Urology Interagency Coordinating Committee Virtual Meeting
December 10, 2021
9 AM- noon ET
Meeting Minutes

Meeting Participants (* denotes absence)**:**

Kevin Abbott (NIDDK)
Kathryn Argue (CDMRP)*
Linda Bambrick (NINDS)*
Lionel Banz (AHRQ)*
Julie Barthold (NIDDK)
Tyler Best (NIH/OD)*
Joe Bonner (NICHD)*
Eric Brunskill (NIDDK)
Gene Civillico (SPARC)*
Theresa Cruz (NICHD)*
Emily Duggan (NIDDK)
Bill Elwood (OBSSR)*
Eleanor Hoff (NIDDK)
Chris Ketchum (NIDDK)
Ziya Kirkali (NIDDK)
Melissa Miller (DoD)*
Joan Nagel (NCATS)*
Deepak Nihalani (NIDDK)
Ralph Nitkin (NICHD)
Jenna Norton (NIDDK)*
Matt Oldham (NIDDK)
Tracy Rankin (NIDDK)
Jen Rymaruk (NIDDK)*
Anna Sadusky (NIDDK)
Marcel Salive (NIA)
Victoria Spruance (NIDDK)
Robert Star (NIDDK)
Roger Weiderhorn (FDA)*
Joan Weiss (HRSA)

Welcome & Introductions

Dr. Star opened the meeting and noted that the topic of today's meeting will focus on benign urology disease with a focus on translational research. Dr. Star noted this research has been implemented into the Centers program. Participants introduced themselves to the group.

Benign Prostate Disorders: Building an Investigator Base to Advance Clinical and Translational Research

Dr. Barthold noted that NIDDK funding for BPH began in 1987-2001, largely promoted by the funding of the George M. O'Brien Urology Centers. The NIDDK urology portfolio includes funding for the O'Brien Urology Centers as well as umbrella efforts within the Centers which includes Collaborating for the Advancement of Interdisciplinary Research in Benign Urology (CAIRIBU). The CAIRIBU consortium, initiated in 2018, promotes interactions among the Directors of the NIDDK U54 O'Brien Urology Centers and their research teams, the Directors and research teams of the P20 Developmental Centers for Interdisciplinary Research in Benign Urology, and the Directors for the Multidisciplinary K12 Urologic Research (KURe) and Urologic Epidemiology (KEpi) Career Development Program and their scholars. Most recently, NIDDK staff supplemented this effort with an interactions core to this program to boost collaborations among investigators. Additionally, the NIDDK urology portfolio supports funding for individual grants and training efforts. Dr. Barthold commented this portfolio has seen strides made in increasing the number of investigator-initiated R01s. Dr. Mullins commented that previous NIDDK efforts within BPH research include:

- From 1995-2001, the Medical Therapy of Prostatic Symptoms (MTOPS) trial demonstrated that combination medical therapy reduced the risk of overall clinical progression, urinary retention and need for invasive therapy for BPH significantly more than either drug alone.
- In 2009, the NIDDK Prostate Research Strategic Plan was released to provide a guide for the research and clinical communities, identify key research questions of the highest relevance, and foster research infrastructure for new investigators, projects, and resources.
- From 1987-2021, NIDDK funding for BPH has primarily focused on human subjects and vertebrate animals, with a portion of funds being distributed to projects involving both and some siloing between more basic and clinical studies.

Dr. Mullins detailed that current targeted funding efforts within the NIDDK's urology programs include:

- Opportunity Pool programs using the newly implemented U24 interactions core within the CAIRIBU consortium to seed efforts for investigator-initiated R01s.
- P20 Fostering Research With Additional Resources and Development (FORWARD) Centers are designed to foster collaborations and generate data for follow-on R01s.
- Ancillary Study R01s for NIDDK large Urology Consortium (e.g., MAPP, PLUS, LURN, etc).
- Small R01s for Clinical Trials Targeting Diseases within the Mission of NIDDK; PAS-20-160.
- Stimulating Urology Interdisciplinary Team Opportunity Research (SUITOR); PAS-22-074; Theme: "Neuro-urology."
- Early-Stage Investigator (ESI) R01 Policy (FY21): 25% Pay-line, full project period (when possible), improved pay-line for first competing renewal, etc.
- NIH "Parent" Solicitations for R01s.

Drs. Barthold and Mullins emphasized that the NIDDK urology program continues to focus on building the benign urologic research community; fostering highly meritorious research using basic, translational, and clinical studies; and maintaining flexibility in the changing urology field.

Dr. Rankin commented on an upcoming workshop titled "Male LUTS and BPH: Intersection between Pathology and Disease," and she noted that the workshop will focus on reviewing our understanding of BPH etiology and how BPH does or does not result in LUTS in men. This will include presentations and breakout to assist in framing research priorities and needs. Dr. Rankin noted that registration for this workshop is now live, and participants can register at https://www.niddk.nih.gov/news/meetings-workshops/2021/male-luts-prostate-workshop.

Advancing Translational BPH Research: What Are We Missing?

Dr. Barthold introduced Dr. William A. Ricke, Professor of Urology and Director of the University of Wisconsin-Madison's O'Brien Center. Dr. Ricke noted that BPH research within the past 20 years had limited clinical advances and has centered primarily on efforts such as MTOPS, which focused on alpha blockers and 5ARIs as well as research on PDE5A inhibitors. As the individual lifespan increases, treatments for BPH remain incomplete and impact individual quality of life (QoL), resulting in increased morbidity worldwide. Dr. Ricke emphasized that more BPH research is needed and suggested advancements in this area may include:

- A better scientific understanding of BPH/LUTS development and progression, which may include studies in the cellular and molecular mechanisms.
- Talented researchers, especially early stage
- Increased and targeted funding
- Awareness in the general population that worldwide BPH/LUTS incidence is increasing and more people are likely to die from complications of BPH than prostate cancer, hence, it is not just a "bothersome" disease/condition.
- Increased resources for the biomedical community
- High impact journals for BPH research
- Clinical trials which evaluate the alternatives to standard medical treatment, including the role of fibrosis
- New ideas that include testable hypotheses and translation

Dr. Ricke expanded on this topic and detailed several studies at his O'Brien Urology Research Center, including:

- Defining benign prostatic hyperplasia/hypertrophy using an unobstructed view for the normal urethra and an obstructed view to evaluate the urethra with hyperplasia, smooth muscle, and/or fibrosis.
- Biomarker discoveries using mass spectrometry that apply this technology non-invasively to human and animal models' urine samples, which enables researchers to view metabolite and protein fractions to assist in the stratification of patients as well as the response to medical therapies.

- Multi-omics integration using genomics, epigenetics, and mass spec based-omics in combination with imaging and clinical information to determine the "type" of BPH in a given patient.
- Increased prostatic collagen (PSR) in aging using murine and human models
- Collagen-I gain of function
- Anti-fibrotic effects on aged mice and estrogen induced collagen expression
- Imaging efforts including MRI, MRI-elastography, and imaging-collagen tracer to study prostate fibrosis.
- Pilot efforts on biomarker development using imaging and collagen contrast imaging agent: EP-3533 (unpublished) and other biomarkers/tools related to prostate fibrosis imaging efforts such as MRI on compound #2-active fibrogenesis, which detects prior to histochemical or EP3533 detection. Dr. Ricke added that this would predict prostate/LUT fibrosis and potentially progression of BPH/LUTS. He added that PET analogue studies would also be valuable.

In addition to these research opportunities and projects, Dr. Ricke commented that many factors are important in the development of fibrosis, including hormones, inflammation, and aging (mitochondrial dysfunction, senescence, frailty). He commented that translational benign prostate research promotes bench (models, biomarkers, preclinical testing) to bedside (define BPH, stratification, and new therapies) care. Dr. Ricke thanked NIDDK staff for the opportunity to present findings during this meeting as well as their support.

Phenotyping BPH to Improve Therapeutics

Dr. Barthold introduced Dr. Brooks, Professor at Stanford University's Department of Urology. Dr. Brooks presented information on phenotyping BPH to improve therapeutics in terms of long-term aspirations, the shorter term goal of precision medicine, and opportunities and challenges in translating molecular taxonomies of BPH into the clinic.

Long-term aspirations include gene expression profiling, cell interaction networks using candidate ligand receptor pairs, and fibrosis associated with LUTS. Dr. Brooks detailed needs for the development of therapeutics:

- Credentialled pathways demonstrating functional roles in BPH genesis, progression, symptoms
- In vitro model systems for candidate therapeutic testing that replicate the human disease with high fidelity: cells, organoids, and tissue slice cultures
- With a target pathway and in vitro model, can perform high throughput screens for biologically active compounds. Consider new PROTAC approaches for targeting critical proteins
- In vivo model systems for therapeutic testing that replicate the human disease with high fidelity to do pharmacokinetics and allow for toxicity testing: animal models including PDX systems

Dr. Brooks commented that BPH does not have driver mutations or other types of vulnerabilities that are obvious therapeutic targets that will make it uniquely sensitive to therapies that would otherwise not affect normal tissue. In fact, BPH structurally resembles the normal prostate. He noted that investigators should consider what the disease specific targets to use and the clinical goal (stabilizing BPH or regression of BPH) since regression, in particular, will be difficult. Dr. Brooks also advised that treatment could involve slowing progression as an endpoint although this does imply long-term therapy. He added that investigators should consider what frequency and side effects can be tolerated in a therapeutic that will be given over a long time period. Since the goal of treating BPH is mainly improvement of QoL, the drug must achieve that goal without worsening QoL due to side effects.

During the second segment of his presentation, Dr. Brooks emphasized that efforts directed toward precision medicine is a short-term goal as existing therapies for BPH are only effective for some patients. Biomarker research is needed to better select the appropriate treatment for each patient as well as the following elements needed for precision therapy:

- New taxonomy of BPH (molecular, cellular, imaging)
- Technologies to measure these subtypes in the clinic
- Defined clinical applications and clean clinical trial designs

With regard to the molecular cellular taxonomy of BPH, preliminary studies suggest that this disease can be categorized into distinct subtypes based on transcriptome or cellular composition and these subtypes could be measured once assays are developed. Additionally, these subtypes provide a toehold for testing whether distinct subtypes respond differently to therapies. To leverage this effort, investigators should focus on obtaining a large number of samples to assess molecular subtypes. While considering the heterogeneity of this population and what clinical endpoints require biomarkers, investigators are also able to study new technologies to assess BPH phenotypes such as DNA methylation as well as proteomics and other single cell technologies.

Dr. Brooks described several opportunities and challenges in translating molecular taxonomies of BPH into the clinic. He noted several studies reporting candidate biomarkers for BPH and discovery-based studies such as omics analyses will yield differences. However, this poses a series of questions, including:

- What is the clinical use? Do we need biomarkers to tell us who has BPH?
- What are the endpoints for BPH?
- How will biomarkers influence clinical decision making?

Dr. Brooks detailed that commonly used clinical endpoints are imperfect as urinary retention is relatively uncommon and might not capture irritative voiding symptoms as a hard endpoint, while surgical endpoints show tremendous variation in practice patterns. In addition, IPSS is subjective, prone to misinterpretation and misalignment in IPSS and bother index (BI), and prostate volume is not an accurate endpoint.

Dr. Brooks concluded his presentation with the following takeaway points:

- Molecular taxonomy of BPH will help develop new therapies and better apply existing therapies
- Need new models for testing new therapeutics
- Need strategies for non-invasive measurements
- Thoughtful trial designs for meaningful endpoints

How Clinical Guidelines Can Impact Translational Research

Dr. Barthold introduced Dr. Steve Kaplan, Chair of Research, American Urologic Association, Professor of Urology at the Icahn School of Medicine at Mount Sinai and Director, Men's Health Program at the Mount Sinai Health System. Dr. Kaplan discussed how clinical guidelines can impact translational research. Dr. Kaplan noted an update of the AUA guidelines which was done to analyze the latest evidence on the medical and surgical management of LUTS associated with BPH and commented that the 2021 iteration is the latest which reflects evolutionary changes in both minimally invasive and surgical therapies for BPH.

Dr. Kaplan commented that in order to maximize the patient's QoL and minimize patient burden and adverse events related to BPH, it is important to understand and implement evidence-based medical and surgical management for men with LUTS attributed to BPH. He added that this is a timely initiative for this effort as many new technologies have been developed over the past few years. Dr. Kaplan emphasized issues within the healthcare delivery system related to the quality of patient care and commented that more efforts are needed related to assessing medical quality and defining quality in the context of patient outcomes.

Dr. Kaplan remarked that while clinical practice guidelines are available, these are often used more by professionals in industry rather than clinicians. Patients often fail therapy because there is no clear statement of a clinical problem, and it is unclear what evidence-based therapies should be used. Dr. Kaplan commented that, when surveyed, just under 90% of clinicians noted that additional clinical practice guidelines would not change clinical practice or encourage clinicians to reference updated guidelines. Clinicians cited a lack of familiarity/agreement and significant resource barriers as reasons for not implementing clinical practice guidelines. From a patient perspective, many fail therapies due to inflammation, metabolic dysfunction, obesity, and other comorbidities.

From a clinical standpoint, there are enormous gaps in knowledge and, therefore, ensuing opportunities for discovery. These include but are not limited to many unanswered questions related to the role of inflammation, metabolic dysfunction, obesity, and environmental factors in etiology, as well as the role of behavior modification, self-management, and evolving therapeutic algorithms in both the prevention and progression of disease. Specifically, recommendations include:

- disease etiology (lack of good animal models);
- management of Nocturia;
- urodynamic evaluation and imaging (precision diagnosis on molecular and technology level);
- new therapeutic options which focus on the prostate, treatment failure (no data on how many patients fail therapy), and comparative treatment efficacy;
- addressing healthcare disparities and cultural competency (Paucity of data on racial and ethnic variations in LUTS /BPH. Implementation and study of educational endeavors focused on improving cultural competency); and
- the development of a patient-centered approach to improve adherence and competence.

Dr. Kaplan added that these recommendations will address treatment and definition of efficacy and treatment failure. Dr. Kaplan closed his presentation by reiterating that the AUA is interested in promoting these opportunities to ensure better patient care.

Evolution of the CAIRIBU Interactions Core as a Model to Advance Research in Benign Urology

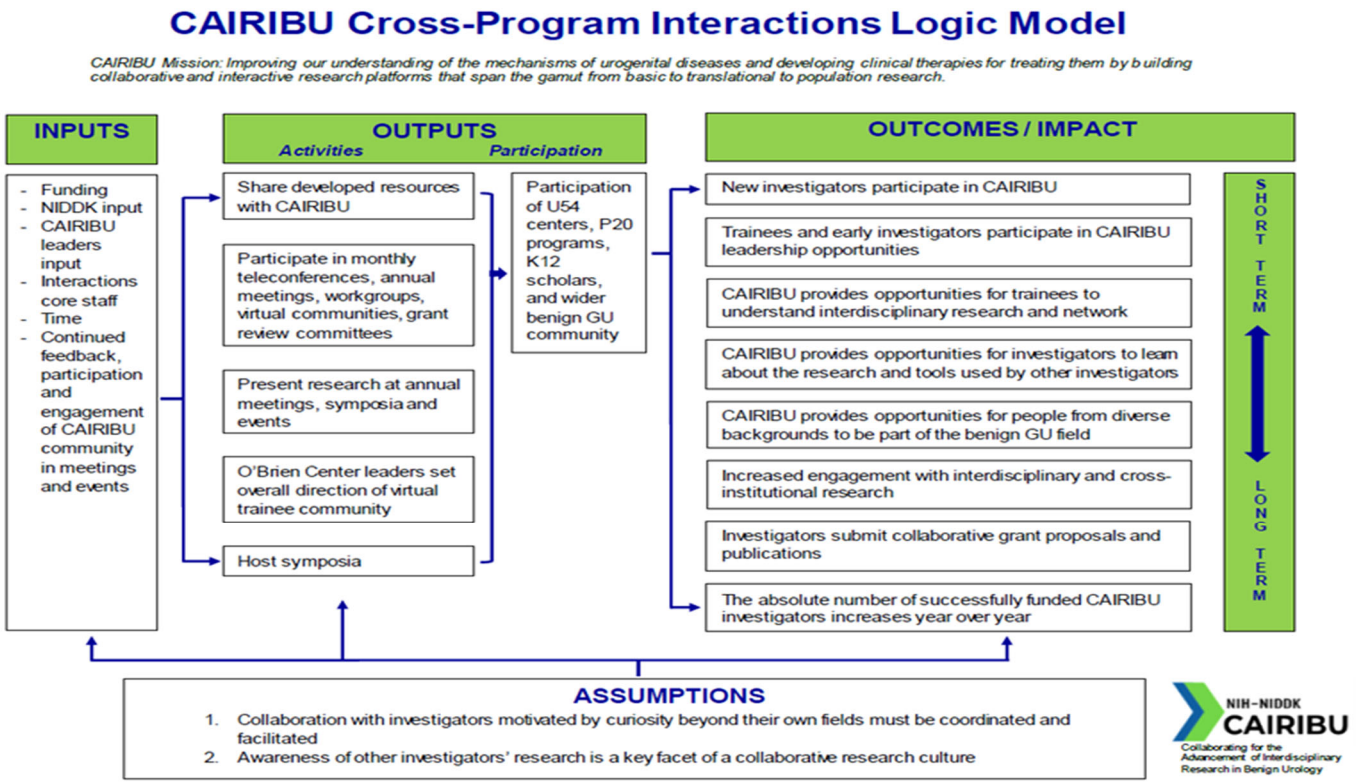
Dr. Barthold introduced Dr. Kristina Penniston, Senior Scientist at the University of Wisconsin School of Medicine and Public Health and PI for the CAIRIBU Interactions Core. Dr. Penniston commented that CAIRIBU is a multidisciplinary effort that engages clinicians, epidemiologists and basic researchers. Dr. Penniston acknowledged staff within the interactions core, including Program Officers for CAIRIBU, and through the O'Brien Urology Centers' Consortia Management Board Chair, Dr. Nelson as well as NIDDK Program Officers. She detailed that CAIRIBU leadership was launched in 2018, using a pilot initiative to encourage collaboration and discussion among various stakeholders. Two years later, NIDDK released a funding announcement to develop an Interactions Core to coordinate collaborations among multiple urology consortiums. Guiding principles being applied to the CAIRIBU effort include:

- Fostering inter- and transdisciplinary research collaborations will help to address knowledge gaps in benign genitourinary diseases and conditions to create synergy,
- Creating opportunities for CAIRIBU leaders to come together to develop and share their visions and agendas,
- Collaboration between investigators who will listen to and learn from each other,
- Developing and executing interactive processes by work to understand the history, dynamics, and objectives of CAIRIBU Centers and Programs,
- Using the sustainability of CAIRIBU as a vehicle for addressing knowledge gaps, which requires consortium investigators to continually assess who is inside and outside the collaborative process,
- Ensuring ample diversity of background, perspective, and research areas for consortium members, and
- Agreeing on a shared mission and goals are essential.

Dr. Penniston detailed the CAIRIBU mission and goals, noting that the CAIRIBU community will foster collaboration across multiple basic science and clinical disciplines to identify and address gaps in knowledge related to the biology, physiology, biochemistry, genomics, genetics, and metabolism of benign GU diseases. CAIRIBU also serves to create a transdisciplinary infrastructure to promote benign urologic research collaborations, encourage and embrace new investigators into the field, to train and mentor the next generation of benign urologic basic scientists.

Dr. Penniston explained the foundational structure of CAIRIBU leadership, commenting that leadership efforts focus on a stakeholder engagement approach which focuses on the flow of information from and between the Interactions Core and the CAIRIBU community. She described how this approach was recently used in a discussion among CAIRIBU investigators that identified barriers to getting benign prostate research published and to enhancing the impact and visibility of benign prostate research. CAIRIBU focuses on building collaborative mentality to promote sharing and creating infrastructure to enable research through use of a CAIRIBU intranet, where PIs can share data and ideas. Dr. Penniston also commented on open and transparent communication efforts from the Interactions Core to the broader community, which include a CAIRIBU youtube channel; virtual seminars, forums, and discussions; and research interest groups such as the Urobiome research interest group that was formed.

Dr. Penniston also discussed the CAIRIBU Cross-Program Interactions Logic Model, pictured below:



Dr. Penniston commented on several challenging consortium efforts, including evaluating the role and level of support from the Interactions Core in forming research interest groups, strengthening the O'Brien Center summer student enrichment programs, and promoting patient engagement in research. In closing, Dr. Penniston highlighted the new Fostering Research With Additional Resources and Development (FORWARD) Urology Centers FOA and discussed future directions within the CAIRIBU Consortium:

- **CAIRIBU evaluation program**
  - Engage PIs in CAIRIBU evaluation metrics
  - Disseminate findings

- **Diversity in benign GU research**
  - Workforce: Develop "blueprint" to be adapted locally for diversifying investigator pipeline
  - Study participation: Develop and share model for building community partnerships

- **Enhance activity and visibility within broader benign GU research community**
    - Provide leadership, momentum, and logistical support to nascent CAIRIBU Research Interest Groups (RIGs)
    - Be involved with relevant organizations and societies
    - Organize CAIRIBU "presence" at urologic research meetings
    - Communicate and organize
        - Quarterly CAIRIBU Connections
        - Quarterly CAIRIBU Catalyst Conversations
        - CAIRIBU ARCTICS Community Forums
        - CAIRIBU K12 Seminar Series
        - CAIRIBU YouTube Channel and other social media venues

Discussion with Panel

- Dr. Barthold solicited feedback from participants and speakers on what types of translational research projects could be readily done to make progress in this field. Dr. Brooks suggested efforts directed at broadening profiling of BPH. In addition, he recommended developing a dataset similar to how The Cancer Genome Atlas dataset benefitted cancer research. He added that there are benefits to building a dataset and commented that an interest group under CAIRIBU could undertake this effort. Dr. Star queried what cohorts of men should be recruited to answer this question using biopsy tissue, imaging, urine, and serum. Dr. Brooks suggested collecting biosamples from men who have undergone successful and non-successful transurethral resection of the prostate (TURP) and green light laser TURP procedures. Dr. Brooks commented that there are several considerations for a project on this effort:
    - Consider how to define "failure" to collect the biomarkers needed.
    - Although endpoints are unclear, consider how treatment failures for oral medications as another cohort; longitudinal, and prevention studies are needed in this area.
    - Dr. Kaplan suggested a landmark MTOPs trial for treatment to include collection of biomarkers. Dr. Brooks noted support for an MTOPs trial that would add an imaging feature and machine learning approaches to analyze images in trial design. It would be helpful to include patients who have hard endpoints.
    - Additionally, he noted that a BPH taxonomy study is needed to define measurement on phenotypes as well as the inclusion of a fibrosis phenotype.
- Dr. Kaplan queried how the urology community can further communication efforts with the AUA. Dr. Penniston noted one goal of CAIRIBU is to disseminate and publish scientific information and added that it would be helpful to publish in benign urology journals rather than translational journals and journals focused on urologic cancer. Dr. Ricke noted the bigger picture would need more funding from NIDDK and possibly collaborative funding from agencies such as NIA.
- Dr. Star commented on the LURN phenotyping studies and queried if there is a project such as KPMP or the NCI's Cancer Moonshot to fund and also noted that ideas may be generated from the upcoming urology/BPH workshop this spring. He highlighted the need to propose a technology and patient cohorts needed for a feasible research target. Dr. Star emphasized the need to investigate the "bother" phenotype and queried if there is a molecular signature to "Bother." Dr. Kirkali commented that there is a need to view the patient in terms of holistic health and added that biomarkers are needed to further basic research.
- Dr. Penniston mentioned that CAIRIBU leaders have identified community awareness/engagement as a key factor in disseminating information and commented that more public involvement in benign urology research may result in more funding. In 2022, CAIRIBU will be unveiling a patient and community engagement initiative that the Consortium hopes will permeate all types of investigations, not just clinical. She noted that there will be more information on these efforts on these over next few months. She also commented on the need to address stigma of some urologic diseases and the need to recruit patients to answer questions on "bother" and "QoL." Dr. Penniston emphasized that a research agenda is needed to

guide patient research in these areas of patient and community engagement as these communities will advocate for more urologic funds to advance research in this area.

- Dr. Kirkali echoed Dr. Kaplan's earlier comments about the heterogeneity of population in the research studies and added that, using a multi-pronged approach, the LURN study is identifying subtypes of patients with LUTS with a focus on the bladder as well as the prostate. Dr. Kirkali emphasized that previous research in this area does not involve a patient-centered approach. Dr. Kaplan also commented that stress and anxiety of the individual play a role as a contributor and noted that biomarkers for the prostate may help differentiate this variable. Dr. Mullins emphasized that identifying phenotypic subgroups is needed to define a heterogenous population. Dr. Ricke commented that the upcoming NIDDK workshop could address some of these issues, including the impact of brain function on benign urologic disease and added that this effort could also address racial aspects of benign disease and cell types in the prostate. Dr. Brooks commented that the bladder/prostate relationship is complex, but responders can be identified through some of these domains.
- Dr. Penniston commented on need for more research on differences in the microbiome and exposure to benign prostate disease as it relates to patient coping strategies, racial disparities, and other underlying mechanisms behind prostate disease. She noted that there is a need to engage investigators who are efficient at collecting patient information.
- Dr. Kaplan noted long term use of medication, particularly several medications, can contribute to urologic symptoms. Dr. Star suggested that investigators interested in studying this topic should develop a list of research questions, define a cohort, and demonstrate feasibility for such a study, considering patient and organ heterogeneity. He emphasized that there is a need to consider all the steps that are needed as well as recruiting patients that meet the patient inclusion/exclusion criteria.
- Dr. Brooks suggested extending the LURN study to look at bladder function in females and noted that this effort would leverage male versus female in clinical and basic studies (animal models). Dr. Star commented that human precision medicine efforts can guide finding pathways in animal models.
- Dr. Kaplan reiterated the importance of communication within the urology field within the Office of Research at the AUA. Dr. Barthold noted NIDDK will widely publicize Dr. Rankin's upcoming workshop.

Adjourn