

**Urology Interagency Coordinating Committee (UICC)
Ad Hoc Women's Urologic Health Research Program Planning Meeting**

**November 4, 2013
National Institutes of Health (NIH)
6707 Democracy Boulevard (Democracy II)
Room 400
Bethesda, MD
8:00 a.m.-3:30 p.m.**

Summary Report

Welcome

Robert Star, M.D., Director, Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK, NIH

Dr. Star welcomed attendees and guests on behalf of the NIDDK/KUH and indicated the NIDDK interest in pursuing research on prevention of lower urinary tract symptoms (LUTS), the focus of this meeting.

Janine Clayton, M.D., Director, Office of Research in Women's Health (ORWH), NIH

Dr. Clayton welcomed everyone on behalf of the ORWH, emphasizing the importance of LUTS to overall women's health and the support of the ORWH in the LUTS prevention efforts.

Tamara Bavendam, M.D., M.S., Senior Advisor, Women's Urologic Health, NIDDK, NIH

Dr. Bavendam reviewed the meeting objectives and agenda, emphasizing the desire to have as much time as possible for discussion and input.

Introductions

All meeting attendees introduced themselves.

Framing Lower Urinary Tract Symptoms in Women

Dr. Bavendam

Dr. Bavendam presented the definitions of LUTS and the complexity of research in the area because symptoms do not always indicate lower urinary tract dysfunction, dysfunction does not necessarily cause symptoms, and the connection between healthy bladder habits and presence or absence of symptoms is unknown. Dr. Bavendam defined LUTS in women as an umbrella term to include all symptoms associated with any type of lower urinary tract dysfunction/condition. Research in the area of LUTS is also hampered by the fact that LUTS are often not considered outside of urology, even though there is substantial evidence indicating associations with many medical conditions with a high public health burden, such as obesity, diabetes, cardiovascular disease, and depression. Risk for bladder conditions extends throughout the lifespan of a female. There are specific events that seem to be risk factors for LUTS in women, such as sexual activity and childbirth. The boundaries around the specialties that deliver care for women with pelvic conditions contribute to a nonholistic approach to care. Care for LUTS/bladder conditions is delivered by primary care, specialty care, and "superspecialty" care (i.e., female pelvic medicine and reconstructive surgeons). Traditionally, reproductive related risk factors have been perceived as non-modifiable, with the research focus being on the treatments for LUTS. Studies indicate that most women often do not seek medical care until very late in the symptom evolution, seemingly accepting the symptoms as their fate. Women need to understand what normal bladder function is and is not so they will know when their experience is not normal and seek help through self-management or a health care provider. Once women begin to understand that bladder problems are not their fate because of their unique reproductive capability, primary and

secondary prevention become possible. In addition, researchers need to expand their thinking with respect to characteristics that may define populations at risk and women who will be the best targets for prevention efforts to include nonbiological factors such as beliefs, values and cognitive factors.

LUTS Epidemiology

Susan A. Hall, Ph.D., Senior Research Scientist, Department of Epidemiology, New England Research Institute

Dr. Hall used data from the NIDDK-supported Boston Area Community Health Survey (BACH) to present an overview of LUTS epidemiology, focusing on the female subjects with relevant comparisons to males. BACH is a population-based random sample of 5,502 Caucasian, Hispanic, and non-Hispanic Black adults, 30 to 79 years old. BACH researchers collected data via two 2-hour, in-home interviews administered about five years apart, and evaluated a broad range of urologic symptoms. Dr. Hall presented comparisons between women and men in four symptom areas—urinary incontinence, LUTS (as defined in BACH), nocturia (a LUTS symptom also evaluated separately), and painful bladder syndrome (PBS, also known as interstitial cystitis/painful bladder syndrome (IC/PBS)).

BACH findings reinforced that persons with LUTS who present for medical care and are treated represent a small fraction of those with prevalent LUTS, around 18 percent for both women and men. Prevalence was slightly higher in Blacks and slightly lower in Hispanics. Nocturia was the most common symptom in women, followed by overall LUTS, urinary incontinence and PBS. Prevalence increases with age except for PBS. Incidence of LUTS as defined in BACH is fairly stable until age 70, when it doubles compared to younger age groups. BACH also found significant overlap in symptom categories.

BACH data revealed a significant impact of LUTS on both mental and physical quality of life. The impact of LUTS on mental quality of life was similar to that seen with diabetes and heart conditions. The impact of LUTS on physical quality of life was similar to that seen with high blood pressure, diabetes, and heart conditions. From data collected during the initial interview, modifiable factors related to LUTS or urinary incontinence included low physical activity, obesity, low dietary vitamin C, high caloric intake, ratio of saturated to polyunsaturated fat, and certain medications (atypical antipsychotic drugs, calcium channel blockers, certain antihistamines, estrogens, and other drugs).

Based on longitudinal data from BACH, LUTS incidence is associated with low physical activity (voiding symptoms), cigarette smoking (storage symptoms) and alcohol intake (voiding symptoms). Incidence of urinary incontinence is associated with age, greater waist circumference and increase in waist circumference from baseline. Data also suggested that higher levels of physical activity decreased the risk incident urinary incontinence. Seventy percent of women with mild LUTS remain unchanged over time, while only 47 percent of moderate LUTS and 18 percent of severe LUTS remain unchanged. Of those that change, the majority improve. A similar pattern is seen for urinary incontinence: when change occurs, it is more likely to be improvement rather than worsening.

BACH knowledge gains important to LUTS:

- **52 million adults** in the U.S. will have symptoms of LUTS, UI, PBS or prostatitis in 2025
- Urologic symptoms are significantly associated with and precursors of other **major medical conditions** (e.g. type 2 diabetes, cardiac disease)
- Evidence of **dose-response relationship** of severity and duration of urologic symptoms and chronic illnesses above
- **Progression and remission of symptoms** suggest modifiable factors are at hand
- **Prevention** is likely possible with greater physical activity, not smoking, and maintenance of a healthy waist circumference and healthy dietary habits
- **Medications** and **sleep** may contribute

LUTS Impact

Alayne D. Markland, D.O., M.Sc., Associate Professor of Medicine, Division of Gerontology, Geriatrics, and Palliative Care, University of Alabama

Dr. Markland presented briefly what is known about the impact of LUTS (including urinary incontinence) on health and healthcare:

- Significant impact on quality of life
- Costly condition
 - Direct costs \$5.3 billion
 - Compared to: \$17.4 billion (Estimated cost to Medicare of unplanned re-hospitalizations in 2004)
- Negative effect on life-altering events
 - Falls
 - Fractures
 - Long-term care or Nursing home need

Dr. Markland referred to data from BACH and other studies to underscore that LUTS is on par with other chronic conditions in terms of impact on quality of life.

She remarked that the annual growth rate of incontinence absorbent products is projected at 6 percent, the highest of any hygiene sector including baby diapers. Whereas these products allow urinary incontinence to be managed, it would be better to identify and treat UI at an early stage to prevent its devastating impact on patients later in life. Dr. Markland also noted that there are a number of key knowledge gaps about the impact of LUTS—“what we *should* know”—and suggested ways to obtain that knowledge.

LUTS Treatment – Behavioral and Pharmacological

Diane K. Newman, D.N.P., A.N.P.-B.C., F.A.A.N., Co-director, Penn Center for Continence and Pelvic Health, Division of Urology, University of Pennsylvania Medical Center, and Adjunct Associate Professor of Urology in Surgery and Research Investigator Senior, Perelman School of Medicine, University of Pennsylvania

Dr. Newman presented a brief, overview of behavioral and pharmacological interventions for LUTS (including urinary incontinence). She stated that there is a strong evidence base for behavioral interventions and drugs for treating overactive bladder (OAB) and urge urinary incontinence. According to Dr. Newman, combining approaches is the best. For stress urinary incontinence, there are no FDA-approved medications; however, she noted that there is solid evidence supporting behavioral intervention for treatment. Dr. Newman is an investigator in an NINR funded TULIP study comparing 2 methods of delivering education regarding behavioral interventions to prevent urinary incontinence in midlife and older women.

Management of LUTS – Role of Physical Therapy

Diane Borello-France P.T., Ph.D., Associate Professor of Physical Therapy, Duquesne University; Adjunct Assistant Professor, School of Medicine, University of Pittsburgh

Dr. Borello-France used an anonymous patient case, a young women with urinary frequency, urgency, and pain, to inform the group briefly about the involvement of multiple systems in LUTS (e.g., posture can contribute to symptoms), and to demonstrate the role of musculoskeletal assessment and physical therapy in treating LUTS in women. The evidence base is limited but growing. She noted that there is a need for standardization of assessments, treatments, and outcome measures.

Surgical Treatment of Female LUTS

Jennifer Anger, M.D., M.P.H., Associate Professor of Urology, Associate Director of Urological Research, Cedars-Sinai Health System; Adjunct Assistant Professor of Urology, UCLA

Dr. Anger focused on and defined the different types of urinary incontinence (stress, urge, mixed, and incontinence resulting from lack of sensory awareness) and described surgery-based treatments that are currently available. For stress urinary incontinence, these are bulking agents and sling procedures to support the urethra. For overactive bladder and urge urinary incontinence, treatments include botulinum toxin injected into the bladder and implantation of devices that allow neuromodulation of the bladder or pelvic floor to reduce urgency.

Discussion of Research Needs in Women's Urologic Health

Facilitator: Phil Lee, President, The Results Leadership Group

To provide more time for discussion, the external experts were asked before the meeting to consider what knowledge gaps need to be addressed through research to achieve the following vision: Preserve and improve bladder health for women across the lifespan. From the ideas she received, Dr. Bavendam developed an extensive list of gaps and challenges to be addressed through research, summarized below:

- *Common knowledge gaps*
 - *What females across the lifespan know about their bodies/bladders*
 - *Comprehensive information about females' voiding patterns and toileting behaviors across the lifespan*
 - *What clinicians know about bladder health and LUTS*
 - *Additional modifiable LUTS risk factors*
 - *Impact of LUTS on sexual function and vice versa*
 - *How to activate sufferers to do something*
 - *Impact of absorbent products on self-management and health care seeking, as well as on downstream health conditions such as vulvovaginal inflammation and infection, as well as bladder infections*
 - *Sex and gender differences in LUTS occurrence and impact*
 - *Relationship of LUTS to falls and fractures and ability to live independently*
 - *How to approach underserved populations (e.g., non-English-speaking, racial/ethnic minority, Hispanic, and lesbian/gay/bisexual/transgender populations)*
 - *Women who will most likely engage in prevention interventions*
 - *What broad spectrum of stakeholders would value in bladder health and LUTS prevention initiatives (women, family, caregivers, healthcare providers, medical institutions, retirement, assisted-living and long-term care facilities, payers, and policy makers)*
- *Expand the understanding of the relationship between obesity and LUTS – common underlying mechanism*
- *Recurrent urinary tract infections – prevention is crucial because of increasing emergence of antimicrobial resistance*
- *Identify successful models for prevention and study in target populations*
- *Expanded understanding of detrusor and urothelium through the spectrum of dysfunctions: diminished to increased detrusor contractility and diminished to increased bladder sensation.*

Individual opinions expressed during the group discussion of these various knowledge gaps were consistent with a goal to establish a knowledge base that will allow for future primary and secondary LUTS prevention research. Because of the overlapping of symptoms and the potential for continuation of risk factors from childhood to adulthood into old age, there was a general recognition by participants that the knowledge base should be established broadly – understanding risk factors for LUTS across the lifespan, recognizing that future prevention efforts would be targeted at specific high-risk populations for specific aspects of LUTS.

Introduction to Prevention Research

Denise Simons-Morton, M.D., Ph.D., Senior Advisor, Office of Disease Prevention, NIH

To help set the stage for continued discussion of LUTS prevention research needs and gaps, Dr. Simons-Morton presented an overview of prevention research across the natural history of disease (which can encompass the lifespan) and the ideal sequence for prevention studies, from observational studies to clinical trials, using cardiovascular disease prevention research as a model.

Summary key points from Dr. Simons-Morton's presentation include:

- One can only prevent diseases if one knows what causes them, therefore prevention studies are needed at all phases of natural history of disease to determine the causal chain
- Observational studies:
 - identify associations between potential risk factors and disease onset or outcomes
 - can provide some evidence for causality
 - identify hypotheses for RCTs
- Randomized controlled trials (RCTs)
 - can provide experimental evidence that changing a risk factor can reduce disease risk or improve outcomes – this is the highest level of evidence for causality
 - can be designed to have high generalizability for effectiveness questions in real-world settings

Review of LUTS Prevention Intervention Research

Ananias Diokno, M.D., Professor of Urology, Oakland University William Beaumont School of Medicine; Physician, William Beaumont Hospital

Dr. Diokno briefly presented the results of the only randomized clinical trial for UI prevention using group behavioral modification program (BMP). It was supported by the NIA and the results were published 10 years ago. A group educational intervention was employed in postmenopausal women aged 55-80 years. For inclusion, potential participants could be fully continent or have had < 6 days of urine loss in the past year; criteria for excluding potential participants included a positive stress test for urine leakage and not being able to contract pelvic floor muscles on baseline examination.

In the study, 195 subjects were randomized to a control group that did not receive the behavioral modification; 164 were assigned to receive the BMP at the beginning of the study. Twelve months later, the absolute continence level among participants was 37 percent in the BMP group versus 28 percent in the control group. Moreover, 56 percent of participants in the BMP group had the same or better continence versus 44 percent in the control group. Thus, BMP participants were twice as likely to remain or become absolute continent as the control group and were 97 percent more likely to have the same or better continence level after 12 months.

LUTS Risk Factors - Biological

Emily Lukacz, M.D., M.S. Professor of Clinical Reproductive Medicine and Director, Female Pelvic Medicine and Reconstructive Surgery Fellowship Program, University of California, San Diego Health Systems

Dr. Lukacz presented a brief overview of what is known about biological risk factors for LUTS, covering factors that can come into play across the lifespan. There is limited knowledge about the impact of genetics and race. Some findings include that, among women who are incontinent, Blacks/African American women have lower rates of stress urinary incontinence and higher rates of urge urinary incontinence than white women. In twin studies, there appears to be a 1.5 percent genetic contribution to stress urinary incontinence and 35 to 55 percent contribution to overactive

bladder/urge urinary incontinence. Genetic factors are likely to account for less than 30 percent of IC/PBS.

Turning to pregnancy, Dr. Lukacz noted that vaginal delivery is a risk factor for both stress urinary incontinence and urge urinary incontinence. There is currently no evidence for a relationship between mode of delivery and urinary tract infections (UTIs) and IC/PBS. Pregnancy itself increases risk for UTI, but may be protective for IC/PBS.

Obesity, diabetes, hysterectomy, chronic coughing/high impact activities, osteoporosis, arthritis and neurologic conditions are risk factors for stress urinary incontinence and overactive bladder. Diabetes and conditions requiring catheterization are risk factors for UTI. There is co-occurrence of IC/PBS with fibromyalgia, irritable bowel syndrome, chronic pain, and headaches.

There is also evidence for the impact of the menopausal transition on LUTS. Research has shown an increased risk of urinary incontinence with oral postmenopausal hormone replacement therapy. The rate of UTIs increases with menopause, but it appears it can be reduced with treatment with vaginal estrogen.

While risk of urinary incontinence increases with age, adjusted analyses suggest that age alone is not the issue. Twin studies suggest that IC/PBS decreases with age. Dr. Lukacz closed by highlighting what still needs to be learned about these risk factor areas to help with prevention studies and how they might feed into LUTS prevention strategies.

LUTS Risk Factors – Nonbiologic and Behavioral

*Mary H. Palmer, Ph.D., R.N.C., F.A.A.N., A.G.S.F., Helen W. and Thomas L. Umphlet
Distinguished Professor in Aging and Interim Co-director of the Institute on Aging, University of
North Carolina Chapel Hill*

Dr. Palmer presented the nonbiologic risk factors dividing them into three broad categories: sociocultural, environmental, and behavioral.

Sociocultural risk factors include the stigma associated with LUTS as well as knowledge, attitudes and beliefs. Environmental factors include workplace issues, such as toilet facilities and ability to leave job to use the facilities; such accessibility is also an issue in schools, public facilities, and prisons. Behavioral risk factors include type and volume of fluids and habitual low physical activity. Toileting behaviors (incomplete relaxation for voiding) and use of absorbent products are common behaviors and may be risk factors. Delayed voiding out of convenience or need may be a risk, as well as going “just in case” because of lack of access to toilets, resulting in voiding whenever there is a toilet available rather than based on bladder signals. Reduced expectation of continence could also be a major risk exacerbated by the availability of superabsorbent products that virtually eliminate socially embarrassing incontinent episodes (i.e., a person may not consider herself or himself incontinent as long as she or he can contain it and avoid embarrassment).

Discussion – Prioritization of Research

Meeting participants resumed discussion of the research needs and knowledge gaps, this time providing ideas and opinions on opportunities for prevention research in the short term and longer term, in different populations of females (e.g., youth, reproductive age). The individual opinions and ideas provided during this session were collected by Dr. Bavendam and Dr. Star for later use to help inform the ongoing development of a new NIDDK led program on LUTS prevention research.

Closing Remarks

Drs. Bavendam and Star thanked participants for their time and ideas and also acknowledged the support of the ORWH and individuals at NIH who are aiding the development of the LUTS prevention research program.

Meeting Adjourned at 3:25 PM

Federal Attendees:

T. Bavendam (NIDDK/KUH)
L. Begg (ORWH/NIH)
D. Burwen (NHLBI)
J. Clayton (ORWH/NIH)
P. Donohue (NIDDK/OSPPA)
E. Duggan (NIDDK/KUH)
P. Eggers (NIDDK/KUH)
L. Hardy (NINR)
E. Hoff (NIDDK/OSPPA)
A. Hruszkewycz, (NIH/NCI)
Z. Kirkali (NIDDK/KUH)
J. Kusek (NIDDK/KUH)
S. Meikle (NICHD)
C. Mullins (NIDDK/KUH)
E. Newman (NIDDK)
B. Nilsen (OBSSR/NIH)
E. Parrott (NICHD)
B. Polglase (NIDDK/OCPL)
M. Salive (NIA)
D. Simons-Morton (ODP/NIH)
R. Star (NIDDK/KUH)
M. Worstell (HHS OWH)
S. Yanovski (NIDDK/DDN)

Nonfederal Attendees:

J. Anger (Los Angeles, CA)
D. Borello-France (Pittsburgh, PA)
C. Close (Las Vegas, NV)
A. Diokno (Detroit, MI)
S. Hall (Boston, MA)
J. Hebert-Beirne (Chicago, IL)
M. Jenkins (Amarillo, TX)
E. Lukacz (San Diego, CA)
P. Lee (Bethesda, MD)
A. Markland (Birmingham, AL)
D. Newman (Philadelphia, PA)
M.H. Palmer (Chapel Hill, NC)
R. Roberts (Madison, WI)
A. Stapleton (Seattle, WA)

Guests:

L. Giambaressi (AUA)
V. Hoffman (BCAN)
A. Roach (ICA)