

**BLADDER**[NRF2 promotes urothelial cell response to bacterial infection by regulating reactive oxygen species and RAB27B expression](#)

Chetanchandra S Joshi, Amy Mora, Paul A Felder, **Indira U Mysorekar**  
*Cell Rep.* 2021 Oct 19;37(3):109856. doi: 10.1016/j.celrep.2021.109856.  
 PMID: 34686330

Uropathogenic Escherichia coli (UPEC) cause urinary tract infections (UTIs) by invading urothelial cells. In response, the host mounts an inflammatory response to expel bacteria. Here, we show that the NF-E2-related factor 2 (NRF2) pathway is activated in response to UPEC-triggered reactive oxygen species (ROS) production. We demonstrate the molecular sequence of events wherein NRF2 activation in urothelial cells reduces ROS production, inflammation, and cell death, promotes UPEC expulsion, and reduces the bacterial load. In contrast, loss of NRF2 leads to increased ROS production, bacterial burden, and inflammation, both in vitro and in vivo. NRF2 promotes UPEC expulsion by regulating transcription of the RAB-GTPase RAB27B. Finally, dimethyl fumarate, a US Food and Administration-approved NRF2 inducer, reduces the inflammatory response, increases RAB27B expression, and lowers bacterial burden in urothelial cells and in a mouse UTI model. Our findings elucidate mechanisms underlying the host response to UPEC and provide a potential strategy to combat UTIs.

[Personalized application of machine learning algorithms to identify pediatric patients at risk for recurrent ureteropelvic junction obstruction after dismembered pyeloplasty](#)

Erik Drysdale, Adree Khondker, Jin K Kim, Jethro C C Kwong, Lauren Erdman, Michael Chua, Daniel T Keefe, Marisol Lolas, Joana Dos Santos, **Gregory Tasian**, Mandy Rickard, Armando J Lorenzo  
*World J Urol.* 2021 Nov 13. doi: 10.1007/s00345-021-03879-z. Online ahead of print.  
 PMID: 34773476

We reviewed patients undergoing pyeloplasty from 2008 to 2020 at our institution, including all children and adolescents younger than 18 years. We developed a two-stage machine learning

model from 34 clinical fields, which included patient characteristics, ultrasound findings, and anatomical variation. We fit and trained with a logistic lasso model for binary cure model and subsequent survival model. Feature importance on the model was determined with post-selection inference. Performance metrics included area under the receiver-operating-characteristic (AUROC), concordance, and leave-one-out cross validation. A total of 543 patients were identified, with a median preoperative and postoperative anteroposterior diameter of 23 and 10 mm, respectively. 39 of 232 patients included in the survival model required re-intervention. The cure and survival models performed well with a leave-one-out cross validation AUROC and concordance of 0.86 and 0.78, respectively. Post-selective inference showed that larger anteroposterior diameter at the second post-op follow-up, and anatomical variation in the form of concurrent anomalies were significant model features predicting negative outcomes. The model can be used at <https://sickkidsurology.shinyapps.io/PyeloplastyReOpRisk/>. Our ML-based model performed well in predicting the risk of and time to re-intervention after pyeloplasty. The implementation of this ML-based approach is novel in pediatric urology and will likely help achieve personalized risk stratification for patients undergoing pyeloplasty. Further real-world validation is warranted.

[Multidisciplinary approaches for elucidating genetics and molecular pathogenesis of urinary tract malformations](#)

Kamal Khan, **Dina F Ahram**, Yangfan P Liu, Rik Westland, Rosemary V Sampogna, Nicholas Katsanis, Erica E Davis, **Simone Sanna-Cherchi**  
*Kidney Int.* 2021 Nov 12;S0085-2538(21)01060-7. doi: 10.1016/j.kint.2021.09.034. Online ahead of print.  
 PMID: 34780871

Advances in clinical diagnostics and molecular tools have improved our understanding of the genetically heterogeneous causes underlying congenital anomalies of kidney and urinary tract (CAKUT). However, despite a sharp incline of CAKUT reports in the

literature within the past two decades, there remains a plateau in the genetic diagnostic yield that is disproportionate with the accelerated ability to generate robust genome-wide data. Explanations for this observation include: (1) diverse inheritance patterns with incomplete penetrance and variable expressivity; (2) rarity of single-gene drivers such that large sample sizes are required to meet the burden of proof; and (3) multi-gene interactions that might produce either intra- (e.g. copy number variants) or inter- (e.g. effects in trans) locus effects. These challenges present an opportunity for the community to implement innovative genetic and molecular avenues to explain the missing heritability and to better elucidate the mechanisms that underscore CAKUT. Here, we review recent multidisciplinary approaches at the intersection of genetics, genomics, in vivo modeling and in vitro systems toward refining a blueprint for overcoming the diagnostic hurdles that are pervasive in urinary tract malformation cohorts. These approaches will not only benefit clinical management by reducing age at molecular diagnosis and prompting early evaluation for comorbid features, but will also serve as a springboard for therapeutic development.

[Innate Bacteriostatic Mechanisms Defend the Urinary Tract](#)

Jose A Munoz, **Anne-Catrin Uhlemann**, **Jonathan Barasch**  
*Annu Rev Physiol.* 2021 Nov 15. doi: 10.1146/annurev-physiol-052521-121810. Online ahead of print.  
 PMID: 34780258

Urinary tract infection (UTI) is the most common type of urogenital disease. UTI affects the urethra, bladder, ureter, and kidney. A total of 13.3% of women, 2.3% of men, and 3.4% of children in the United States will require treatment for UTI. Traditionally, bladder (cystitis) and kidney (pyelonephritis) infections are considered independently. However, both infections induce host defenses that are either shared or coordinated across the urinary tract. Here, we review the chemical and biophysical mechanisms of bacteriostasis, which limit the duration and severity of the illness. Urinary

bacteria attempt to overcome each of these defenses, complicating description of the natural history of UTI.

### [Assessment of the Pelvic Floor and Associated Musculoskeletal System: Guide for Medical Practitioners](#)

Ingrid Harm-Ermandes, Valerie Boyle, Dee Hartmann, Colleen M Fitzgerald, **Jerry L Lowder**, Rhonda Kotarinos, Emily Whitcomb  
*Female Pelvic Med Reconstr Surg.* 2021 Dec 1;27(12):711-718. doi: 10.1097/SPV.0000000000001121. PMID: 34807882

This study aimed to assist practitioners in performing an accurate assessment of the external and internal pelvic musculoskeletal (MSK) systems to improve appropriate diagnosis and referral of patients with pelvic floor disorders or pelvic pain and to improve understanding of physical therapy (PT) treatment principles, thereby improving communication between practitioners and encouraging a multidisciplinary approach. A referenced review of the anatomy of the pelvic floor muscles, pelvis, and surrounding structures, followed by a detailed assessment of anatomy, posture, and gait, is presented. A thorough description of PT assessment and treatment is included with clinical relevance. When proper assessments are routinely performed, MSK conditions can be recognized, allowing for prompt and appropriate referrals to PT. Assessment and treatment by qualified physical therapists are integral to pelvic health care. After efficient medical assessment, MSK dysfunction can be addressed expeditiously, thereby avoiding further decline. Left unaddressed, pelvic dysfunction may become chronic. We propose a guide for MSK assessment of the pelvis and associated structures that can be used for both clinical and research purposes. This guide is designed for health care providers caring for women with pelvic floor disorders, including physicians, advanced practice providers, and nurses. This guide serves to improve communication among multidisciplinary practitioners to refine MSK assessment and treatment approaches and thereby advance clinical care and research.

## LUTS

### [Diabetic Peripheral Neuropathy and Urological Complications in Type 1 Diabetes: Findings From the Epidemiology of Diabetes Interventions and Complications Study](#)

Rodica Pop-Busui, Barbara H Braffett, Hunter Wessells, William H Herman, Catherine L Martin, Alan M Jacobson, **Aruna V Sarma**, DCCT/EDIC Research Group  
*Diabetes Care.* 2021 Nov 2;dc211276. doi: 10.2337/dc21-1276. Online ahead of print. PMID: 34728530

To evaluate associations between diabetic peripheral neuropathy (DPN) and urological complications in men and women with type 1 diabetes (T1D). Measurements of DPN at Epidemiology of Diabetes Intervention and Complications (EDIC) years 1, 14, and 17 and urological complications at EDIC year 17 were examined in 635 men (mean age 51.6 years, diabetes duration 29.5 years) and 371 women (mean age 50.6 years, diabetes duration 29.8 years) enrolled in the Diabetes Control and Complications Trial (DCCT)/EDIC study. DPN was defined by symptoms, signs, and abnormal electrophysiology or by abnormal Michigan Neuropathy Screening Instrument (MNSI) examination or questionnaire scores. Erectile dysfunction (ED) in combination with lower urinary tract symptoms (LUTS) was reported in 15% of men and female sexual dysfunction (FSD), LUTS, and urinary incontinence (UI) in 16% of women. Adjusted for age, drinking status, BMI, depression, DCCT/EDIC time-weighted mean HbA1c, microalbuminuria, hypertension, triglycerides, and statin medication use, the odds of reporting ED and LUTS versus no ED or LUTS at EDIC year 17 were 3.52 (95% CI 1.69, 7.31) times greater in men with confirmed DPN at EDIC year 13/14 compared to men without confirmed DPN. Compared to men without DPN, men with DPN based on abnormal MNSI examination or questionnaire scores had significantly higher odds of reporting ED and LUTS vs. no ED or LUTS at EDIC year 17. There were no significant differences in DPN between women reporting both FSD and LUTS/UI compared with those without FSD or LUTS/UI at EDIC year 17. In long-standing T1D, DPN is associated

with the later development of urological complications in men.

## STONES

### [Laser access and utilization preferences for pediatric ureteroscopy: A survey of the Societies of Pediatric Urology](#)

Ray Yong, **Gregory E Tasian**, Kate H Kraft, William W Roberts, Adam Maxwell, **Jonathan S Ellison**  
*Can Urol Assoc J.* 2021 Oct 18. doi: 10.5489/cuaj.7326. Online ahead of print. PMID: 34672934

We sought to evaluate laser access and practice variability for pediatric ureteroscopy (URS) across the Societies of Pediatric Urology (SPU) to identify opportunities and barriers for future technology promulgation and evidence dissemination. A 25-question survey was sent electronically to members of the SPU. The questionnaire assessed surgeon and hospital characteristics, treatment preferences based on an index case, and information about available laser units. Descriptive and comparative statistical analyses were performed to assess patterns of care and laser accessibility across the SPU. A total of 105 of 711 (15%) recipients responded. Seventy-seven respondents (73%) reported laser ownership, which was associated with greater after-hours laser access (87% vs. 13%,  $p < 0.01$ ). Fifty-eight individuals provided additional laser specifications, of whom 21 (36%) used a high-power laser unit ( $>60$  W). Standard-power lasers were used more frequently in free-standing children's hospitals, as compared to those working within a larger hospital complex (75% vs. 50%,  $p = 0.049$ ). Variation existed in treatment preferences with respect to dusting (33, 34%), fragmentation (18, 19%), or a hybrid approach (46 respondents, 48%). Stone clearance was the most important consideration irrespective of treatment choice. Variability in surgical preferences and accessibility to laser units exist across pediatric urologists who performing URS. Laser ownership and access to newer technologies vary across practices and may influence treatment options. Understanding access to laser technology will be important when considering opportunities for surgical optimization to improve patient outcomes through future studies.

## [Cavitation Plays a Vital Role in Stone Dusting during Short Pulse Holmium: YAG Laser Lithotripsy](#)

Junqin Chen, **Derek S Ho**, Gaoming Xiang, Georgy Sankin, Glenn M Preminger, **Michael Eric Lipkin**, **Pei Zhong**

J Endourol. 2021 Nov 22. doi: 10.1089/end.2021.0526. Online ahead of print. PMID: 34806899

Cylindrical BegoStone samples (6 x 6 mm, H x D) were treated in water using a clinical Ho: YAG laser lithotripter in dusting mode (0.2 ~ 0.4 J with 70 ~ 78  $\mu$ s in pulse duration, 20 Hz) at various fiber tip to stone standoff distances (SD = 0, 0.5, and 1 mm). Stone damage craters were quantified by optical coherence tomography and bubble dynamics were captured by high-speed video imaging. To differentiate the contribution of cavitation vs. thermal ablation to stone damage, three additional experiments were performed. First, pre-soaked wet stones were treated in air to assess stone damage without cavitation. Second, the laser fiber was advanced at various offset distances (OSD = 0.25, 1, 2, 3, and 10 mm) from the tip of a flexible ureteroscope to alter the dynamics of bubble collapse. Third, stones were treated with parallel fiber to minimize photothermal damage while isolating the contribution of cavitation to stone damage. Treatment in water resulted in 2.5- to 90-fold increase in stone damage compared to those produced in air where thermal ablation dominates. With the fiber tip placed at OSD = 0.25 mm, the collapse of the bubble was distracted away from the stone surface by the ureteroscope tip, leading to significantly reduced stone damage compared to treatment without the scope or with scope at large OSD of 3 ~ 10 mm. The average crater volume produced by parallel fiber orientation at 0.2 J after 100 pulses where cavitation is the dominant mechanism of stone damage was comparable with those produced by using perpendicular fiber orientation within SD = 0.25 ~ 1 mm. Cavitation plays a dominant role over photothermal ablation in stone dusting during short pulse Ho: YAG LL.

## PATIENT-CENTERED RESEARCH

### [Impact of Pre-visit Contextual Data Collection on Patient-Physician Communication and Patient Activation: a Randomized Trial](#)

Jeanne M Holt, Rachel Cusatis, **Aaron Winn**, Onur Asan, Charles Spanbauer, Joni S Williams, **Kathryn E Flynn**, Melek Somai, AkkeNeel Talsma, Purushottam Laud, Gregory Makoul, **Bradley H Crotty**

J Gen Intern Med. 2021 Nov;36(11):3321-3329. doi: 10.1007/s11606-020-06583-7. Epub 2021 Feb 9.

PMID: 33559067

Patient contextual data (PCD) are often missing from electronic health records, limiting the opportunity to incorporate preferences and life circumstances into care. Engaging patients through tools that collect and summarize such data may improve communication and patient activation. However, differential tool adoption by race might widen health care disparities. Determine if a digital tool designed to collect and present PCD improves communication and patient activation; secondarily, evaluate if use impacts outcomes by race. A pragmatic, two-armed, non-blinded, randomized controlled trial conducted during 2019 in a primary care setting. The PCD tool (PatientWisdom) invited patients to identify preferences, values, goals, and barriers to care. Patients were randomized to a standard pre-visit email or facilitated enrollment with dedicated outreach to encourage use of the tool. Outcomes of interest were post-visit patient communication and patient activation measured by the Communication Assessment Tool (CAT) and Patient Activation Measure (PAM), respectively. Outcomes were evaluated using treatment-on-the-treated (TOT) and intention-to-treat (ITT) principles. A total of 301 patients were enrolled. Facilitated enrollment resulted in a five-fold increase in uptake of the PCD tool. TOT analysis indicated that the PCD tool was associated with notable increases in specific CAT items rated as excellent: "treated me with respect" (+ 13 percentage points;  $p = 0.04$ ), "showed interest in my ideas" (+ 14 percentage points;  $p = 0.03$ ), "showed care and concern" (+ 16 percentage points;  $p = 0.02$ ), and "spent about the right amount of time with me" (+ 11 percentage points;  $p = 0.05$ ). There were no

significant pre/post-visit differences in PAM scores between arms (- 4.41 percentage points;  $p = 0.58$ ). ITT results were similar. We saw no evidence of the treatment effect varying by race in ITT or TOT analyses.

## KIDNEY

### [Posterior Urethral Valves Outcomes Prediction \(PUVOP\): a machine learning tool to predict clinically relevant outcomes in boys with posterior urethral valves](#)

Jethro Cc Kwong, Adree Khondker, Jin Kyu Kim, Michael Chua, Daniel T Keefe, Joana Dos Santos, Marta Skreta, Lauren Erdman, Neeta D'Souza, Antoine Fermin Selman, John Weaver, Dana A Weiss, Christopher Long, **Gregory Tasian**, Chia Wei Teoh, Mandy Rickard, Armando J Lorenzo

Pediatr Nephrol. 2021 Oct 22. doi: 10.1007/s00467-021-05321-3. Online ahead of print. PMID: 34686914

Early kidney and anatomic features may be predictive of future progression and need for additional procedures in patients with posterior urethral valve (PUV). The objective of this study was to use machine learning (ML) to predict clinically relevant outcomes in these patients. Patients diagnosed with PUV with kidney function measurements at our institution between 2000 and 2020 were included. Pertinent clinical measures were abstracted, including estimated glomerular filtration rate (eGFR) at each visit, initial vesicoureteral reflux grade, and renal dysplasia at presentation. ML models were developed to predict clinically relevant outcomes: progression in CKD stage, initiation of kidney replacement therapy (KRT), and need for clean-intermittent catheterization (CIC). Model performance was assessed by concordance index (c-index) and the model was externally validated. A total of 103 patients were included with a median follow-up of 5.7 years. Of these patients, 26 (25%) had CKD progression, 18 (17%) required KRT, and 32 (31%) were prescribed CIC. Additionally, 22 patients were included for external validation. The ML model predicted CKD progression (c-index = 0.77; external C-index = 0.78), KRT (c-index = 0.95; external C-index = 0.89) and indicated CIC (c-index = 0.70; external C-index = 0.64), and all performed better than Cox proportional-hazards regression. The

models have been packaged into a simple easy-to-use tool, available at <https://share.streamlit.io/jcckwong/puvop/main/app.py> CONCLUSION: ML-based approaches for predicting clinically relevant outcomes in PUV are feasible. Further validation is warranted, but this

implementable model can act as a decision-making aid. A higher resolution version of the Graphical abstract is available as Supplementary information.

- Jennifer Allmaras, MPH, 11/23/2021

Email [cairibu@urology.wisc.edu](mailto:cairibu@urology.wisc.edu) to feature your newly published research in next month's communique!