023).

5.2 Metagenomic and Metatranscriptomic Profiling

In nephrolithiasis, urinary and gut metagenomics, in combination with the 16S rRNA sequencing has redefined microbial ecology. Sequencing protocols, contamination-sensitive controls, and nanopore technology have now allowed detection of microbial DNA in urine to be trusted (Kachroo *et al*., 2021). In addition to taxonomy, metatranscriptomics and metabolomics are used to find the functional pathways, including urease expression, oxalate degradation, and short-chain fatty acid metabolism, which have a direct effect on the formation of stones (Pei *et al.*, 2025; Bordier *et al.*, 2024).

5.3 Multi-Omics Integrated Platforms

The combination of genomic, transcriptomic, proteomic, and microbiome data in sophisticated computational systems and structures has become the heart of systems nephrology. Multi-omics methods based on networks compose the network of dynamic interactions between host pathways (e.g., calcium signaling, the inflammatory cytokines) and microbial metabolites (Wang *et al*., 2025). Gene-microbe modules that anticipate recurrence risk and metabolic subtypes of KSD have already been discovered through such integration (Hao *et al*., 2023).

All these technological advances allow filling the gap between research and clinical practice and allow performing precision diagnostics, individualized prevention, and finding new therapeutic targets.

6. Research Future and Global Prospects

The future of KSD studies is in multi-disciplinary, longitudinal, and truly global approaches, as they incorporate the fields of genetics, microbiology and clinical data. Even though there has been a major advancement, there are still major gaps in the knowledge about causal factors and population-specific risk

modifiers (Li *et al*., 2024).

6.1 Longitudinal and Interventional Studies

Majority of the contemporary research is cross-sectional; therefore, to determine causality, there must be prospective cohorts of microbiome changes and genetic markers of stone pre- and post-event changes. There is an urgent need of interventional trials on probiotics as well as dietary modification and targeted pharmacogenomic therapy among stratified genetically population (Koudonas *et al*., 2025).

6.2 Diversity and Global Representation

Available GWAS and microbiome data are overwhelmingly European and East Asian, and thus not very generalizable. Multi-ethnic studies, such as in relation to Middle Eastern, African, and South Asian ethnicities, will enhance the risk prediction of polygenes and will reveal gene-microbe interactions that are specific to ancestry (Cao *et al*., 2025). The international data-sharing programs, including the International Kidney Stone Consortium, are required to standardize the protocols and even the representation (Geraghty *et al*., 2024).

6.3 Translational and Ethical Concerns

Ethical, privacy, and regulatory issues of genomic data and microbial signatures should be addressed in order to translate gene-microbiome findings into clinical use. Multi-omics screening methods need to adopt an informed consent approach, data confidentiality, and cost-effectiveness through implementation frameworks prior to their adoption into the routine practice (Pastuszka *et al*., 2025).

6.4 Emerging Therapeutic Horizons

The second frontier is directed control of the interactions between the host and the microbe. The synthetic-biology-engineered probiotics which include the expression of oxalate-degrading enzymes or anti-urease factors could become the adjunct to pharmacotherapy (Bordier *et al*., 2024). Also, the application of CRISPR-based gene fixing of monogenic hyperoxaluria and an individualized dietary algorithm based on microbiome-genotype data are real-world innovations of the future (Zhou *et al*., 2023).

In total, a globally integrated, ethically responsible research model that will combine the genetic, microbial, and clinical approach will play a central role in transforming KSD prevention into a personalized, predictive field of study.

Discussion

This is an informative review that indicates the multifactorial interaction of host genetics and the urinary microbiome in kidney stone disease (KSD). Recent data of 20182025 show that lithogenesis is not so much a physicochemical reaction of mineral circumstance but a biologically coordinated phenomenon affected by genetic composition, microbial arrangement, immune communication, and ecological exposures (Geraghty *et al*., 2024; Pei *et al*., 2025). Combining genomic and metagenomic information has changed the paradigm of stone pathophysiology to a systems view of kidney as a gene-microbe-metabolite ecosystem.

Recent genome-wide association studies (GWAS) have increased the number of loci that can be associated with KSD up to more than fifty that include genes related to calcium homeostasis (CASR, CLDN14), oxalate metabolism (AGXT, GRHPR) and urate transport (SLC2A9, SLC22A12) (Cao *et al*., 2025; Chen *et al*., 2024). The results support the prior studies that up to 60 percent of KSD susceptibility is heritable (Siener, 2023). At the same time, dysbiotic urinary ecosystems have been identified by metagenomic profiling, which is enriched with urease-producing and biofilm-forming bacteria (*Proteus*, *Enterococcus*, *Corynebacterium*) (Lu *et al*., 2025; Zhang *et al*., 2023).

Taken collectively, the two sets of data indicate that the microbial metabolites and genetic variants focus on overlapping lithogenic pathways, urease-mediated alkalinization, which has synergistically increased

calcium phosphate supersaturation, is synergistic with CASR or CLDN14 variants; microbial depletion of calcium salts due to the action of oxalate degraders is strong synergistically with biopsies due to AGXT mutations (Hao *et al*., 2023).

Previous reviews were mostly interested in metabolic and nutritional aspects as the main KSD driving factors (Sorokin *et al*., 2018). Nevertheless, more recent studies have expanded the mechanistic considerate by finding that microbe-host crosstalk is a significant predictor of disease relapse and disease phenotype variation (Thomas-White *et al*., 2022; Kachroo *et al.*, 2021). The results expand the body of prior experimental evidence that supports the reduction of urinary oxalate secretion by the presence of the *Oxalobacter formigenes* colonization (Stern *et al*., 2019), but they extend the idea to a larger microbial community in which several taxa cooperate or compete in the process of oxalate metabolism (He *et al*., 2023; Pei *et al*., 2025).

Also, the introduction of polygenic risk sets (PRS), in the period from 2022 to 2025, has allowed the keyword of cumulative genetic risk to be quantified, meaning a significant methodological turn with respect to an analysis based on a single gene (Chen *et al.,* 2024). In combination with microbial diversity indices, PRS play an important role in increasing predictive power on recurrence and onset to support a risk assessment framework that is personalized (Wang *et al*., 2025).

The genomic and microbiome data both point towards a number of different mechanistic axes. Cytokine and Toll-like receptor genetic variants (NLRP3, IL1B, TLR4) are also the product of interactions between bacterial endotoxins and biofilms and epithelial injury and immuno-crystal retention (Kumar *et al*., 2024). Microbe metabolism of oxalate, urea and citrate affects the chemistry of the urine and host transporter polymorphisms can affect the flux of substrates through the renal tubules (Li *et al*., 2024). Both the biofilm matrix and crystals protect the microbes to persist in the body in the kidney tissue, the biofilm is strengthened by different variants of the host that dysregulate the epithelium (Razi *et al*., 2024). This kind of evidence can be used to support a model of cooperative lithogenesis, where microbial and genetic determinants interact to influence the urinary milieu to become supersaturated, inflamed, and retain crystals.

Genetic and microbial convergence clinically allows a precision method of prevention. Genetic testing is capable of defining patients with high polygenic risk or a particular monogenic variant who might have pharmacogenomic therapies (Geraghty *et al*., 2024; Spasiano *et al*., 2025). At the same time, the urinary microbiome profiling provides dynamic biomarkers of the environmental and therapeutic modulation (Bordier *et al*., 2024).

The combination of both layers in multi-omic risk models may offer better stratification of patients for preventive programmers, such as thiazides in CASR and potentially probiotics in oxygenases (Na+ oxalate) or a new and interesting treatment, alkali therapy in urase dominant dysbiosis (Li *et al*., 2024; Koudonas *et al*., 2025). The recent study examining Lactobacillus and Bifidobacterium supplementation has shown a decrease in the oxalate excretion, but the findings are still preliminary, and need to gain considerable credibility and validation among larger and multicenter studies (Pei *et al*., 2025). There are a number of barriers to complete clinical implementation. One, urinary microbiome research is difficult because of sampling bias and contamination caused by small bacterial biomass (Kachroo *et al*., 2021). Second, genetic studies continue to be biased in terms of the population samples used, the vast majority of GWAS cohorts are of European or East Asian descent, and it is necessary to include populations of Middle East, African, and South Asian descent (Cao *et al*., 2025). Third, it is hard to determine causality: it is not known yet whether microbial dysbiosis is the cause or effect of lithogenesis (Liu *et al*., 2023). The limitations can only be overcome by using standardized methodologies, longitudinal follow-up, and integrative statistical models.

The following step in the research will probably be gene-microbiome therapeutics, where CRISPR-based gene correction to treat monogenic diseases is combined with microbiome engineering to alter metabolism (Zhou *et al*., 2023). Data fusion Multi-omics Data Multi-omics Data fusion and collaboration

of global consortia will play a main role in the validation of gene-microbiome interactions in different clinical scenarios (Wang *et a*l., 2025). However, in the end, it is hoped to transition to association to intervention, to turn KSD management into a predictive, preventive, and personalized paradigm in which genetic and microbial signatures inform all phases of risk screening to treatment.

Conclusion

Kidney stone disease (KSD) has gone full circle from being regarded as merely a physicochemical disorder, to a multi-dimensional disease pathology influenced by complex interactions between host genetics, urinary microbiota and environmental factors. As discussed above, evidence from the past decade (especially from 2022 to 2025), clearly proves that there is an intimate interaction between the urinary microbiome and genetic architecture of the host, which are determinant in the lithogenic environment. Genetic variants have a role in metabolic homeostasis, biofilm formation, the urinary pH, and the metabolism of calcium, oxalate, and uric acid, while microbial communities affect urinary pH, the biofilm, and metabolism. Taken as a whole they characterize multiple features of the risk, recurrence and phenotypic spectrum of stone disease.

The combination of genomic and metagenomic technologies has created a unique opportunity to redefine nephrolithiasis with the framework of systems biology. Polygenic risk scores (PRS) could be used to identify the individuals who are genetically predisposed to certain diseases long before they manifest and urinary metagenomic signatures could provide dynamic biomarkers of metabolic disequilibrium and treatment response. The interdisciplinary synergy between these two areas, genomics and microbiomics, is the beginning of the paradigm shift towards precision urolithiasis, where prevention and treatment are individually personalized based on the biology of the patient.

From a transitional perspective the combination of genetic test, microbiome modulation and lifestyle management can introduce a revolution in KSD prevention. Complementary strategies towards individualized care are being taken in the form of genotype-guided pharmacotherapy (i.e. thiazides for CASR variants, pyridoxine for AGXT mutations) and microbiome-friendly interventions (i.e. probiotics replenishing *Oxalobacter* and *Lactobacillus*). However, the way to clinical implementation leads through standardised methodologies, multi ethnic validation and longitudinal interventional studies to verify causality and therapeutic efficacy. Future research on kidney stones is in the interweaving of gene, microbiome, and metabolite information within worldwide diagnostics of collaborative networks. In addition to leading to improved early diagnosis and prevention, these initiatives will open new therapeutic targets for precision medicine, specifically in the nephrology field. By taking this holistic approach, the field is closer to a revolution in kidney stone disease management from being solely reactive to proactive, and precision-driven preventive.

Clinician and Investigator Issues

1. Kidney stone disease (KSD) is a complex disease resulting from an interconnected network involving host genetics, urinary microbiota and environmental factors. Moreover, the interaction between genetic variants (e.g., CASR, CLDN14, AGXT) and microbial dysbiosis is a critical factor in the modulation of the urinary chemical composition, biofilm production, as well as inflammation.
2. Recent genome-wide association studies (GWAS) and polygenic risk scores (PRS) have identified individuals at high risk before they have clinical onset. Focusing prevention through relevant genotype specific interventions, such as thiazidine diuretics in CASR carriers or pyridoxine in AGXT mutations
3. Loss of *Lactobacillus* and *Oxalobacter* and enrichment of urease producing bacteria predicts recurrence and stone composition. Handling metagenomic profiling of urine therefore signifies a noninvasive device for early risk evaluation and therapeutic monitoring.
4. Combining genomic, transcriptomic, metabolism and microbial data sets provides a better prediction and allows to carry out individualized management. The multi-omics models provide a way of pushing basic biology into the clinic in nephrolithiasis.

5. Also, when implementing the development of gene-microbiome-based diagnostics, standard sampling procedures, multi-ethnic validation worldwide must be established, with ethical frameworks for data privacy in place. Introduction of these advancements into clinical nephrology will facilitate an era of precision urolithiasis paradigm with prevention rather than treatment.

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