

**National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)**

**Individualizing Treatment—Broadening the Framework for  
Urinary Incontinence Research**

**Natcher Conference Center, Building 45  
National Institutes of Health  
Bethesda, MD 20894  
March 30–31, 2017**

**Executive Summary**

**THURSDAY, MARCH 30, 2017**

**Welcome from the NIDDK Director**

*Griffin P. Rodgers, M.D., M.P.H., Director of NIDDK*

Dr. Griffin P. Rodgers welcomed the participants to the meeting and acknowledged the major advancements in UI treatments from the urology research supported by the NIH, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's (NICHD) Pelvic Floor Disorder Network, the NIDDK, and the NICHD-funded UI Treatment Network. Dr. Rodgers recognized that much remains to be accomplished regarding treatment options and prevention research for LUTS. The NIDDK believes that there should be a shift from traditional approaches to novel research questions and methodologies to improve our ability to individualize the treatment of UI. This shift focuses on developing broader perspectives for UI treatments, such as the role of the microbiome and looking beyond the urinary tract for the contributors and influences of UI treatment success or failure. He described the importance of forging transdisciplinary, interdisciplinary, and multidisciplinary researcher teams that offer novel approaches and work together toward a common research problem. Dr. Rodgers tasked the meeting participants to “think outside of the box” when discussing UI treatment options—to use a more inter-, multi-, and transdisciplinary approach to brainstorm novel ideas. He recommended that the participants read the book *Six Thinking Hats*, by Edward De Bono, which describes the different thinking techniques for problem solving. To facilitate fruitful discussion, Dr. Rodgers encouraged the participants to have clinical suspicions during the meeting’s activities to generate better targets for UI treatments. He concluded by thanking the organizers, presenters, and participants of the meeting.

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## **Introduction to the Meeting**

*Robert Star, M.D., Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK, National Institutes of Health (NIH); Tamara Bavendam, M.D., Program Director of Women's Urologic Health, NIDDK, NIH*

Dr. Robert Star welcomed the participants and thanked the meeting organizers and speakers. Dr. Star provided a historical overview of the NIDDK's research networks for women's urological conditions. The Urinary Incontinence (UI) Treatment Network (2000–2012) and the networks for treatment of Interstitial Cystitis (1998–2008) were important initiatives, but they did not provide sufficient insight into how to individualize treatment. To take on a more phenotypic approach, the NIDDK implemented the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (2008–ongoing) and the Symptoms of Lower Urinary Tract Dysfunction Research Network (2012–ongoing) initiatives both adopting a broader perspective than previous efforts in hopes of identifying subgroups that will demonstrate efficacy to currently available treatments. During a series of meetings regarding research needs in women's urologic health, prevention emerged in 2013 as a unmet need leading to the formation of the Prevention of Lower Urinary Symptoms (PLUS) Research Consortium in 2015, PLUS has coalesced diverse disciplines that are striving to identify a common and novel approach toward preventing LUTS in girls and women.

NIDDK sponsored 4 other meetings that contributed to the decision to convene this meeting: Review of NIDDK and NICHD funded studies for UI treatment: Future Directions for UI Research in Women (2014), Research Needs in Transitional Urology (2015), Urology Think Tank: Science of Urine (2015), and Behavioral and Psychosocial Factors in Women with Urinary Incontinence (2015).

Dr. Tamara Bavendam introduced the significant theme of the meeting by highlighting her work that illustrates a path toward a more comprehensive approach to studying LUTS. The path includes many determinants of health, including biology, behaviors, beliefs, values, personality attributes, cognitive abilities, and social determinants. She commented that selecting the appropriate UI treatment is challenging because treatment efficacy varies with each patient. Determining which patient is the best candidate for the current treatment options is of paramount significance. By combining current UI treatments (behavioral, pharmacological, neuromodulation, and surgery), broad patient characterization, and novel research strategies, one can determine the differences between treatment responders and non-responders and, more broadly, can identify the appropriate patient-specific treatments. She concluded by saying that the goal of the meeting is to generate new ideas without prioritizing specific topics or developing conclusions. The meeting is intended to develop novel interdisciplinary research questions regarding UI.

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## **Session 1: Basics of Anatomy and Function—Where Are We Now with UI Treatment?**

*Moderator: Eric Rovner, M.D., Professor of Urology, Medical University of South Carolina*

Dr. Eric Rovner thanked Dr. Bavendam, Dr. Linda Brubaker, and the other meeting organizers. Dr. Rovner delivered an overview of the basic anatomy and function of the urinary tract, and the current methods of UI treatment. Continence is not only dependent on anatomic and physiological parameters, but also, at least in part, a behavioral and psychosocial condition. Continence depends on the sum-total of urethral closure forces (i.e., anatomical support, pressure, and urethral length) that keep the urethra closed, being greater than bladder expulsive forces (intrinsic and extrinsic). Other factors that may affect continence are behavior, motivation, cognitive and mobility functions. UI is a failure to store urine, which may be caused by changes of the urethra or bladder or both. Incontinence may be result from stress (due to a “faulty” sphincter caused by muscular, neurological, or connective tissue deficiencies) or by an involuntary urge for urination (“bad” bladder, detrusor contraction that may be caused by myogenic, neurogenic abnormalities). There is considerable overlap among individuals who have UI, urgency UI (UII), or stress UI (SUI). Factors that may increase the complexity of UI include, pelvic pain, infection, dysfunctional voiding, and other comorbidities. In addition, pediatric and male populations have different anatomy and etiologic factors as compared to adult women, Treatment of the outlet (urethra) or the bladder is the typical approach for UI. Dr. Rovner concluded that a realistic goal is to improve the clinical condition where possible, and improve quality of life, as many of the current therapies are unsuccessful at curing UI; this reality should be communicated to patients.

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### **Behavioral Interventions for UI**

*Mikel Gray, Ph.D., Professor, Department of Urology, University of Virginia School of Medicine*

Dr. Mikel Gray described the current behavioral (nonpharmacological and nonsurgical) treatment options for UI, explaining that a behavioral intervention is a major component of conservative therapy for UI and LUTS. A behavioral approach consists of interventions related to lifestyle—fluid intake, caffeine or alcoholic beverage consumption, weight loss, smoking, constipation management, and pelvic floor muscle (PFM) therapy (PFMT). A requirement when developing behavioral interventions is deciphering who constitutes an “ideal” or “poor” candidate for such approaches. Ideal candidates are patients who have an excessive intake of caffeine or alcoholic beverages, who smoke, or who have obesity. Poor candidates for intervention exhibit restricted or moderate intake of caffeine, alcohol, and tobacco and have a normal weight.

Dr. Gray outlined specific behavioral interventions. Fluid intake is directly linked to urine production; reducing your fluid intake affects UI, nocturia, and LUTS of overactive bladder (OAB). Optimizing treatment requires determining the target range and optimal timing of fluid intake, without causing constipation by too severe restrictions in fluid intake. For caffeine users, caffeine intake is mainly associated with OAB and urgency. Designing methods to optimize treatment in caffeine drinkers is challenging because of the undefined recommended daily allowance for caffeine and the potential benefits of moderate consumption. Interventions for alcoholic beverage intake consist of an abating of multiple physiological and psychosocial effects, inhibition of vasopressin release, and an increase of urine

production. Treatment approaches for consumers of alcoholic beverages consist of individualized counseling that recognizes that defining “moderate consumption” depends partly on the patient’s gender. Regarding diet and weight loss intervention, obesity is associated with a higher likelihood of developing UI and SUI, particularly in women. Optimizing treatment for patients with obesity or morbidly obese women with SUI should consider counseling and modest weight loss. In addition to the aforementioned interventions, weight loss is an important behavioral intervention for UI. Treatment focused on reducing caloric intake and saturated fats and increasing physical activity both improves weight loss and alleviates UI. Interventions for smoking are challenging. The outcomes of interventions for smoking are inconsistent in linking smoking with UI and related LUTS. Interdisciplinary teams are required to assist patients with smoking cessation; counseling and ongoing encouragement are important. Dr. Gray asserted that smoking interventions should incorporate an interdisciplinary approach. Regarding interventions for individuals experiencing constipation, prevention or management of constipation should acknowledge the cross-talk between the bladder and bowel. What constitutes a poor candidate for constipation intervention is unknown; monitoring fluid and fiber intake along with food recipes is recommended. PFMT comprises three components: identifying and isolating the PFM, PFM exercises, and skill training. Evidence supports a benefit of PFMT in women and men with stress, urge, and mixed UI. Current approaches to optimize PFMT may include identifying predictors of adherence to PFMT and using brain magnetic resonance imaging (MRI) to predict the efficacy of therapy or exercise readiness. Incorporating behavioral-based theoretical modes into PFMT training programs, clinician-directed individualized assessment, evaluating the effect of exercises, and individualized skill training may be appropriate methods for behavioral interventions.

Dr. Gray concluded that of the types of behavioral interventions, diet and PFMT should be tested first. There is limited evidence and ability to limit randomized control trials (RCTs) to support these approaches. Nevertheless, clinical data suggest these therapies are effective. In his experience, analyzing several “bundled” intervention strategies, rather than conducting RCTs, may assist in optimizing individualize treatment, which should integrate an interdisciplinary approach.

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### **Individualized UI Treatment, Medicines and Neuromodulation**

*Cindy L. Amundsen, M.D., Roy T. Parker Professor in Obstetrics and Gynecology, Division of Urogynecology and Reconstructive Surgery, Duke University School of Medicine*

Dr. Cindy Amundsen discussed the current medicines and neuromodulation approaches for treating UI. Dr. Amundsen alluded to the fact that no “one size” treatment is applicable to all patients. Treatments for UUI include behavioral and physical therapy, medicine, posterior tibial nerve stimulation, botulinum toxin A (Botox), and sacral neuromodulation (InterStim). These treatments have various side effects and success rates; the goal is to improve efficacy and reduce side effects. Individualizing treatment for UUI may include identifying phenotypes of subgroups that comprise patient-specific measurements, neuroimaging and sensory testing, bladder and urethral testing, and identifying biomarkers. This strategy is the current implementation of the Lower Urinary Tract Dysfunction Research Network (LURN). The two current classes of drugs, anticholinergics and antimuscarinic inhibitors, both function to block the parasympathetic nervous system and detrusor contractions (bladder contraction); the beta-3 adrenergic agonist augments the sympathetic nervous system (bladder relaxation). Individuals most likely to respond to pharmacological management are motivated to take medicines, are taking few medicines, and have mild to moderate symptoms. Older adults or those who are hypertensive or have severe UI, low tolerance for side effects, or narrow-angle glaucoma are not ideal candidates for medical management.

Dr. Amundsen mentioned that pharmacological therapy optimization should consider the patient’s genetics (pharmacogenetics), which may alter drug metabolism and the response to treatment, as well as reduce side effects. The ideal candidate for Botox therapy is a person with moderate to severe UI who has the ability to empty their bladder and amenable to possibly performing intermittent self-catheterization, or multiple sclerosis patients. Not recommended for Botox therapy are individuals who have detrusor hypocontractility with incomplete bladder emptying or who are unwilling to perform self-catheterization or undergo multiple procedures for injections throughout their lifetime. Looking forward, Botox therapy

may be optimized by utilizing pharmacogenetics, developing individualized treatment doses and techniques, and identifying microbiome profiles that lead to urinary tract infection (UTI).

Dr. Amundsen described a treatment option of neuromodulation—stimulation of the somatic afferent input of the sacral nerve that activates the spinal nerve inhibitory pathways. More specifically, this involves the modulation of motor efferent activity to the PFM and striated urethral sphincter to induce detrusor relaxation. Posterior tibial nerve stimulation (PTNS) is the simplest form of neuromodulation that modulates bladder function. PTNS may benefit individuals with mild to moderate UUI or those who have comorbidities that preclude the use of anesthesia. Treatment is not suited for those who are severely incontinent, have peripheral neuropathy, or have a cardiac pacemaker. Another method of neuromodulation is sacral nerve stimulation (SNP)—a two-step procedure involving a test phase for patient selection and a programming phase. Those who should benefit from SNP have moderate to severe UUI with concomitant fecal incontinence, are willing to learn how to use the programmer, and have committed caregivers. Conversely, persons who may require an MRI in the future or who have comorbidities that increase the risk of infection may not be suitable for SNP. Optimization for neuromodulation treatments might include simplifying the process of reprogramming for health care providers, optimizing training, and developing a home use system for PTNS. Dr. Amundsen concluded by identifying the following important directions for new research directions to individualize UUI treatment: inhibiting bladder activity with urethral stimulation, combining therapies to examine synergistic effects, developing an implantable peripheral neuromodulator, investigating central nervous system neuromodulation, and developing different delivery mechanisms for medicines that target diverse bladder or urethra receptors.

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#### **Individualizing UI Treatment Surgery**

*Michael Albo, M.D., Professor and Vice Chair, Department of Urology, UC San Diego*

Dr. Michael Albo discussed the individualized surgical options for UI. Dr. Albo described SUI as a “perfect” candidate for individualized treatment. Treatment well suited for the individual patient involves diagnosing the cause of incontinence, the patient-specific factors that are associated with success or failure, and the patient-specific goals and expectations regarding incontinence and complications. The goal of incontinence surgery is not a cure, but a restoration of voluntary bladder control through correction or augmentation of normal anatomic structures without additional complications. The current surgical therapies either increase structural support of the urethra or augment urethral closure pressure. He noted that despite the current surgical options, the search for the “holy grail” surgical procedure is ongoing. Dr. Albo described the historic “gold standard” procedures for female stress incontinence, the Burch colposuspension and pubovaginal autologous sling as well as the procedure that has largely replaced those procedures, the midurethral sling with mesh. While success rates are similar between the procedures, they each have different potential adverse effects. There has been considerable attention

directed at the complications associated with mesh and the FDA has released a warning to physicians and patients to keep them better informed. To improve patient treatment options, conducting comparative studies and assessing the safety and efficacy of new procedures and techniques are essential. It is clear that not all techniques and sling materials are equally safe and effective; informed consent, long-term data, and increased provider training are needed. The ideal sling material has durability, lack of antigenicity (inflammation), and minimal invasiveness. Other procedures include urethral injections that augment intrinsic sphincter resistance, but these require more ideal agents that are durable, stimulate regeneration, and are nonimmunogenic. Treatments for male stress incontinence include a synthetic sling (nonrelaxing during voiding) and the artificial urinary sphincter (AUS). While the most effective therapy for male stress incontinence, the AUS is associated with urethral atrophy, infection and device failure over time.

Dr. Albo commented about surgical options still being tested that could have favorable outcomes. Regenerative medicine approaches that use stem cell therapy or tissue engineering are potential treatment options. The goals of regenerative medicine are to restore or regenerate the functional activity of the urethral sphincter, restore support of the urethra, and prevent incontinence at the time of surgery. The success of regenerative approaches requires an enhanced understanding of the functional and anatomical defects specific to each patient. Dr. Albo concluded by discussing areas of future research, including seeking a better understanding of the causes of incontinence and identifying factors associated with efficacy and failure.

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## **Session 2: What (Nontraditional) Factors Might Affect UI Success?**

*Moderator: Daniel Gossett, Ph.D., Program Director, Division of Kidney, Urological, and Hematological Diseases, NIDDK, NIH*

### **How Might Social Determinants of Health Affect UI Treatment**

*Jennifer Hebert-Beirne, Ph.D., M.P.H., Assistant Professor, School of Public Health, University of Illinois at Chicago*

Dr. Jennifer Hebert-Beirne outlined how social determinants of health might affect UI treatment and overall health. Social determinants are the conditions in which people live, learn, work and play such as their environment, social and community context, and economic stability; these affect what opportunities people have to be healthy. Dr. Hebert-Beirne described a common framework developed by the Centers for Disease Control and Prevention (CDC) to consider key social determinants. She described that social influences occur across a social gradient with lower levels of education and income correlating with poorer health outcomes. Dr. Hebert-Beirne noted that clinical care contributes proportionately less to health outcomes than social factors, yet it is where most funding and effort for health care is placed. Using the World Health Organizations framework, she described that social determinants of health are shaped by structural drivers, such as socioeconomic and political context; these influence social positions,

which, in turn, affect intermediary determinants of health. Interventions for UI typically are given at the treatment, behavioral, or pharmaceutical levels, but these are downstream to social determinants. Those who are in better social positions are likely to have increased opportunities to follow the treatment regimen and thus experience better health outcomes. Distribution of power and resources shapes the social factors that influence UI treatment success. Treatments involving access to resources or sustained behavior change or those that involve overcoming deep stigmas all show better outcomes for those with social and economic advantages. Dr. Hebert-Beirne described the CDC's categories of social determinants of health and explained how they relate to UI treatment, such as access to safe, clean toilets; work context; or cultural norms. These issues should be addressed in a systematic way emphasizing health equity for all.

Knowledge of social determinants of health and UI is limited, but Dr. Hebert-Beirne suggested using more widely studied conditions, such as type 2 diabetes and obesity, to predict the effects of social determinants for UI. Like UI, treatment for these conditions involves behavior modification and other downstream factors, so those with greater social position will have better outcomes. Diabetes treatment models incorporating social determinants of health utilize community laypersons, financial assistance, and cultural adaptations. For obesity treatment, it is important to build a culture of health and support policies, systems, and environmental changes that promote health. Dr. Hebert-Beirne noted that health care often has focused on treating a single patient, which requires a large amount of effort from that patient with limited impact, but treatments that focus on community systems both require less individual effort and have larger impacts on the population level. When considering the individualization of treatment, it is important to remember that successful treatment will be more difficult for those whose conditions and resources do not support health, such as members of groups affected by health inequities, including low-income, low-education, and racial and ethnic minority populations.

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## **Behavioral Psychological and Cognitive Considerations in Self-Management for UI**

*Carol Musil, Ph.D., M.S.N., B.S.N., Professor of Nursing, Frances Payne Bolton School of Nursing, Case Western Reserve University*

Dr. Carol Musil presented a diagram of the many factors affecting the self-rated health of UI patients, based on the Patient-Reported Outcomes Measurement Information System (PROMIS), noting that it is a continual theme of UI research that medical care can affect health, but the patient needs to actively participate. She added that self-rated health, such as in the PROMIS measures, shows a substantial relationship to morbidity and mortality, because the patients' rating of their health can be affected by a wide variety of factors. Dr. Musil emphasized that UI is an interdisciplinary problem; the field of cognitive science, which encompasses psychology, neuroscience, anthropology, artificial intelligence, and philosophy, can inform treatment. Areas of focus within these disciplines include intelligence, language, perception, learning, memory, attention, consciousness, reasoning, and emotion.

Dr. Musil pointed out that depressive symptoms are ubiquitous in society and are more debilitating in terms of physical and social functioning than diabetes, arthritis, gastrointestinal disorders, back problems, or hypertension. She mentioned some current concepts that tie into the interdisciplinary nature of treatment for both physical and mental symptoms. Mindfulness, a technique to help individuals center themselves in the present in a nonevaluative way with an awareness of the self, can be coupled with decentering, the ability to observe one's own thoughts and feelings dispassionately. Another consideration is interoception or body awareness, which is associated with emotional reactivity; yet awareness of what is happening in the body also helps people practice self-regulation and self-control skills, such as biofeedback. It also is important for patients to practice self-compassion and forgiveness. Dr. Musil remarked on observed neuroplastic changes as a result of mindfulness, meditation, and yoga and the potential for mindfulness techniques to decrease stress and thus lead to better outcomes in urinary disorders. The health belief model proposes that the patient should think he or she is susceptible to a bad outcome and that changing behavior will improve this outcome. The transtheoretical model of change is the model used most often; this model depends on the patient's awareness that they have a problem and includes steps for resuming the treatment after a relapse, which happens often and requires the patient to plan for how to overcome these challenges. Self-management is the ability of an individual, in conjunction with their social supports, to manage the lifestyle, treatment, and consequences of chronic illnesses like UI. Self-management includes targeted goal-setting, planning, and reevaluation, as well as a system of training and support for the individual to teach them the skills necessary to make changes. It is also critical to include emotional support in these programs.

Dr. Musil described the **Self-Management through Research and Translation (SMART) Center** pilot studies at Case Western Reserve University, which test mindfulness as an intervention. Individuals should attend to both task-oriented and emotional stimuli when managing their health, and those who can switch between those modes as the situation demands, are expected to be more successful at self-managing their health. In the case of UI, proximal outcomes include such self-management behaviors as Kegel exercises and water intake. Good self-managers are able to differentiate between tasks requiring emotional regulation, social cognition, and analytic thinking. She noted that the ultimate goal of the SMART Center studies is to identify phenotypes of good self-managers and help these different phenotypes be successful.

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### **Musculoskeletal Impact on UI**

*Colleen Fitzgerald, M.D., Associate Professor, Department(s) of Obstetrics and Gynecology, Urology & Orthopedics & Rehabilitation, Loyola University Medical Center*

Dr. Colleen M. Fitzgerald noted that as a specialist in physical medicine, she focuses on pelvic medicine as it relates to rehabilitation. She described the predominant musculoskeletal conditions, natural anatomic changes, and relationship of the pelvic floor musculature to the whole body in the stages of a woman’s life. Dr. Fitzgerald commented on the myriad benefits for girls and women who participate in sports, but noted that the natural anatomic structure girls bring to sports results in between two and ten times more musculoskeletal injuries. A wider, broader pelvis and greater femoral neck anteversion contribute to common musculoskeletal injuries in women, such as foot imbalances and anterior cruciate ligament injuries and lower back pain. In relation to the pelvic floor and physical activity, studies have shown that UI during exercise is common and is more prevalent in women during high-impact sports. However, mild to moderate physical activity, such as brisk walking, decreases both the odds of having UI and the risk of developing it. Women with lower back pain also are likely to report UI.

Dr. Fitzgerald described pregnancy as a “core disruption” that naturally involves many musculoskeletal changes. In the pelvic floor, the rectus abdominus lengthens and the pelvic floor stretches to support the increasing size of the uterus; breathing also is impaired. Many pregnant women experience pelvic girdle pain—the structural relationship between pelvic structures and UI leads to a frequent association between pelvic girdle pain and UI. Additional disruption of the core occurs during labor and delivery; pelvic floor muscles stretch more than three times their normal length during vaginal delivery, and many first-time mothers experience muscle tears, which can affect UI later in life and have additional unknown effects on musculoskeletal pain. Postpartum musculoskeletal changes also are common, including pelvic floor muscle defects, persistent diastasis in the rectus abdominus, and scarring that can interfere with fascial support, as well as changes in load transfer or core strength, affecting a woman’s ability to move. Breast feeding also can cause musculoskeletal issues, such as spinal curving due to poor posture. Dr. Fitzgerald explained the structure of the pelvic floor muscles, noting that they co-activate with core muscles during

exercise and upright sitting postures to maintain stability. Half of women with postpartum lumbopelvic pain experienced pelvic floor muscle dysfunction; lumbar pelvic stability is needed to maintain muscle balance in the more external, global muscles.

Dr. Fitzgerald commented on studies demonstrating an association between musculoskeletal conditions and UI and noted that, because many studies consider patients with catheters to be continent, the available data likely underestimate the prevalence of UI. Those with UI also are more likely to experience greater overall pain, and patients who are older, have cognitive difficulties, or have less functional improvement are more likely to remain incontinent. For orthopedic patients, in particular, UI is associated with a 71 percent increase in the likelihood of being institutionalized. Disorders of breathing and continence also have a higher likelihood than obesity to be associated with back pain.

Dr. Fitzgerald commented on methods of individualized pelvic floor muscle physical therapy, including manual soft tissue and joint mobilization; biofeedback, including surface electromyography and ultrasound; electrical stimulation; pressure biofeedback; weighted cones; and vaginal dilators. She also noted that studies have shown no difference in outcome for individual treatment compared to group treatment, so physical therapy is more efficient in a group setting. She presented a concept proposal to identify physical activity predictors and musculoskeletal risk factors for LUTS across female life stages. She included a prevention strategy incorporating both core and pelvic floor exercises and physical therapy to prevent LUTS in women with lower back pain and musculoskeletal issues. Dr. Fitzgerald commented on a 2016 study incorporating stabilization and pelvic floor exercises to decrease UI, noting that patients do not necessarily always need internal therapy. She reiterated that anatomical and biomechanical variability predisposes women to specific musculoskeletal conditions, but the prevention opportunities discussed can be used to treat both musculoskeletal disease and UI.

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#### **Non-Urological Factors and Lower Urinary Tract Symptoms**

*Catherine Bradley, M.D., Professor of Obstetrics and Gynecology and Epidemiology, Division Director of Urogynecology, University of Iowa Hospitals and Clinics*

Dr. Catherine Bradley reviewed the activities of the NIDDK's Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) focused on non-urologic factors (NUFs), which are factors outside the LUT that may affect urinary symptoms and function. She commented on the phenotyping efforts of LURN, which aim for a detailed characterization of LUTS patients using a wide range of potential explanatory factors, such as NUFs, clinical factors, and biological factors. In addition to phenotyping, LURN aims to improve measurement of patient experiences of LUTS, disseminate information, and generate large data sets for future studies. Dr. Bradley displayed the locations of LURN

participating centers and the organizational structure of LURN, including the NUF Workgroup, and she noted the existence of several network studies, including studies on self-reported measures, neuroimaging, biomarkers, and NUFs.

In a conceptual model of LURN, disorders of urinary sensation are connected to the larger detailed characterization of patients with LUTS, including NUFs that affect LUTS by influencing the human organism on multiple levels, often in ways researchers do not yet understand. The NUF Workgroup within LURN has defined and developed a list of NUFs. They also conducted a systematic review of associations of certain NUFs—diet, fluid, caffeine, tobacco, and alcoholic beverages—with LUTS. The Workgroup’s definition noted that these NUFs related to LUTS may be a primary or contributing cause of LUTS or may mediate the patient’s experience of LUTS. Such factors affect clinical care in multiple areas—including symptoms, risk, treatment effects, and disease progression—and may suggest common etiologic pathways or help identify phenotypes.

Dr. Bradley described the NUF Observational Cohort and its specific aims and hypotheses. One aim was to characterize the organized function of men and women seeking care for LUTS, including a number of related functional and psychological factors. Many potential NUFs were proposed, but when researchers attempted to discover previous data on associations between many of these factors and LUTS, evidence often was lacking and systematic research on every factor was not possible. The study team narrowed the search to five factors and conducted a systematic review to determine evidence to support the frequent recommendations for patients with LUTS to modify these lifestyle behaviors. Dr. Bradley provided an overview of the methods used to identify papers using PubMed search strings, conduct full-text review, and abstract the data, resulting in the inclusion of 110 unique articles with a generally low level of evidence. Ultimately, evidence for associations between LUTS and diet, fluid intake, caffeine, alcoholic beverages, and tobacco use was sparse and mostly observational, although evidence was identified for associations between fluid intake and urinary frequency and urgency and between modest alcoholic beverage intake and decreased BPH diagnosis and LUTS. However, given the importance of diet, fluid intake, caffeine, alcoholic beverages, and tobacco in daily life, higher quality evidence is needed to continue recommending behavioral modifications to patients.

Dr. Bradley emphasized that the expert consensus is that NUFs have significant effect on LUTS and function, but evidence confirming the associations of NUFs with urinary symptoms is limited. The LURN phenotyping studies may be able to provide some answers and direct future research, including the identification of which NUFs are most promising for impacting treatment outcomes.

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## Does Urine Composition Affect UI Treatment Success?

Jeffrey Henderson, M.D., Ph.D., Assistant Professor, Department of Medicine, Washington University School of Medicine in St. Louis

Dr. Jeffrey P. Henderson proposed the possibility that urine may be something other than a vehicle for waste; he asked attendees to consider that it may play a mechanistic role with diseases and that its composition may reflect pathophysiologic conditions. He reviewed the composition of urine, which includes human cells from both outside and inside the urinary tract, medicines in both native and metabolite forms, dietary byproducts, and components of the microbiome. These components can be separated into biotic components—human cells and microbes—and abiotic components, which include protons, metal ions, salts, small molecules, peptides, and proteins.

Dr. Henderson described a study on urinary siderocalin, which increases in UTIs. Siderocalin is a protein with an antimicrobial effect, but the strength of its effects varies widely between individuals. Some urine infected with *Escherichia coli* (*E. coli*) is more permissive to the bacteria and exhibits no siderocalin activity; other urine samples were restrictive to *E. coli*, meaning siderocalin was functioning. Small molecules in the catechol category were discovered to support siderocalin's antimicrobial activity; these catechols likely were metabolites of dietary intake. Siderocalin uses urinary catechols to sequester iron, preventing bacteria from using the iron to grow. These results suggest that urine has functionality beyond waste elimination.

Another study, which focused on the biotic components of urine, used 16s ribosomal ribonucleic acid sequencing and intensive bacterial culture approach to determine the role of the urinary microbiome in UI. Results suggested a correlation between increased microbiome diversity and increased severity of UI. Dr. Henderson noted that the presence of a urinary microbiome has been confirmed via suprapubic aspiration, a sterile method that prevents potential contamination. Such a microbiome may be present in more than half of all individuals, and its high diversity often includes many species not generally recognized as uropathogens. This raises questions about whether the urinary microbiome is a cause or effect of UI pathophysiology. The high diversity of urine constituents and UI symptoms provides many potential connections that have yet to be studied. Dr. Henderson referred those interested in further discussion of urine as a functional fluid to the minutes of the NIDDK's Urinology Think Tank meeting (February 9, 2015). [https://www.niddk.nih.gov/news/events-calendar/pages/urinology-think-tank\\_02-2015.aspx#tab-minutes](https://www.niddk.nih.gov/news/events-calendar/pages/urinology-think-tank_02-2015.aspx#tab-minutes)

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### **Session 3: How Are Other Fields Starting to Individualize Treatment?**

*Moderator: Marcel Salive, M.D., M.P.H., Medical Officer, Division of Geriatrics and Gerontology, National Institute on Aging, NIH*

#### **How Are Other Fields Starting to Individualize Treatment? Role for Multicomponent Interventions**

*Theodore M Johnson, II, M.D., M.P.H., Atlanta Site and Associate Director, Birmingham/Atlanta Veterans Affairs Geriatric Research, Education and Clinical Center (GRECC), Decatur, GA; Seavey Chair and Chief, Division of General Medicine and Geriatrics, Emory University School of Medicine*

Dr. Theodore Johnson summarized the published evidence in gerontology toward individualizing treatment for geriatric syndromes and their risk factors and the rationale for the role for multi-level, multicomponent interventions. Geriatric syndromes are conditions that occur in older, vulnerable adults, and predispose them to further functional decline. Examples of geriatric syndromes recognized among researchers in aging include delirium, urinary incontinence, and accidental falls. The causes of these syndromes are multifactorial and interacting acute and chronic insults. In a typology advanced by Inouye et al in 2007, there are three types of models for understanding how risk factors result in disease: linear; concentric; and interactive concentric. Johnson gave examples of each of these. Linear encompasses such risk factors (aging, or microscopic benign prostatic hyperplasia) that lead to early disease (gross enlargement of the prostate gland) and then advanced disease (clinical symptoms of BPH). An example of concentric risk factors would be the clinical symptom of nocturia, where risk factors are multiple (overproduction of urine at night, low-volume voiding, BPH, and hypertension). For the last category, Johnson gave the example of bothersome nocturia as a result of interactive concentric risk factors. In addition to the risk factors described previously, Johnson pointed out the interaction between nocturnal polyuria and sleep problems. When broadening the investigative framework of nocturia that causes distress to the patient, it turns out that the interplay between nighttime overproduction of urine and difficulty returning to sleep after awakening and feeling fatigued in the morning produce the clinical scenario that likely causes the most patient distress. He referenced an article that defines three levels of “bothersomeness” when individuals experienced two or three episodes of nocturia—low, medium, and high. The study concluded that experiencing longer estimated times to return to sleep after nocturia correlates with a higher level of bothersomeness of LUTS.

Dr. Johnson pointed out further that age-related functional loss and disability show that they are risk factors for diverse geriatric syndromes (urinary incontinence, accidental falls, and functional decline). He reviewed another finding demonstrating that shared risk factors for geriatric syndrome involve a single set of causes representing impairment in multiple areas that may predict clinical syndromes. The study concluded that functional measures are highly predictive and provide a different incidence of these outcomes depending on the prevalence of certain risk factors.

Dr. Johnson advanced the notion that conditions in the elderly are often multifactorial in nature and merit an approach of multicomponent interventions. In describing the usage of multicomponent interventions that are used frequently across various conditions, he brought up several examples that have been used across the whole lifespan (e.g., smoking cessation, asthma management, reduced “buzzed” driving, weight loss, HIV elimination) and not just in geriatric patients. The interventions are multilevel and are used for conditions having multiple risk factors.

Dr. Johnson also introduced a theoretical framework to illustrate multicomponent interventions for multiple outcomes. A study of recommendations for prevention found that screening for multiple risk factors across multiple conditions in adults (older than 65 years) who are at a high risk for multiple negative functional outcomes intervening on multiple risk factors and improving multiple geriatric syndromes. Dr. Johnson then highlighted an important multifactorial intervention study demonstrating

that targeting the risk factors of accidental falls and delirium in geriatric patients by providing them with physical therapy and an assessment from a registered nurse reduced the number of falls. Another study found that nonpharmacological approaches, such as substituting nighttime sedatives with tea drinks and back rubs, were effective measures to prevent delirium in a hospital setting. These findings, along with other intervention strategies for nocturia prevention, were implemented for a clinical study at the GRECC. Dr. Johnson highlighted a study from his GRECC group that looked at a novel intervention—multicomponent behavioral treatment and exercise therapy (M-BET)—to treat nocturia. The intervention reduced nocturia and improved sleep in men. M-BET incorporated time-based fluid restrictions, sleep hygiene instructions, PFMT with urge suppression strategies, delayed voiding, and management of peripheral edema. Surprisingly, M-BET provided a level of performance equal to that of alpha-adrenergic antagonist therapy.

Dr. Johnson reviewed the current knowledge gaps and limitations of using multicomponent intervention strategies. There is no Medical Subject Headings terminology for multicomponent intervention, therefore more useful and complete standardized terminology for this type of intervention is required. The elements required for intervention are not completely understood. *Another important strategy is the resource management principle, Multiphase Optimization Strategy (MOST). MOST is designed to develop and maximize the effectiveness of multicomponent bundles, and with a maximized bundle, it could then be tested in a randomized control clinical trial.*

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## “N-of-1” Trials

*Christopher Schmid, Ph.D., Professor, Department of Biostatistics, Brown University*

Dr. Christopher Schmid presented a rationale, design features, statistical analysis, and examples of the use of “n-of-1” (one study subject) trials. Dr. Schmid discussed the difference between research versus practice—clinical practice is often anecdotal, local, and based on trial and error; research is knowledge that is most often produced centrally (e.g., at academic centers) and may not be relevant to locally practiced medicine. Therefore, there are missed opportunities to learn systematically from local practice, which can be run via an n-of-1 trial. The n-of-1 study design can be run as a clinical practice and is personalized; personalized medicine involves various individual-specific features (e.g., genetics, predictive models, electronic health records). Although RCTs develop average effects for study subjects, the heterogeneity of the impact of treatment may not benefit a large proportion of people. Dr. Schmid suggested that individualized treatment is a suitable option to assess the efficacy of patient-specific treatment. An n-of-1 trial provides a more personalized protocol in which the clinical and patient have more control over study design. Indications for n-of-1 trials include a substantial therapeutic uncertainty about treatment, presence of a chronic condition, heterogeneous treatment effects, short-acting treatments, no carryover effect from previous treatment, measurable collected outcomes, and that the outcome returns to baseline after each period of treatment. To circumvent the inherent difficulty of measuring carryover in a single individual, multiple measurements within each period may be taken. An important point to consider with predicting multiple outcomes is that patients often are interested in several outcomes. Regarding statistical analysis, there should be a structured time series with treatment factors and a run of basic statistics (e.g., paired *t* test or Wilcoxin test). Dr. Schmid noted another study that compared n-of-1 trials versus usual care for treating chronic musculoskeletal pain—Personalized Research for Monitoring Pain Treatment (PREEMPT). The PREEMPT n-of-1 study arm of the protocol was a mobile application that participants used to monitor their treatment, collect data, and choose their own type of treatment. A Bayesian model was used for n-of-1 trials because it permits a personalized decision for treatment, allowances for external patient and clinician information, and interpretation of probability. Dr. Schmid explained that 88 percent of study participants of the n-of-1 fibromyalgia trial indicated that they would undertake another n-of-1 study and recommend it to a friend. He added that meta-analysis can be performed to combine the results of n-of-1 studies for the purposes of calculating the average and individual efficacy of treatment. An expanded network through PREEMPT was implemented by combining data from several patients treated from various centers that collectively formed the network. Dr. Schmid concluded by saying n-of-1 trials have social benefits, including engaging patients in their own personalized medical care.

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## Questions and Answers

Dr. Linda Brubaker asked whether n-of-1 trials can be applied to episodic events (e.g., common cold). Dr. Schmid responded that this design may work for some episodic episodes that occur regularly.

Dr. Johnson asked Dr. Musil to elaborate regarding the importance of body awareness. Dr. Musil said that body awareness in older male adults is associated with worse health outcomes. Extreme interoception may lead to somatization versus those who have lowered awareness and require a biofeedback in order to increase awareness; there is much to be learned about body awareness.

A participant wondered whether social determinants of health can be used to identify populations for whom treatment intervention is ineffective and if clinical trials are needed to identify health outcomes. Dr. Hebert-Beirne replied that social determinants of health are not amenable to a RCT. A scaled-down analysis (e.g., in a work setting) may be a more suitable approach to approximate more structural social determinants. Structural drivers for social determinants affect several common health conditions and may influence health policies.

Dr. Julie Weiner wondered if the n-of-1 trials for behavioral or nutrition interventions might have learning effects and if the mobile app is available. Dr. Schmid replied that it is possible for the study design to incorporate learning, which may require changing the intervention to implement the study. He added that the mobile app was specific to the trial he presented.

Dr. Judy Siegel inquired about the effect of manipulating the gastrointestinal microbiome on the bladder. Dr. Henderson stated that he has not looked at this aspect; however, related studies exist. He referenced a future longitudinal study—urine specimens will be collected from individuals after antibiotic treatment.

In response to a participant's question, Dr. Henderson stated that coffee, foods rich in polyphenol, red wine, and chocolate are sources of catechol.

A participant suggested to phenotype women who are unwilling to come forward about their UI. She wondered why there is insufficient data collection for this group. Another participant responded that fear is one reason, along with the primary care provider deciding to prioritize treatment of more serious medical conditions. Dr. Musil added that social stigma may be a contributing factor; patient advocacy is required. Dr. Tina Allen stressed that pelvic health medical education is needed to train people how to ask for help, as is more training for physicians. A participant added that when looking at conceptual models of chronic disease, individuals do not prioritize UI when comparing other life issues (e.g., children, finances); more education for patients, their family, and providers is required. A participant agreed with the assertion that there are several causative agents for not seeking care, but added that the cost of care may be prohibitive. Dr. Bavendam added that research needs to be moved from academic centers to a broader setting, such as the primary care office.

Dr. Albo expressed caution about believing that individuals who experience UI are not concerned with their medical condition. He said that finding new ways to reach those who desire to seek treatment is needed to improve their quality of life. Dr. Bavendam speculated about a role for qualitative research to address these issues. A participant suggested that improved methods to communicate care options to individuals who do not seek medical attention is needed and that because providers are often overworked, additional mechanisms should be incorporated into treatment. Another participant commented that for the Pregnancy Centering Program at Kaiser Permanente, PFMT training will be incorporated into the childbirth education program. In response, a participant commented that childhood is the appropriate time for PFMT.

## PRESENTED POSTERS

### **On-demand voiding induced by a neurokinin-2 receptor agonist in minipig and dog**

Ed Burgard, Mary Katofiasc, Lesley Marson, Karl B. Thor  
*Dignify Therapeutics, Research Triangle Park, NC*

### **Does hyperglycemic memory play a role in diabetic bladder dysfunction?**

Kelvin Davies, PhD and Nitya Abraham, MD  
Department of Urology, Albert Einstein College of Medicine

### **Psychodynamics Works!**

Judith Geizhals, PhD, MS  
*New York, NY*

### **OAB Without an Overactive Bladder: Insights from an Acute Prostaglandin E2 Rat Model**

James A. Hokanson<sup>1</sup>, Christopher L Langdale<sup>1</sup>, ArunSridhar<sup>5</sup>, Warren M Grill<sup>1, 2,3,4</sup>  
<sup>1</sup>*Departments of Biomedical Engineering, <sup>2</sup>Electrical and Computer Engineering, <sup>3</sup>Neurobiology, and*  
<sup>4</sup>*Surgery, Duke University, Durham, NC*  
<sup>5</sup>*Bioelectronics R&D, GlaxoSmithKline, Stevenage, United Kingdom*

### **Reverse Engineering of LUT Dysfunction of Organic Phenotypes Based on Patient Treatment Response**

Matthew O. Fraser, PhD  
*Duke University and Durham Veterans Affairs Medical Centers*

### **Impact of Vaginal Microbiota on Urinary Tract Health and Disease**

Nicole Gilbert, PhD, Valerie P. O'Brien, and Amanda L. Lewis, PhD  
*Departments of Obstetrics and Gynecology and Molecular Microbiology, Washington University, St. Louis, MO*

### **Elastin and Elastin Homeostasis Vary with Age, Parity, & Prolapse**

Slater Jameson, C. Emi Bretschneider, Shataakshi Dahal, Anna Rietsch, Mel Kuang, Beri Ridgeway, Matthew Barber, Anand Ramamurthi and Margot Damasar  
*Department of Biomedical Engineering, Lerner Research Institute; Advanced Platform Technology Center of Excellence, Louis Stokes Cleveland Veterans Affairs Medical Center; Glickman Urology and Kidney Institute Cleveland Clinic; Women's Health Institute Cleveland Clinic, Cleveland Ohio*

### **Understanding Heterogenous Mechanisms that Contribute to Overactive Bladder**

Lisa Karstens, PhD<sup>1,2</sup> James T. Rosenbaum,<sup>3,4</sup> Shannon McWeeny, PhD<sup>1</sup> Damien Fair, PhD<sup>5</sup>, W. Thomas Gregory, MD<sup>2</sup> Rahel Nardos, MD<sup>2</sup>  
*Oregon Health & Science University 1. Division of Bioinformatics and Computational Biology, 2. Division of Urogynecology, 3. Division of Arthritis & Rheumatic Diseases, 4. Devers Eye Institute, 5. Department of Psychiatry, 6. Department of Behavioral Neuroscience*

### **Individualizing Treatment and Translating Clinical Research into Practice**

Anna Kirby, MD, MAS, Tina Allen, PT, Erika Wolff, PhD, Danielle Lavalley, PharmD, David Flum, MD MPH  
*University of Washington*

### **What do these Women have in Common? OAB and a Pelvic Floor**

Rhonda Kotarinos, DPT, MS

*Department of Obstetrics and Gynecology, USF Morsani College of Medicine*

### **Moving “Goal Posts and Playing Fields”**

John Lavelle, MD

*Veterans Affairs Palo Alto HSC, Palo Alto, CA*

### **Postpartum Treatment vs. Delayed Treatment of Stress Urinary Incontinence**

Jan Rohozinski<sup>1</sup>, Margot Damaser<sup>2,3</sup> and Yuanyuan Zhang<sup>1</sup>

<sup>1</sup>*Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC*

<sup>2</sup>*Lerner Research Institute and Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA*

<sup>3</sup>*Advanced Platform Technology Center, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA*

### **Urine Derived Stem Cells, A Novel Predictor of the Body’s Regenerative Capacity**

Jan Rohozinski<sup>1</sup>, Margot Damaser<sup>2,3</sup> and Yuanyuan Zhang<sup>1</sup>

<sup>1</sup>*Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC*

<sup>2</sup>*Lerner Research Institute and Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA*

<sup>3</sup>*Advanced Platform Technology Center, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA*

### **Tailoring Urinary Incontinence Treatment for Frail Older Women**

Kristine Talley, PhD, RN, Becky Olson-Kellogg, DPT, Teresa McCarthy, MD, Jean Wyman, PhD, RN  
*University of Minnesota, Minneapolis, MN*

### **Ornithine Decarboxylase (ODC) Overexpression in Urothelium Leads To OAB/LUTS Voiding Phenotype and Results in Increased Urine Cytokines: A Translationally Relevant Transgenic Female Murine Model of OAB**

Judy Y. Yeh MD<sup>2</sup>, Lery Alvarez-Lugo MS<sup>1</sup>, Ming Lu, MD<sup>1</sup>, Warren G. Hill PhD<sup>3</sup>, Toby C. Chai MD<sup>1,2</sup>

<sup>1</sup>*Departments of Urology, <sup>2</sup>Obstetrics Gynecology & Reproductive Science, Yale University School of Medicine, New Haven, CT,*

<sup>3</sup>*Department of Medicine, Beth Israel Deaconess Hospital and Harvard Medical School, Boston, MA*

### **Origins of Pelvic Muscle Weakness: CNS, PNS or Muscles?**

Yingchun Zhang, PhD

*Department of Biomedical Engineering, University of Houston, Houston, TX*

**FRIDAY, MARCH 31, 2017**

**Session 4: Building Successful Transdisciplinary Teams/Conceptual Models**

*Moderator: Tamara Bavendam, M.D.*

**Building Successful Transdisciplinary Teams**

*Linda Brubaker, M.D., Professor, Department of Reproductive Medicine, University of California, San Diego*

Dr. Brubaker, member of the PLUS Research Consortium, highlighted the importance of incorporating new ways of building research projects related to LUTS prevention. She described the inherent “truncation” of new perspectives that occur when individuals from similar points of view discuss problem-solving approaches. LUTS research has been narrowly focused on detection and treatment; it has not incorporated the possibility of a prevention. The PLUS Research Consortium is harnessing the benefits of diverse perspectives by building an interdisciplinary team. These benefits include, but are not limited to, better problem solving and stronger research teams. The pathway leading to diverse thinking is multidimensional, enriches discussion, and facilitates problem solving. Dr. Brubaker introduced the concept that when individuals are working together as a team and sharing their ideas, a broader perspective is attained and problem solving is more likely to occur. A key question that is central to UI research is how LUTS can be prevented. To address this, the PLUS leadership model was created to leverage a diverse and talented group professionals, with a vast array of expertise (e.g., epidemiologists, a wide spectrum of clinicians, and *biostatisticians*); each perspective and voice is equally important. An essential component of the Consortium is an intentional effort by the PLUS members to break down the traditional scientific silos across natural, social, and health sciences by learning about each other and participating in web-based seminars to promote transdisciplinary thinking. Developing effective prevention measures of LUTS requires defining bladder health and identifying risk factors of LUTS across a broad age spectrum. Dr. Brubaker concluded by stating that the ultimate goal of LUTS research is to benefit the next generation of women through strategies that improve bladder health.

**Building Conceptual Frameworks and Models**

*Sonya Brady, Ph.D., Associate Professor, Division of Epidemiology and Community Health, University of Minnesota School of Public Health*

Dr. Sonya Brady introduced the topic of conceptual models and explained how this differs from conceptual frameworks (CFs). A CF is intended to be broad and comprehensive; it characterizes and organizes potential determinants of health and illness and encapsulates what is possible to study. The outcome of a CF is to generate information about the factors that may be involved in influencing a patient’s health or illness. Dr. Brady outlined the elements of the current working PLUS CF: environment, life course, and biology. Throughout an individual’s life course (from childhood to older adult), several factors influence health—such as society, individual behaviors, interpersonal relationships, and biological factors—and all these factors affect bladder health and influence LUTS development. Dr. Brady emphasized that this broad framework allows the discovery of additional LUTS contributing factors. This model is based on concepts generated by Glass and McAtee, who used the terms “facilitators” and “constraints” on health to describe factors that are imposed on an individual by society. Another example is the World Health Organization CF for Action on the Social Determinants of Health. Structural determinants of health inequities, such as inequitable distribution of power and policies that favor some social groups over others, contribute to the stratification of society into different socioeconomic positions. Individuals with different socioeconomic positions are embedded within communities that are more or less conducive to health (e.g., neighborhood safety and walkability, availability of fresh produce). Thus, the structural factors of a society influence more intermediary, social

determinants of health, which in turn influence differences in health equity and well-being. Social cohesion and social capital refer to the unification and shared resources of a community. While social cohesion and social capital can enhance the health of a community, they are not sufficient; shared power and equitable policies at the societal level are necessary.

Conceptual models (CMs) refer to a specific research question and population and can guide research, individual level clinical treatment, and population-level prevention efforts. A CM encapsulates a particular study and is informed by theory, empirical findings, or practice. It is a visual picture of concepts denoted by boxes and processes delineated by arrows. Dr. Brady presented an example CM provided by her colleague, Dr. Hebert-Beirne, that depicted the effect of poor economic status and social determinants of health on the treatment of type 2 diabetes disease. She noted that the most “proximal” factors (e.g., biological and psychological responses, lifestyle) are essential to a comprehensive treatment approach and outcome. However, a patient’s physiological functioning, psychological responses, and lifestyle are a function of the larger ecological context. Therefore, targeting more upstream determinants, such as poverty, is important for intervention treatment. Dr. Brady then presented a mediation model—surgery as a method to treat UI—that illustrated the associations between surgery and improved functioning, and between improved functioning and reduced UI. Changing the anatomy of an individual through surgery reduced UI symptoms through improved functioning. She noted that the effect of social factors, such as an individual deciding to perform heavy lifting after surgery, results in the alteration (in this case, a weakening) of the associations between surgery and improved functioning, and between improved functioning and reduced UI. If a provider knew in advance that a patient’s work required heavy lifting, the provider might alter the treatment plan. Dr. Brady concluded by saying that the purpose of formulating a CF prior to developing specific models is to broaden the view of possible study areas, learn more about understudied determinants of UI, and design interventions that target the most important UI determinants.

### *Discussion*

Dr. Johnson asked whether the PLUS Consortium developed the leadership model for its own self-governance or if it received the model from another source. Dr. Brady replied that each research institution offered an idea for a CF or CM that was then considered by the PLUS Consortium. Dr. Brady explained that the Glass and McAtee CF is the broadest model and was adopted by Consortium members. Dr. Brubaker added that the leadership model was expected to be developed by the PLUS consortium and was planned in advance to be self-governed, collaborative, and aligned with the transdisciplinary team effort.

A participant noted that the outcome is often considered as health-related quality of life for an individual, and asked how perception fits into the model that Dr. Brady presented. Dr. Brady replied that the focus is not only on preventing LUTS, but also on defining and measuring bladder health. The patient’s perception is an important component of bladder health. Another participant added that the concept of bladder health is not merely the absence of disease, but involves the ability of a women to pursue physical activities that she deems desirable. Measuring patients’ adaptability of their lifestyle to their environment is important.

A participant asked about the effect of the current U.S. government administration on the discussed approaches to UI treatment and prevention. Dr. Brady informed the participants that the planning to develop the model occurred prior to the recent U.S. election. Dr. Bavendam added that the Consortium is proceeding with their plans and focusing on the science. Dr. Diane Newman (PLUS member) added that acknowledging the process of “how girls pee” or the associated physiological alterations are important considerations to address regardless of the political climate. Dr. Bavendam noted that the Request for Application submitted was about women and girls; she added that the Consortium’s work will focus on

UI in cisgender versus transgender populations. Dr. Brady thanked Dr. Newman for assisting with the PLUS consortium's planned focus group to assess adolescent girls' understanding of bladder health.

A participant remarked that the PLUS initiative should consider the ethnic diversity of the patient population and their providers; culturally based world views may affect health. Dr. Brady said that as part of a study currently being planned, focus groups will obtain different perspectives from young girls and women across the seven research centers, which serve ethnically diverse communities. Regarding the providers' perspective, this is already part of the broader framework of the CF; it is important to consider the provider-patient interaction.

Dr. Brady introduced the main goal of the small group exercise: to consider different factors that identify the most effective treatments for individuals, taking into account biological and nonbiological factors. The small groups serve as an interdisciplinary team that will generate a framework and CM based on a preselected topic; the model will depict testable hypotheses that will fill specific knowledge gaps in the ability to provide individualized UI treatment. The models developed by each table address different factors that make the best currently available UI treatments more or less effective for subsets of patients. The models show how biological predisposition or social ecological conditions or both affect the efficacy of UI treatment. Current approved treatments that were discussed during the meeting include behavioral and physical therapy, prescription medicines, Botox, neuromodulation, and surgery.

### **Small Group Session 1**

Dr. Brady described the potential treatment effect modifiers that are key to "broad and deep" patient characterization. During the small group discussion, participants were tasked to generate effect modifiers or factors that could affect various treatment options. Groups were organized by particular patient populations: children (1 group), men (2 groups), neurogenic (2 groups), and women (6 groups).

#### **Small Group Report Back and Discussion**

*Moderator: Tamara Bavendam, M.D.*

Dr. Brubaker invited the participants to report the results from their discussions and also to comment on their experience working with people with various perspectives. Group representatives presented the following discussion points:

##### Group 1: Children

- *Neuromodulation as a treatment option*—the group reported the following modifiers: UTIs; congenital LUTS; the individual's microbiome (local biology); obesity and constipation (systemic biology); mother and child dyad, bowel habits, care of genitals, and sexual abuse (behavior); unnamed emotional, behavioral issues, signals of readiness for toilet training, education (psychological and executive functioning); insurance coverage, transportation to appointment, parental involvement and knowledge of socioeconomic status, pediatrician knowledge, school environment, stigma, and preschool policies (social determinants of health).
- Strong evidence that links constipation to urinary habits does not exist; however, children with urinary symptoms often are treated for constipation.
- Children in the clinical setting are often "overtreated" for UTI.
- No standard exists for collecting information regarding readiness for toilet training; the age of 3 years old may be associated with a readiness to self-report toileting behaviors.
- Congenital disorders affect UI treatment.
- Socioeconomic status does not necessary negatively affect the ability of the child to engage in these treatment options.

- Separating the topics of psychological function from executive function in children was difficult for the group.
- There is a potential stigma regarding the discussion of anatomy and UTI.
- Obtaining parental consent when collecting data from children and adolescents is a necessary component of clinical trials. Partnering with charter schools or “teen-friendly” clinics is beneficial to the process of data collection in younger-aged populations.

#### Group 2: Men

- *Surgery as a treatment option (artificial urinary sphincter)*—prior external radiation therapy, poor bladder compliance (local biology); poor wound healing, personal dexterity, body mass index, metabolic syndrome, polypharmacy (systemic biology); cognitive function (psychological and executive functioning); cost and insurance coverage, the dexterity required to manipulate surgical devices, access to toilets, access to fluids, and access to expert care, and the presence of stigma (social determinants of health).
- *Neuromodulation as a treatment option*—peripheral neuropathy (systemic biology); access to expert care (social determinants of health).
- *Pharmacological intervention as a treatment option*—prostate enlargement, 5-alpha reductase, oral versus transdermal drugs, phosphodiesterase type 5 inhibitors that co-treat erectile dysfunction and LUTS (local biology); age and genetics (systemic biology); personal dexterity and adherence (behavior); the cognitive effects of the antimuscarinic drug class on cognitive function (psychological and executive functioning); formulary placement: the adherence to a particular medicine is affected by cost, which may harm the patient (social determinants of health).
- *Behavioral or rehabilitative therapy as a treatment option*—total incontinence as a potential contraindication to behavioral intervention strategies (LUT); sexual function and LUTS (local biology); brain differences and responses (systemic biology); individual knowledge deficits, personal dexterity, adherence, and mobility function (behavior); motivation (psychological and executive functioning); workplace toilet access, formulary and insurance coverage (social determinants of health).
- LUTS is a broader descriptive term associated with males.
- An enlarged prostate may not be the cause of all urinary storage problems and symptoms.

#### Group 3: Men

- Discussed various aspects of men’s urinary health; particularly men 70 years old and older.
- *Pharmacological intervention as a treatment option*—LUT constituents may affect the efficacy of pharmacological agents. Urinary constituents, local microbiome, and UTI (LUT); the prostate gland is often a contributing modifier (local biology); age, genetics, and comorbidities affect treatment options (systemic biology); adherence is an important modifier (behavior).

#### Group 4: Neurogenic

- *Surgery as a treatment option*—the spasticity is a limiting factor for surgical treatment, comorbidities are modifiers (systemic biology); sexual activity, a patient’s belief in a desirable outcome of treatment, drug and alcoholic beverage use, and dexterity (behavior); cognitive impairment, mental health and post-traumatic stress disorder, particularly with individuals who have spinal cord injuries (psychological and executive functioning); education, access to care, lack of technology for toileting aids, such as intermittent catheterization (social determinants of health).
- *Neuromodulation as a treatment option*—the need for an MRI may hinder the ability to use an InterStim (systemic biology); neuromodulation is the costliest option for patients who often are underemployed and underinsured (social determinants of health).
- *Pharmacological intervention as a treatment option*—genetics (local biology).

- *Behavioral or rehabilitative therapy as a treatment option*—urine storage ability (LUT); UTI, bowel dysfunction, kidney stones, and prolonged catheterization (local biology); pelvic floor denervation, functional ability and mobility (systemic biology); patient compliance (behavior).
- Cultural factors influence the efficacy of all of the treatment options or interventions.
- A health care consensus for treatment can skew the plan of care for certain patients.

#### Group 5: Neurogenic

- *Surgery as a treatment option*—the ability to retain urine, tissue, and patient compliance (LUT); reparative and degenerative effects of local or systemic tissue, genetics, and duration of disease (local biology); depression, understanding of therapy, need for treatment, and acceptance of incontinence as a part of life (psychological and executive functioning); costs of such products as catheters, geography and income, caregiver support, and stigma (social determinants of health).
- *Neuromodulation as a treatment option*—receptor density and expression, epigenetics, smooth-muscle density, changes in innervation or pattern of defective or intact neurological innervation, and completeness of lesions (LUT); habituation may cause loss of efficacy over time. Neuroplasticity, fibrosis, microbiome, and traumatic conditions, such as Parkinson’s disease (local biology).
- Age, diabetes, obesity, and racial differences all are modifiers.
- Genetically determined drug metabolism is a modifier.

#### Group 6: Women

- *Surgery as a treatment option*—muscle atrophy, types of incontinence (e.g., intermittent), self-catheterization and innervation, pelvic pain and pelvic muscle function (LUT); microbiome, recurrent UTI (local biology); cardiovascular diseases (e.g., peripheral edema), functional status, diabetes and other comorbidities, obesity, metabolism of pharmacological drugs, and comorbidities (systemic biology); history of vigorous exercise, tobacco use, voiding habits, fluid intake, InterStim, patient compliance, health-seeking behaviors, patient history of therapy influencing the patient’s expectation of treatment, and a patient’s positions or postural habits supporting a need for physical therapy (behavior); self-regulation, anxiety and stress somatization, health literacy, capacity of patient, and the patient’s values and perception of health care (psychological and executive functioning); health literacy, ability to get to a medical appointment, flexibility of schedules, and transportation access (social determinants of health).
- The side effects (e.g., dry mouth, constipation) of pharmacological drugs affect treatment.

#### Group 7: Women

- *Surgery as a treatment option*—chemotherapy and other immunosuppressant therapies, ongoing metabolic disorders, bowel function, hearing loss, sexual function (systemic biology); presence of a caregiver, patient values, and perception of health care (psychological and executive functioning), family dynamics, insurance issues, policies governing treatment, and cost (social determinants of health).
- Medical interventions that require adequate training of physicians in different modalities so they select the most appropriate treatment options. Time constraints that prevent obtaining a complete medical history of patient. These may result in insufficient insight and poor application of treatment. The legal milieu that may affect the medical provider’s treatment decision.
- *Behavioral or rehabilitative therapy as a treatment option*—insurance cost, lack of awareness of behavioral treatment availability, lack of education to prepare physicians to be aware of research on treatment adherence or how to increase adherence (social determinants of health).



#### Group 8: Women

- *Surgery as a treatment option*—pelvic floor function (LUT); cardiovascular disease, such as peripheral edema (systemic biology).
- *Behavioral or rehabilitative therapy as a treatment option*—mobility impairment or frailty (systemic biology); self-efficacy and stage of readiness for treatment, and patient expectation for improvement (psychological and executive functioning); social norm of managing LUTS with female sanitary napkins, unwillingness to seek care, and identifying the optimal pelvic floor exercise regimen (social determinants of health).
- *Pharmacological intervention as a treatment option*—the use of Botox requires locating the correct injection site (local biology); lack of information regarding normative fluid intake (behavior);

#### Group 9: Women

- *Surgery as a treatment option*—willingness to participate with treatment (behavior); provide a basis for training, knowledge (social determinants of health).
- *Neuromodulation as a treatment option*—smooth muscle function, urethral instability, urodynamic testing, potassium channel drugs (LUT); nerve projections and variability of where nerves project, neuropathy, urethral sensitivity and contraction measurement, back pain, hysterectomy, estrogen levels (local biology).
- Analyzing the ability of the provider to predict a patient’s response to treatment before care is provided is important. Individualized prediction of treatment can be used to guide further questions.
- Age, weight, and the provider’s access to patient data affect what treatment intervention is chosen.

#### Group 10: Women

- *Surgery as a treatment option*—mesh tissue compatibility, immune response, and vascularity (local biology); imbalance of power in the patient consent process (social determinants of health).
- *Behavioral or rehabilitative therapy as a treatment option*—low-level application of systemic medicine (systemic biology); excess fluid intake for women, self-management (behavior); determining the measure of successful treatments to determine the best outcomes (psychological and executive functioning); insurance provides only a set amount of coverage per year and, therefore, does not cover continued therapy (social determinants of health).
- Determine the mechanisms that contribute to adverse symptoms as a result of surgical intervention.

#### Group 11: Women

- *Surgery as a treatment option*—the ratio of alpha-beta adrenoceptors in the body, urinary biomarkers (local biology); multimorbidity, which is the effect on treatment when the patient has multiple ailments, such as diabetes (systemic biology); patient compliance, health-seeking behaviors, and nutrition intake or status (behavior); patient’s values, perception of health care, preconceived notions, shared decision making, depression, and executive functioning within cognitive impairment (psychological and executive functioning); education on health literacy, the ergonomics of fashion (e.g., height of shoe heels), bias of providers and their interpretation of the medical conditions based on the women’s description of her symptoms, gender bias, “gatekeepers” to access such as family members, older adult housing facilities, and partner support (social determinants of health).

### *Additional comments from the women population groups*

- The individual history of pediatric LUT problems, response to previous treatment, management of multimorbidity issues, perceived safety of using public restrooms, and voiding after sexual activity all are important behavioral modifiers to surgery as a treatment option for UI.
- The interpersonal relationship between doctor and patient and the capacity of a caregiver are important social determinants of health that may modify surgery as a treatment option for UI.
- Local reflexes (LUT), muscle stretching, and regenerative potential through new treatments are components of local biology that may modify behavioral, rehabilitative approaches for UI treatment.

### **Discussion**

Dr. Rovner commented that the neurogenic population is the costliest to treat for UI; individuals in this category typically have difficulty gaining and maintaining employment. Dr. Newman added that there is a lack of understanding that paraplegics often prefer to gain normal bladder control rather than walking ability. Dr. Bavendam remarked that there are efforts to better understand this phenomenon; the National Institute of Neurological Disorders and Stroke and the NIH's recent 2017 meeting to discuss neurology, rehabilitation, and urology discussed the issue of bladder health in disabled people.

Dr. Brubaker and a meeting participant mentioned that prolonged catheterization confounds treatment options.

A participant commented that other areas of medicine (e.g., dermatology) should be considered when discussing treatment interventions.

Dr. Brubaker informed the participants that this meeting is the first of its kind. She thanked Dr. Brady and the rest of the attendees for their participation in the meeting and expressed her belief that the information captured from the small groups is useful.

### **Small Group Session 2**

Dr. Brady explained that the group would be shifting its attention to CMs. CMs can help researchers think through possible study designs for a chosen topic and can make writing research questions easier.

Dr. Brady presented an example, asking whether mindfulness training would strengthen the effects of treatment, considering both surgery and neuromodulation. Experimental groups in such a study could include those being treated with neuromodulation with and without mindfulness training, those receiving surgery with or without mindfulness training, and a control group of patients on the waiting list who are not receiving any treatment. In this example, mindfulness training is the treatment effect modifier.

Dr. Brady presented additional examples using topics discussed on the first day of the workshop. One study could assess the effect of clinician-directed biofeedback on PFMT. She pointed out that biofeedback itself cannot easily be isolated from PFMT, but it is possible to study clinician-directed effects. In this case, the clinician-directed biofeedback is the treatment effect modifier, and a conceptual model allows researchers to easily test various treatments, factors, and modifiers. Dr. Brady also suggested a study that could assess ways to help patients develop realistic expectations of treatment. Managing expectations is important to treatment satisfaction, and one of the most critical parts of this question is the quality of provider or patient communication. In the example model, providers would check the patient's understanding of provided health literacy materials. One option that could be added to this model is combined intervention, in which researchers talk to both the provider and the patient to help

caregivers communicate better. The CM also could include outcomes and additional treatments. Dr. Brady pointed out that choosing a small number of factors helps to formulate a clear study design. The groups then worked on building their own CMs.

### **Small Group Report Back and Discussion**

*Moderator: Tamara Bavendam, M.D.*

- Table 1 started with a simple trial design, but developed many potential factors that could be integrated. Their study compared a behavioral treatment bundle to a drug combination for men over 50 years of age. Potential modifiers include cognition, mobility, and the presence or support of a partner. These additional factors could be added or subtracted to adjust the complexity of the model. Outcomes include counts of UI with a secondary outcome of patient-perceived benefit.
- Table 2 explored the effect of padded diaper use on the urinary microbiome in men and women. Frequency of changing could be affected by socioeconomic factors, and the type of pad also could have effects on the microbiome. The group noted that some of these questions could be useful as individual studies, because pad use often is based on patient preference; it would be more difficult to randomize treatment groups. This study also would allow assessment of both the treatment outcome and the microbiome itself.
- Table 3 focused on interventions for pediatric patients. In patients who have failed first-line behavioral modification, parental attitudes and engagement are important components to treatment. The group proposed use of gamification to increase treatment adherence, as well as supplemental factors, such as nurse educator intervention. They emphasized the importance of assessing and understanding the relationship between parent and child.
- Table 4 proposed a study of self-catheterization in men with spinal cord injury. These patients are trained in clinic, but many cease self-catheterization within 6 months to 1 year of treatment. This table proposed adding support to reinforce education and intervene when problems arise. Their suggested methods include telehealth monitoring and more frequent follow-up appointments. This study also targets a social support aspect of treatment.
- Table 5 proposed studying sacral nerve stimulation for neurogenic bladder. In cases of spinal cord injury, there could be a difference in outcome between immediate intervention and intervention only after incontinence symptoms arise. This group also proposed using metformin as an anti-aging treatment in older-aged populations. Another proposed research topic was the overtreatment of catheter-associated UTIs with antibiotics. Group members pointed out that the discussed treatments are affected by individual factors, so patients could be phenotyped to determine which ones would respond better.
- Table 6 talked about the role of predictors for treatment success in women, specifically urinary and serum biomarkers, which can affect outcomes. Vitamin D levels also can be markers for treatment success. They noted that some biomarkers, including vitamin D levels, can be changed, but others cannot; the presence of biomarkers that cannot be changed could hint at which treatments will not be effective.
- Table 7 proposed studying factors that affect the success of pelvic floor muscle training in women. Women may not complete them due to busyness or a low expectation of success, or they may not do them correctly. The group proposed a phone or iPad app that could send the patient reminders to do the exercises and provide feedback on whether they are being performed correctly using a wireless vaginal

probe. Another group could receive in-clinic instructions. Measures could include UI, quality of life, and measurement of muscle strength.

- Table 8 discussed early intervention for high-risk populations, such as college-aged high-impact female athletes. One idea is the use of a prophylactic pessary, but because this is a younger population, many factors may affect whether they are willing to try a pessary, including religion, stigma, and the frequency of exercise. An educational early intervention—distributing information on the prevalence of pelvic floor disorders—could improve college athletes’ willingness to seek treatment and overcome stigma. Because this is a younger population, social media could be a good avenue for distribution. The primary outcome would be incontinence in the future, so this study would require long-term follow-up.
- Table 9 addressed the effect of pelvic floor muscle condition on the treatment of urgency in women. PFMT specifically to lengthen the pelvic floor muscle could make patients more responsive to neuromodulation. The group discussed whether to select patients with specific conditions and how a control group could help isolate which treatments was effective. It was also pointed out that the treatments proposed address different aspects of the individual.
- Table 10 talked about the high rate of UTIs when Botox is used as a therapy in women. Potential modulators include the installation of *gentomycin* in the bladder, use of vaginal estrogen, and diet. A study on this topic also could assess the length of time before a UTI develops. The group also discussed the problem of anxiety in agreeing to surgery. This population frequently is successful if patients agree to treatment, so a potential intervention could be group classes to help alleviate anxiety around surgery.
- Table 11 proposed studying the effect of chronic stress on treatment outcome, including both medical and neuromodulation treatments in women. The group discussed whether stressors could be changed and, if not, whether patients’ ability to deal with it could be improved. Dr. Brady pointed out that this study includes social factors.

### **Meeting Adjournment**

Dr. Bavendam thanked the moderators, presenters, and attendees for attending the meeting and noted that a peer-reviewed publication of the meeting’s proceedings is planned. She adjourned the meeting at 2:30 p.m.