

## BLADDER

### [Characterization of the GU microbiome in women with self-perceived bladder health over the life course](#)

Mueller MG, Das P, Andy U, Dieter AA, Dwarica D, Kirby AC, Shepherd JP, Gregory WT, **Amundsen CL**, Kenton K

A variety of factors influence bladder health, including environmental factors, life experiences, biologic foundations, and coexistent medical conditions. A biologically diverse microbial community exists in the urine that is likely influenced by the microbial inhabitants of the vagina. The relationship between the genitourinary (GU) microbiome and self-perceived bladder health is unknown. Women with no reported lower urinary tract dysfunction or symptoms (LUTS) were recruited from six clinical sites and assessed every 6 weeks for 1 year. Voided urine and vaginal samples were longitudinally collected. Self-perceived bladder health was assessed with select items from the LURN comprehensive assessment of self-reported urinary symptoms (CASUS) tool. We defined four life phases as follows: young (18-34 years, nulliparous), midlife (35-45 years, menstruating), transitional (46-60 years, perimenopausal), mature (>60 years, not using vaginal and/or systemic hormone replacement therapy). In conclusion, women with a self-perceived healthy bladder, the GU microbiome remained stable in all age groups over a 1 year period. Differences were seen with respect to life phase, where mature women were distinct from all other groups, and with respect to self-reported LUTS

### [Incidence of New or Worsening Overactive Bladder Among Patients with a Prior SARS-CoV-2 Infection: A Cohort Study](#)

Hoang Roberts L, **Zwaans BMM**, Peters KM, **Chancellor M**, Padmanabhan P

Literature is sparse on COVID-19-associated cystitis (CAC), a novel condition comprising frequency, urgency, and nocturia after COVID-19 infection. This was a retrospective study

in which urinary symptoms were scored using the International Consultation on Incontinence Questionnaire-overactive bladder (ICIQ-OAB) at three time points: before the pandemic (January 2020), 2 mo after COVID-19 infection (if applicable), and at the time of the study (May 2021). The setting was a regional health care system. The 18 785 healthcare employees who took part in the BLAST COVID study group were invited to participate, of whom 1895 responded. The outcome measured was the percentage of COVID-positive patients with a significant change on ICIQ-OAB over time. Pearson's  $\chi^2$  test was used for comparison of categorical data, and one-way analysis of variance for continuous data and multivariate analysis. A sample size of 618 was calculated for power of 80% and  $\alpha = 0.05$ .

### [Redox-Mediated Inactivation of the Transcriptional Repressor RcrR is Responsible for Uropathogenic Escherichia coli's Increased Resistance to Reactive Chlorine Species](#)

Sultana S, Crompton ME, Meurer K, Jankiewicz O, **Morales GH**, Johnson C, Horbach E, Hoffmann KP, Kr P, Shah R, Anderson GM, Mortimer NT, **Schmitz JE**, **Hadjifrangiskou M**, Foti A, Dahl JU

The ability to overcome stressful environments is critical for pathogen survival in the host. One challenge for bacteria is the exposure to reactive chlorine species (RCS), which are generated by innate immune cells as a critical part of the oxidative burst. Hypochlorous acid (HOCl) is the most potent antimicrobial RCS and is associated with extensive macromolecular damage in the phagocytized pathogen. However, bacteria have evolved defense strategies to alleviate the effects of HOCl-mediated damage. Among these are RCS-sensing transcriptional regulators that control the expression of HOCl-protective genes under non-stress and HOCl stress. Uropathogenic Escherichia coli (UPEC), the major causative agent of urinary tract infections (UTIs), is particularly exposed to infiltrating neutrophils during

pathogenesis; however, their responses to and defenses from HOCl are still completely unexplored. Here, we present evidence that UPEC strains tolerate higher levels of HOCl and are better protected from neutrophil-mediated killing compared with other E. coli. Uropathogenic Escherichia coli (UPEC), the most common etiological agent of urinary tract infections (UTIs), is particularly exposed to infiltrating neutrophils and, therefore, must counter elevated levels of the antimicrobial oxidant HOCl to establish infection. Our study provides fundamentally new insights into a defense mechanism that enables UPEC to fend off the toxic effects of HOCl stress. Intriguingly, the defense system is predominantly found in UPEC and absent in noninvasive enteropathogenic E. coli. Our data suggest expression of the target gene rcrB is exclusively responsible for UPEC's increased HOCl tolerance in culture and contributes to UPEC's survival during phagocytosis. Thus, this novel HOCl stress defense system could potentially serve as an attractive drug target to increase the body's own capacity to fight UTIs.

### [Stimulated whole blood cytokine/chemokine responses are associated with interstitial cystitis/bladder pain syndrome phenotypes and features of nociplastic pain: a MAPP research network study](#)

Schrepf A, Kaplan C, Harris RE, Williams DA, Clauw DJ, As-Sanie S, Till S, **Clemens JQ**, Rodriguez LV, Van Bokhoven A, Landis R, Gallop R, Bradley C, Naliboff B, Pontari M, O'Donnell M, Luo Y, Kreder K, Lutgendorf SK, Harte SE

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a common and debilitating disease with poor treatment outcomes. Studies from the Multidisciplinary Approach to the study of chronic Pelvic Pain (MAPP) research network established that IC/BPS patients with chronic overlapping pain conditions (COPCs) experience poorer quality of life and more severe symptoms, yet the neurobiological correlates of this subtype are largely unknown. We

previously showed that ex-vivo Toll-Like Receptor 4 (TLR4) cytokine/chemokine release is associated with the presence of COPCs, as well as widespread pain and experimental pain sensitivity women with IC/BPS. Here we attempt to confirm these findings in the multisite MAPP Symptom Patterns Study using TLR4 stimulated whole blood (female IC/BPS patients with COPC n=99; without n=36). These results confirm that the IC/BPS + COPCs subtype show higher levels of ex-vivo TLR4 cytokine/chemokine release and support a link between immune priming and nociplastic pain in IC/BPS.

## KIDNEY

### [Genomic Disorders in Chronic Kidney Disease Across the Lifespan](#)

**Verbitsky M**, Krishnamurthy S, Krithivasan P, Hughes D, Khan A, Marasa M, Vena N, Zhang J, Lim T, Glessner J, Khosla P, Weng C, Shang N, Shen Y, Hripcsak G, Hakonarson H, Ionita-Laza I, Levy B, Kenny E, Loos R, Kiryluk K, **Sanna-Cherchi S**, Crosslin D, Furth S, Warady B, Igo R, Iyengar S, Wong C, Parsa A, Feldman H, **Gharavi A**

Genomic Disorders (GDs) are associated with many comorbid outcomes, including chronic kidney disease (CKD). Identification of GDs has diagnostic utility. We examined the prevalence of GDs among participants in the Chronic Kidney Disease in Children (CKiD) cohort II (N=248), Chronic Renal Insufficiency Cohort study (CRIC, N = 3,375), Columbia University CKD Biobank (CU-CKD, N=1,146), and the Family Investigation of Nephropathy and Diabetes (FIND, N=1,318) compared to 30,746 controls. We also performed a phenome-wide association analysis (PheWAS) of GDs in the electronic MEDical Records and GENomics (eMERGE; N=11,146) cohort. We found 9/248 (3.6%) CKiD II participants carried a GD, replicating prior findings in pediatric CKD. We also identified GDs in 72/6,679 (1.1%) adult CKD patients in the CRIC, CU-CKD, and FIND cohorts, compared to 199/30,746 (0.65%) GDs in controls (OR=1.7, 95% CI 1.3-2.2). Among adults with CKD, we found recurrent GDs at the 1q21.1, 16p11.2, 17q12, and 22q11.2 loci. In conclusion, undiagnosed GDs are detected both in children and adults with CKD. Identification of GDs in these patients can enable a precise genetic

diagnosis, inform prognosis, and help stratify risk in clinical studies. GDs could also provide a molecular explanation for nephropathy and comorbidities such as poorer neurocognition for a subset of patients.

### [Multi-institutional Validation of Improved Vesicoureteral Reflux Assessment With Simple and Machine Learning Approaches](#)

Khondker A, Kwong JCC, Yadav P, Chan JYH, Singh A, Skreta M, Erdman L, Keefe DT, **Fischer K**, **Tasian G**, Hannick JH, Papanikolaou F, Cooper BJ, Cooper CS, Rickard M, Lorenzo AJ

Vesicoureteral reflux grading from voiding cystourethrograms is highly subjective with low reliability. We aimed to demonstrate improved reliability for vesicoureteral reflux grading with simple and machine learning approaches using ureteral tortuosity and dilatation on voiding cystourethrograms. Voiding cystourethrograms were collected from our institution for training and 5 external data sets for validation. Each voiding cystourethrogram was graded by 5-7 raters to determine a consensus vesicoureteral reflux grade label and inter- and intra-rater reliability was assessed. Each voiding cystourethrogram was assessed for 4 features: ureteral tortuosity, proximal, distal, and maximum ureteral dilatation. The labels were then assigned to the combination of the 4 features. A machine learning-based model, qVUR, was trained to predict vesicoureteral reflux grade from these features and model performance was assessed by AUROC (area under the receiver-operator-characteristic). In a large pediatric population from multiple institutions, we show that machine learning-based assessment for vesicoureteral reflux improves reliability compared to current grading methods. qVUR is generalizable and robust with similar accuracy to clinicians but the added prognostic value of quantitative measures warrants further study.

### [Multi-Scalar Data Integration Links Glomerular Angiotensin-Tie Signaling Pathway Activation With Progression of Diabetic Kidney Disease](#)

Liu J, Nair V, Zhao YY, Chang DY, Limonte C, Bansal N, Fermin D, Eichinger F, Tanner EC, Bellovich KA, Steigerwalt S, Bhat Z, Hawkins JJ, Subramanian L, Rosas SE, Sedor JR, Vasquez MA, Waikar SS, Bitzer M, Pennathur S, Brosius FC, De Boer I, Chen M, Kretzler M, Ju W, **Barasch J**, Kidney Precision Medicine Project and Michigan Translational Core C-PROBE Investigator Group

Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD). Prognostic biomarkers reflective of underlying molecular mechanisms are critically needed for effective management of DKD. A three-marker panel was derived from a proteomics analysis of plasma samples by an unbiased machine learning approach from participants (N = 58) in the Clinical Phenotyping and Resource Biobank study. In combination with standard clinical parameters, this panel improved prediction of the composite outcome of ESKD or a 40% decline in glomerular filtration rate. The panel was validated in an independent group (N = 68), who also had kidney transcriptomic profiles. One marker, plasma angiotensin 2 (ANGPT2), was significantly associated with outcomes in cohorts from the Cardiovascular Health Study (N = 3,183) and the Chinese Cohort Study of Chronic Kidney Disease (N = 210). Glomerular transcriptional angiotensin/Tie (ANG-TIE) pathway scores, derived from the expression of 154 ANG-TIE signaling mediators, correlated positively with plasma ANGPT2 levels and kidney outcomes. Higher receptor expression in glomeruli and higher ANG-TIE pathway scores in endothelial cells corroborated potential functional effects in the kidney from elevated plasma ANGPT2 levels. Our work suggests that ANGPT2 is a promising prognostic endothelial biomarker with likely functional impact on glomerular pathogenesis in DKD.

## PROSTATE

### [The IL-4/IL-13 signaling axis promotes prostatic fibrosis](#)

**D'Arcy Q**, Gharaee-Kermani M, Zhilin-Roth A, **Macoska JA**

Lower urinary tract symptoms (LUTS) are a costly and pervasive medical problem for millions of aging men. Recent studies have showed that peri-urethral tissue fibrosis is an untreated pathobiology

contributing to LUTS. Fibrosis results from excessive extracellular matrix deposition which increases transition zone and peri-urethral tissue stiffness and compromises prostatic urethral flexibility and compliance, producing urinary obstructive symptoms. Inflammatory cells, including neutrophils, macrophages, and T-lymphocytes, secrete a medley of pro-fibrotic proteins into the prostatic microenvironment, including IFN $\gamma$ , TNF $\alpha$ , CXC-type chemokines, and interleukins, all of which have been implicated in inflammation-mediated fibrosis. Among these, IL-4 and IL-13 are of particular interest because they share a common signaling axis that, as shown here for the first time, promotes the expression and maintenance of IL-4, IL-13, their cognate receptors, and ECM components by prostate fibroblasts, even in the absence of immune cells. Based on studies presented here, we hypothesize that the IL-4/IL-13 axis promotes prostate fibroblast activation to ECM-secreting cells. Taken together, these studies show that IL-4 and IL-13 signal through the IL-4R $\alpha$  receptor to activate JAK/STAT signaling, thereby promoting their own expression, that of their cognate receptors, and collagens. These findings suggest that the IL-4/IL-13 signaling axis is a powerful, but therapeutically targetable, pro-fibrotic mechanism in the lower urinary tract.

## STONES

### [Financial Toxicity of Nephrolithiasis: The First Assessment of the Economic Stresses of Kidney Stone Treatment](#)

Green BW, Labagnara K, Feiertag N, Gupta K, Donnelly J, Watts KL, Crivelli JJ, Assimos DG, Small AC

The objective of this study is to investigate the financial toxicity (FT) related to kidney stone treatment. We performed a cross-sectional cohort study with multi-institutional in-person and online cohorts of stone formers. Participants were surveyed using the validated COST tool (Comprehensive Score for financial Toxicity). The maximum score is 44 and lower scores indicate increased FT. "Moderate FT" was defined by COST scores between 25

and 14 points and "severe FT" for scores <14. Descriptive statistics, X<sup>2</sup> tests, T tests, Spearman correlation, and logistic regression were performed using SPSS v28. Two hundred and forty-one participants were surveyed, including 126 in-person participants and 115 online. A total of 60% of participants reported at least moderate FT (COST score <26) and 26% reported severe FT (COST score <14). In conclusion, most participants reported moderate to severe FT. As prior studies have shown that patients with "moderate FT" employ cost-coping strategies (i.e., medication rationing) and those with "severe FT" have worse health outcomes, urologists need to be sensitive to the financial burdens of treatment experienced by such patients undergoing kidney stone treatment.

### [Ureteroscopy and Shock Wave Lithotripsy Trends from 2012-2019 within the US Medicare Dataset: Sharp Growth in Ureteroscopy Utilization](#)

Haas CR, Li S, Knoedler M, Penniston KL, Nakada SY  
Both ureteroscopy (URS) and shock wave lithotripsy (SWL) are cornerstones in the surgical management of urolithiasis in the United States. We hypothesized that URS utilization outpaced SWL utilization in recent years and quantified the magnitude of change over time for caseloads of URS and SWL amongst urologists from a national Medicare database. Methods Using the public "Medicare Physician & Other Practitioners" database (<https://data.cms.gov>), we determined case numbers of SWL (CPT 50590) and URS (CPT 52356 or 52353) from 2012-2019. Between 2012 - 2019, total URS cases annually increased by 5,700 (15%/year, p <0.001) while the number of SWL cases peaked in 2015 and has since declined on average -1.6%/year (p = 0.020). The number of urologists performing URS steadily rose from 1,147 in 2012 to 2,809 in 2019, reflecting an additional 246 urologists (21%/year) performing URS annually. The caseload of high-volume stone urologists showed similar trends with average URS cases increasing by 2.9/year/urologist

(9.8%/year, p <0.001) and average SWL cases declining by 0.9/year/urologist (-1.7%/year, p = 0.023). The conclusion shows that URS utilization has increased dramatically and outpaced SWL utilization from 2012-2019 within the Medicare population. URS was increasingly used by both the general urologist population and high-volume stone urologists while SWL utilization has begun to decline.

- Jennifer Allmaras, MPH, Muen Wang, 11/4/2022

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