

Project Title: Validating the kidney injury test (KIT) as a point of care diagnostic for urinary stone disease

Endourology Society Summer Student Scholar: Xavier Cortez

Mentor: Thomas Chi, MD

AUA Awardee Report: The main focus of my research has been to further validate the Kidney Injury Test (KIT) assay as a diagnostic for stone disease by measuring urine biomarkers in patients with recurrent nephrolithiasis. The Kidney Injury Test (KIT) assay measures 6 biomarkers in 1 spot urine sample at the time of suspected nephrolithiasis: measured cell-free DNA (cfDNA), methylated cfDNA, clusterin, creatinine, protein and CXCL10 [14-18]. The Chi lab previously demonstrated that a KIT stone score, a composite of all 6 biomarkers, accurately demonstrated the presence of kidney stones in patients with imaging-proven stones compared to patients without stones [25]. I spent the summer collecting and identifying clinical and biological samples to form a longitudinal sample cohort based on the urine samples available in our nephrolithiasis registry, ReSKU (Registry for Stones of the Kidneys and Ureter). The inclusion criteria for my cohort includes patients who provided at least 2 urine samples with concurrent imaging studies (ultrasound, KUB, CT) conducted within 2 months of each sample collection date. Each urine sample requires a unique imaging study conducted within 2 months to verify the presence, absence, or recurrence of stones. I coordinated specimen collection and preparation of urine samples to be buffered for use in the KIT assay. At the current time, our cohort is comprised of ~150 patients.

Proper identification of our cohort has been critical to addressing our aims. Our first hypothesis is that KIT score will demonstrate clinically significant positive and negative predictive values in detecting stone recurrence within individuals over time when compared to imaging. Our second hypothesis is that KIT score will demonstrate higher positive and negative predictive values for calcium oxalate stone recurrence when compared to 24-hour urine collections. With 150 patient samples and clinical data collected and the data cleaned, my next step is to analyze the samples with the KIT assay and analyze the data, which will be done this October with plans to submit an abstract by November 1 for the AUA2022 meeting. I have also begun drafting the methods for a manuscript based on our findings.

During this research period, I also took a lead role on several additional projects. Using the ReSKU database, as I learned to use this database for KIT, I discovered several new areas of inquiry to pursue leading me to ask two clinical research questions. A first question focuses on what patient outcomes are following percutaneous nephrolithotomy using different sized access tracts. The second question focuses on differences in stone free rates in patients who underwent shockwave lithotripsy versus ureteroscopy and PCNL. While looking at stone size correlation with KIT score using ReSKU data, I recognized that these are two questions that could be readily examined using our clinical database. I am conducting the analysis on both projects currently with plans to submit 2 abstracts to AUA2022. Additionally, I am collaborating with a resident and medical student on a project that explores whether an intraoperative antegrade injection of methylene blue or ultrasound contrast can predict ureteral patency, helping determine the necessity of post-operative drainage tubes after percutaneous nephrolithotomy procedures. We

plan to submit an abstract to AUA2022 for this project. These projects were identified with my increased familiarity and use of the ReSKU database related to my primary project.

In addition to these projects, I also have taken lead in two quality outcomes research studies. In Dr. Chi's role as Ambulatory Executive Medical Director for Surgical Subspecialties, he and I spoke about opportunities for studying care delivery, which I found to be a fascinating topic. I have gotten involved in 2 quality of care projects in the perioperative space. The first project highlights patient outcomes, including length of stay, case cancellation rate, and rate of patients referred to outpatient rehabilitation services, following the implementation of a workflow that proactively screens patients coming to the hospital for elective surgery for social needs. The second project looks at the impact of electronic consents on efficiency of the operative room workflows on the day of surgery. For these projects, I have helped with data abstraction from patient charts and plan to compose manuscripts for each of these projects over the next 4 months.

Lastly during this research period, I became involved in enrolling patients into 2 clinical trials overseen by Dr. Chi at the UCSF Parnassus Medical Center. The first is a surgical clinical trial, where we are examining efficacy and safety of a new technology for ultrasound-based lithotripsy. This device, called Break Wave, is a new device meant to be a direct competitor to traditional shockwave lithotripsy and uses lower amplitude, higher frequency waves to break stones in the kidneys or at the ureterovesical junctions. I have facilitated the enrollment and follow-up of 4 patients in this trial with a plan to enroll 10 total patients. The second surgical clinical trial utilizes an Acoustic Enhancer to optimize traditional ureteroscopy and laser lithotripsy procedures. The Acoustic Enhancer, consisting of micro bubbles with lipid shells, is injected prior to activation of the laser and surrounds targeted stones. Upon activation of the laser and delivery of acoustic impulses, the Acoustic Enhancer expands and contracts rapidly to trigger cavitation on the stone surface. This supplemental cavitation would ideally make URS procedures more efficient with minimal adverse effects. For this study, I have facilitated the enrollment and follow-up of 2 patients with a plan to enroll ~40 patients. These projects have exposed me to the inner workings of clinical trials, and I have learned about patient recruitment and data collection in this setting.

Overall, the funding from the Endourology Society has enabled me to move projects forward with plans to translate them into at least 4 AUA2022 abstracts and 3 manuscripts as primary author over the coming months. This period also enabled me to understand how urology attendings operationalize clinical trials in their practices, pushing the boundaries of urological care with novel technologies while maintaining the same level of high-quality care. I have also been exposed to translational, data, and clinical trials research projects and have garnered multiple experiences and skills that will serve me in my academic career and training.

Personal Statement: Being a Summer Student Scholar has led to several experiences that have empowered me to make progress in the 2 primary goals for my dedicated research year: to further cultivate my research skills and explore my interest in academic endourology. As a physician scientist in training, I learned the importance of setting myself up for success when moving projects forward. For my main project, I have learned the iterative process of collecting data, looking to see if the data meet outcome needs, and then reviewing my cohort's inclusion and exclusion criteria to ensure that we adequately address our hypotheses. Through my ReSKU projects, I am learning how to collaborate with fellows, residents, and other members of the team to refine my scientific questions, set team deadlines, and clarifying my various roles. In my perioperative research projects, I have learned about establishing and maintaining relationships with teammates in different fields. Each of my projects have underscored the importance of working on how to best operate in the context of team science. It is clear to me that multi-disciplinary approaches to research lead to the most interesting questions and discoveries.

This funding period has also enabled me to further explore my interest in academic endourology. During my urology elective as a 3rd year medical student, I shadowed Dr. Chi in the OR, watching procedures to treat nephrolithiasis and BPH, both common and morbid health conditions. The diagnosis and treatments of these diseases are well-established in the literature, and I continued to wonder what else there was to discover. How are they continuing to push the boundaries of these diseases so patients remain satisfied with their care? Following my elective, I met with Dr. Chi and felt that he would be a great mentor for my career exploration. I admired his passion for teaching and mentorship. I wanted to explore these questions and learn more about the field from him. For these last few months, I've been able to do just that.

Enrolling patients in clinical trials has also taught me about how to operationalize forward thinking research design into clinical practice. In working with Dr. Chi, he has spent time teaching me on the process of implementing a clinical trial from how one initially hears about it, what needs to occur to get approval, what is needed to maintain compliance, and what takes place after the trial is completed. I have observed how he offers this information to patients, ensuring to maintain patient autonomy while offering a clinically viable, innovative procedure. Most importantly, I have been able to work closely with Dr. Chi 5 days a week shadowing him in the OR, seeing patients with him in clinic, and participating in his research meetings.

It was an absolute privilege to be a Summer Student Scholar, and I am extremely grateful to the Endourology Society for empowering me to make progress on my goals these past few months. My direct exposure to the aspects of Dr. Chi's practice has further stimulated my interest in academic endourology. I intend to continue learning within the field of urologic research for the duration of my research year to further develop my research skills. Conducting research over 12 total months in this field will also continue to help me gain a comprehensive picture of what it takes to be an effective academic endourologist and determine if the field ultimately fulfills my career aspirations. The Summer Student Scholarship program has been a cornerstone for skill development in my training as a growing physician scientist.

References

1. Ling XB, Sigdel TK, Lau K, Ying L, Lau I, Schilling J, et al. Integrative urinary peptidomics in renal transplantation identifies biomarkers for acute rejection. *J Am Soc Nephrol. American Society of Nephrology*; 2010 Apr;21(4):646–53. PMID: PMC2844301
2. Sigdel TK, Sarwal MM. Cell-free DNA as a measure of transplant injury. *Clin Transpl.* 2012;;201–5.
3. Wang A, Sarwal MM. Computational Models for Transplant Biomarker Discovery. *Front Immunol. Frontiers*; 2015;6(5):458. PMID: PMC4561798^[1]_{SEP}
4. Sigdel TK, Gao Y, He J, Wang A, Nicora CD, Fillmore TL, et al. Mining the human urine proteome for monitoring renal transplant injury. *Kidney Int.* 2016 Jun;89(6):1244–52. PMID: PMC5221536
5. Sigdel TK, Ng YW, Lee S, Nicora CD, Qian W-J, Smith RD, et al. Perturbations in the urinary exosome in transplant rejection. *Front Med (Lausanne). Frontiers*; 2014;1(2):57. PMID: PMC4292055
6. Yang JYC, Sarwal RD, Ky K, Dong V, Stoller M, Sarwal MM, Chi T. Non-radiological assessment of kidney stones using the kidney injury test (KIT), a spot urine assay. *BJU Int.* 2020 May;125(5):732-738. doi: 10.1111/bju.14978. Epub 2020 Jan 30. PMID: 31869527.