

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

PATH TO PREVENTION OF LOWER URINARY TRACT SYMPTOMS (LUTS) WORKSHOP

**Renaissance Hotel
Washington, DC**

May 3–4, 2014

Meeting Summary

WELCOME

Griffin Rodgers, M.D., M.A.C.P., Director, NIDDK

Dr. Tamara Bavendam welcomed the meeting participants and introduced Dr. Griffin Rodgers, NIDDK Director, to provide welcoming remarks. On behalf of the NIDDK, Dr. Rodgers welcomed the attendees to the Path to Prevention of LUTS Workshop. He remarked that every speaker originally scheduled to present at the February meeting had again agreed to participate in the Workshop, and he was expecting an outstanding meeting.

Dr. Rodgers established the context for the meeting by noting that the NIDDK began its evolution from treatment to prevention two decades ago, when it supported cohort studies of highly symptomatic patients experiencing interstitial cystitis (IC), chronic prostatitis, and urinary incontinence (UI), among other conditions. NIDDK initiated several treatment networks—including the Urinary Incontinence Treatment Network, Interstitial Cystitis Clinical Research Network, and the Chronic Prostatitis Collaborative Research Network—to address these chronic, costly, and consequential conditions. For example, UI is a common condition that leads to an increased rate of falls and nursing home admissions. LUTS is associated with obesity, as well as with decreased physical activity and work productivity. All of these conditions lack curative treatments.

In the past 5 years, realizing that the understanding of lower urinary tract (LUT) conditions was incomplete, the NIDDK initiated two research networks: the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) and Lower Urinary Tract Dysfunction Research Network (LURN). The goal of LURN is to determine whether the right tools existed to define the phenotype of LUTS patients and better understand the factors contributing to symptom development, as well as to develop improved treatment strategies.

Dr. Rodgers noted that Dr. Bavendam's vision of bladder health and prevention has been quickly embraced at the NIDDK since her hiring 1.5 years ago. The NIDDK had invested in prevention efforts for diabetes and obesity, so it was not a new concept for the Institute. The Program To Reduce Incontinence by Diet and Exercise (PRIDE) study, funded by the NIDDK, demonstrated that even modest weight loss can reduce UI. Without reasonable evidence, the treatment and prevention of LUTS will not be prioritized by the U.S. Preventive Services Task Force or healthcare systems. Where feasible, prevention efforts (including early identification and self-management) are more desirable than treatment. Dr. Rodgers announced that he has approved a new network for the **Prevention of Lower Urinary tract Symptoms (PLUS)**, which will be initiated in 2015. The discussions over the next two days will inform the design of the network and upcoming request for applications (RFA).

The bladder has not received the respect it deserves, Dr. Rodgers asserted, and he noted that the attendees are present to help change that fact. He thanked both the planning committee and Dr. Bavendam for their efforts and said that he was looking forward to the participants' input.

SESSION 1: FRAMING WOMEN'S UROLOGIC RESEARCH

Bladder Health—Entrée to LUTS Prevention

Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD

Dr. Bavendam remarked that this meeting is not a typical State-of-the-Science symposium. The meeting is about breaking down boundaries in our thinking about bladder function and dysfunction to expand the population of interest. We need to move from the usual randomized controlled treatment (RCT) trials to other kinds of research for this expanded NIDDK research direction for the Women's Urologic Health Program. The vision is to preserve and improve bladder health for women, which includes prevention. As Dr. Rodgers explained, NIH—including the NIDDK, Office of Research on Women's Health (ORWH), Eunice Kennedy Shriver National Institute of Child Health and Human Development, and National Institute on Aging (NIA)—is quite interested in this topic with plans to issue a Request for Applications/Funding Opportunity Announcement (FOA) soon. The NIDDK arranged this meeting to help us all understand what is known and not known in this area and give us suggestions on how to move forward. The NIDDK will take the output from this meeting into account when writing the RFA/FOA.

Dr. Bavendam clarified that the intent of the Workshop is to keep the discussion at a high level without getting too concerned about the exactness of terminology. The path to prevention for any condition is long, and we are behind other health conditions. We can borrow from what others have learned and hopefully shorten our path.

During the past several decades, we—the professionals who care most about women with LUTS—have obtained data and made the case that UI and overactive bladder (OAB) are quality-of-life (QOL) conditions. By accepting them as QOL conditions, we unknowingly have helped to keep them marginalized with respect to science and clinical care. It is important for us as the clinicians and scientists interested in women's urologic health to broadly raise society's awareness of the importance of a healthy bladder to overall health. While LUTS do have significant QOL impact, we cannot be comfortable having them defined as QOL condition(s), and we need to stop referring to LUTS as such. Instead, we must reframe LUTS as important medical conditions with broad impact. There are data to position LUTS as a barrier to the management of priority medical conditions, and we need to strengthen these data so that we can be more competitive for research funds and make it important for clinicians to proactively identify LUTS in their female patients with obesity, diabetes, depression, and so forth.

Dr. Bavendam explained that for the purposes of this Workshop, the term bladder applied to the bladder, urethra, and pelvic floor support. She used the terms bladder symptoms/conditions interchangeably during the presentation unless she was referring to a specific diagnosis. LUTS was defined broadly; originally, it was coined to describe the symptoms associated with benign prostatic hyperplasia (BPH) after it was recognized that BPH was not always the underlying cause of symptoms in men. However, the symptoms of LUTS are not gender-specific. The symptoms are divided into storage, voiding, and post-micturition. Women most commonly seek care for storage symptoms, either incontinence or OAB. While the symptoms associated with the definition of LUTS include frequent nocturnal urination (nocturia), frequent daytime urination, urgent urination, urgency urinary incontinence (UUI), and stress urinary incontinence (SUI), they are not the only symptoms associated with LUT function for which patients seek care. Pain can be associated with bladder filling, bladder emptying, or after emptying; this is absent from the definition of LUTS. The NIDDK includes pain in its broad view of LUTS, as pain coexists with other symptoms. Typically, any discussion of sensory issues with the bladder includes only urgency—early or too much sensation of bladder filling. Largely because patients rarely complain of diminished bladder sensation or infrequent need to urinate, these symptoms are not on any of our current

patient-reported outcome tools. This is unfortunate, because these symptoms could be early manifestations of a LUT that is abnormally innervated. The LURN currently is incorporating the concepts of decreased sensation and infrequent urination into its qualitative work on development of the LURN battery of questions for comprehensive assessment of LUTS.

LUTS are associated with clinical diagnoses including bladder cancer, urinary tract infection (UTI), Bladder Pain Syndrome/IC, and UI—and there exists overlap of symptoms between the conditions. Diagnoses of the benign conditions are based on symptoms alone with the exception of UTI which can be diagnosed with an objective test (urine culture). A positive urine culture, however, is not always associated with an infection, and classic symptoms for infection are not always associated with a positive culture. Dr. Bavendam noted that bladder cancer is not a benign condition and will not be directly targeted in this LUTS prevention effort; however because LUTS might be the only manifestation of early cancer, and because there are common risk factors (e.g., cigarette smoking), it needs to be a part of healthy bladder messaging.

Dr. Bavendam asserted that it is reasonable to start this bladder health/LUTS prevention research effort with a hypothesis that there are healthy bladder habits and behaviors that play a role in the prevention of all of the conditions, which metaphorically relate to the trunk (representing common healthy behaviors). Different types of trees have different branching patterns (representing the various LUTS conditions). Until we start looking at symptoms and conditions inclusively, we will not know where the branching begins—for example, where there are prevention activities specific to one condition. She remarked that we need to start with a broad view so that we are not missing the possibility that efforts to prevent SUI, may also prevent recurrent UTI, and so forth.

There are many challenges on the path to prevention, including a lack of correlation between symptoms and dysfunction, symptoms that are not unique to clinical diagnoses, lack of objective measures for symptoms, and lack of an easily measurable outcome for successful prevention. Additionally, LUTS are understood only from the perspective of those most severely impacted and are not prioritized by women or primary care physicians (PCPs), relatively few epidemiologists are interested in LUTS, symptoms are not unique to clinical diagnoses, and the public health and prevention fields do not think of LUTS as public health issues with prevention potential. These challenges can be met only if we make a conscious and consistent effort to tear down the silos that exist in our clinical diagnosis, our clinical and research scientists, and our funding bodies.

Dr. Bavendam described the journey to get to this meeting, which began in February 2013. Three key Women's Urology Meetings occurred, thanks to the contribution of numerous planning committee members. Dr. Bavendam also expressed appreciation for the support of key individuals in many NIH Institutes and Centers, as well as the U.S. Department of Health and Human Services (HHS) Office on Women's Health, who participated on the Urology Interagency Coordinating Committee: Women's Urology Group. There are now enough women "of a certain age" in positions of power who recognize the importance of LUTS prevention. Without their support over the past 18 months, this Workshop would not have been possible.

Dr. Bavendam reviewed the Workshop agenda. She noted that the room was set up in round tables to facilitate discussion and that the agenda has allowed as much time for breaks as possible to provide opportunity for interaction. She asked participants to take time at the end of the day to visit the research posters. Dr. Bavendam explained that Day 1 of the Workshop will focus on the "big picture," including talks from many perspectives that would be helpful in getting started on the path to prevention of LUTS, borrowing from what has been learned in other conditions when possible. The speakers were challenged to think outside of the box—the absence of evidence does not mean something is not true; often, it means that we have not yet asked the right question. Day 2 of the Workshop will focus on the LUT. Eight speakers will each address one of the many factors that might contribute to bladder health and LUTS. The speakers were asked to be evidence-based when possible, and also to present what they think but cannot yet support with evidence. Following the presentations, two breakout sessions will pull together each

participant's experience and what was learned at the Workshop, identifying gaps in the evidence and what evidence is first needed. Finally, the attendees will work on detailing key aspects of a LUTS Prevention research agenda.

Meeting deliverables include a prioritized list of research needs for factors associated with normal or healthy bladder function and the identification of behavioral and other risk factors for LUTS. The summaries from the four breakout groups will include a survey of what women know and do (about their bladders), a stakeholder assessment (building support for LUTS prevention), what can be done now (with the evidence that we have), and identification of clinical studies needed to address evidence gaps.

Dr. Bavendam clarified that "bladder health" is defined as the actions a person can take to promote normal bladder function (that will not have a negative impact on their lives). To take any action, a person must know about it. Understanding the actions that contribute to healthy or normal bladder function is an important aspect of prevention. On the other hand, knowledge alone is not sufficient, and our research should uncover ways to encourage women to initiate (and continue) preventive action.

Dr. Bavendam presented a conceptual slide to explain the shift in emphasis from treatment to prevention from a population perspective. The concept begins with an assumption that half of the population has LUTS and half does not have LUTS. Among the half of the population that does not have LUTS, some will have decent bladder behaviors/habits, and some will have adopted behaviors that are not healthy (e.g., restricted fluids to avoid using public restrooms, high caffeine intake, cigarette smoking, straining to have bowel movement, etc.). These individuals have no idea that any of these behaviors may be problematic for their bladder function in the short or long term. Among the population that does have LUTS, some have LUTS with a normal LUT (e.g., they drink too many fluids, causing either daytime frequency or too much urine production at night, causing nocturia). Some will have LUTS that might be intermittent and not yet severe enough to be recognized as a problem (i.e., early lower urinary tract dysfunction [LUTD]) and others have sought care for their symptoms (i.e., advanced LUTD). The advanced LUTD population serves as our current research population.

Of these populations, the two that make the most sense to target for prevention are those that are engaging in behaviors that may contribute to future LUTS, and those that have early LUTD, but the symptoms have not caused enough problems for the individual to seek care. However, these are not populations that we understand well, because we do not see them in practice or widely understand that there are risk factors for LUTS. Women's biologic reproductive capacity brings unique risks. The focus has been on trying to perfect our treatment options— primarily surgical—without wondering if all women are at equal risk for problems.

The vast majority of research has been from the perspective of caring for a very small part of the affected population. The interventions that are being tried for primary and secondary prevention are based on treatments for the most severely affected population; this is not the only perspective that is needed to fully develop bladder health and LUTS prevention; an evolution from treatment to prevention is required. Dr. Bavendam presented a metaphor of a tulip for the frame of reference for understanding LUTS. She showed a picture of the inside of a tulip, which represents the current frame of reference for understanding of LUTS. She noted, however, that it is hard to understand the whole tulip by looking only at one aspect of it. She asserted that we need to expand our frame of reference for our prevention research, which corresponds to a view of almost the whole tulip. Next, she presented a picture depicting the tulip and some of the environment around the tulip, which represents an entirely different frame of reference—closer to where we need to be.

As we adopt a broader perspective representing the full field of tulips, we may find different ways of thinking about mechanistic studies. Currently, questions are framed based on the perspective of the women seeking treatment, who typically present advanced symptoms. How do normal or minimally affected women progress? As we get to a very broad frame of reference being inclusive of all LUTS in a very broad environment, it starts to feel overwhelming, but it does not have to be. Dr. Bavendam

reminded the participants that our focus should not be the branches and the twigs: We want to define the trunk first.

We already have talked about being inclusive of all LUTS and conditions, and now we need to discuss being inclusive of the entire lifespan. For prevention, we have to consider that what happens early in life may be a manifestation of underlying risk or that unhealthy behaviors adopted early on may contribute to problems later in life. Dr. Bavendam presented a slide representing a conceptual framework for the challenges during a female's lifespan, with known and possible mechanisms and opportunities for prevention. She noted that this Workshop is not the first effort in the realm of LUTS prevention, but it is the first meeting associated with funds to start a research initiative. Twenty years ago, the Simon Foundation sponsored the first International Conference for the Prevention of Incontinence. There has been a fair amount of research about the prevention of UTI, as it is easier to study bacteria than a symptom. The availability of cranberry juice or extract as a possible prevention intervention represents a fair amount of the research. The payer interest in preventing catheter-associated infections and concerns about antibiotic-resistant bacteria also have helped this area of research.

In 2007, the NIH sponsored a State-of-the-Science forum in Prevention of Urinary and Fecal Incontinence, and a consensus statement developed by a multidisciplinary group of U.S. experts was published in 2011. In the consensus about bladder health, the experts identified many causes and contributing factors for a healthy bladder (e.g., education, anatomy, behavior, society, environment, and development). There was more evidence about some factors than others, but nonetheless, it was felt that none of these aspects could be ignored. The consensus recommendations included the consumption of an adequate amount of liquid (24–30 ml/kg/day, which is the amount needed to empty the bladder every 3–4 hours), consumption of foods or beverages known to irritate the bladder in moderation, adoption of a relaxed position for urination, use of self-management practices to maintain bladder health, and the avoidance of constipation, obesity, and smoking. They agreed that there is enough evidence to support encouraging these behaviors to promote and maintain bladder health; these behaviors are likely consistent with what many of the participants recommend to their patients as a part of LUTS treatment.

Dr. Bavendam commented that she has practiced in Seattle, WA, and Philadelphia, PA. In Seattle, she encountered what most urologists would consider the “worst of the worst” problems. The women had already tried every medication and had multiple surgeries; thus, they were not interested in what she had been trained to do. As she struggled to help them, what she found is that although they had had undergone plenty of procedures, they really had no understanding of their bodies, their bladders, or what they could/should expect from the treatments. So she started with the basics, teaching women about their bodies and what modifiable behaviors might be contributing to their symptoms. The hardest questions for her to answer were: Why didn't anyone ever tell me any of this before? Why didn't I know that a vaginal delivery could cause bladder problems? Dr. Bavendam stated that she now is in a position to help change that situation. Women need to know the basics, but first there must be an appropriate understanding of what “normal” is and what behaviors are important to being normal. We have ideas based on working backwards from severe dysfunction, but we need to take a fresh look and develop an appropriate level of evidence to support public education initiatives, and we need to improve the education for all levels and types of health care professionals and patients.

With only limited resources, we need to not get overzealous about the evidence we need to move this forward. If we believed that elective Cesarean-section (C-section) was the key to LUTS prevention, we would need a very high level of evidence. Do we need the same high level of evidence to make recommendations about staying adequately hydrated, voiding every 3–4 hours, and assuming a relaxed position to help empty the bladder? Once defined, healthy bladder habits alone might be enough to prevent some LUTS (e.g., daytime frequency or nocturia)—particularly if there are no underlying abnormalities to LUT function. To prevent LUTS, we need to start by ensuring that we know what healthy/normal bladder function is and what behaviors support normal function, and we need to increase our understanding of risk factors for LUTS and LUTD. Only then will we have the foundation that is needed to begin testing LUTS prevention interventions.

Dr. Bavendam emphasized that the NIH—including the NIDDK, ORWH, and others—is interested in this topic, and a formal announcement will be issued within a few months. She said that NIDDK staff are looking forward to the discussions. We are doing this so that all young girls will be armed with information to help them make choices that can help mitigate their risk for having their lives compromised by LUTS.

Women’s Urologic Health Is a Public Health Concern

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

Dr. Hebert-Beirne discussed the public health perspective of LUTS in U.S. females. She explained that LUTS/LUTD is defined by the presence of any one or more of the following symptoms: SUI, UUI, chronic UTIs, chronic pelvic pain, or nocturia. Commonly, what she hears from sufferers is that “something is not right down there.” From a public-health perspective, Dr. Hebert-Beirne is interested in how LUTS affects the QOL of communities.

The traditional determination of public health impact considers severity and prevalence. LUTS typically is considered a high-prevalence but low-severity condition, and therefore of potential concern. The focus on volume and degree of condition, however, obscures the significance. The legendary coping skills of women lead to limited epidemiological evidence due to few healthcare visits and underreporting to public health surveillance systems. Furthermore, the sociocultural stigma of LUTS affects healthcare-seeking behavior and coping mechanisms (e.g., use of menstrual pads), absence from health surveys, and underreporting of symptoms. Health care providers tend to be unaware of and uncomfortable with addressing LUTS.

Public health uses a socioecological model, looking at multiple levels of influence, to consider the impact of conditions from policy, community, organizational, interpersonal, and individual perspectives. It is known that LUTS is common, increases with age, occurs with comorbid conditions, and exhibits disparate impacts on various populations. At least one in three women complains of LUTS, 65 percent of women over 60 years of age have bladder control problems, one-quarter of women with UI experience fecal incontinence. Based on population growth and estimated prevalence, LUTS is expected to affect more than 43 million women over next 30 years, and 6 million women already seek care for pelvic pain.

At an individual level, women with LUTS report decreased social and physical activity, as well as increased depression, interrupted sleep, and increased risk of falls. Research shows that women do not know much about their pelvic area and exhibit behaviors that might contribute to LUTS (e.g., voiding, coping, and health-seeking behaviors). At an interpersonal level, the family and social network influence the impact of LUTS prevention and risk. Women report shame and embarrassment as barriers to seeking care; they tend not to talk to family and friends about these conditions and are unaware of the continuum of options ranging from basic care to surgery. At an organizational and community level, an individual’s work and school settings control voiding behaviors. The media contributes through the normalization of LUTD (protective pads) and stigma of voiding behaviors. At a policy level, the health care system is organized around treatment, not prevention, and research funding emphasizes treatment. LUTS is expensive at a society, community, and family level; associated health care costs total more than \$26 billion.

The socioecological model is used to identify high-risk groups, including older adults, adolescents, pregnant and postpartum women, Muslim women, racial/ethnic minority groups, women with low health literacy, and those in high-risk occupations. Relevant social determinants of health—complex, integrated social and economic systems responsible for most health inequities—include stress, early childhood development, social exclusion and support, unemployment, access to healthy food, and education. Despite the challenges, incorporating LUTS into public health messages provides opportunities for building early

health education and literacy. Attention must be paid to special population groups (e.g., Muslim women), and considering the role of context (e.g., workplace and school situations) in facilitating healthier behaviors must be considered.

Is Prevention Important to Women?

Missy Lavender, M.B.A., Women's Health Foundation (WHF), Chicago, IL

Ms. Lavender, Executive Director of WHF, explained that the Foundation was established in 2004 to advocate for robust research, collect information, and disseminate knowledge about women's issues. It is notoriously difficult to focus on prevention: Prevention is invisible (if successful, no condition develops), undramatic (potentially less interesting), persistent (must always happen), and may conflict with cultural and religious beliefs. Successful prevention campaigns (e.g., smoking cessation for teenagers) apply several common elements: multimedia approaches, sustained messages, application of fear, use of celebrities, and engagement of influencers.

WHF has shifted its focus away from specific conditions to address the promotion of pelvic health overall. Knowledge is power, and teaching women about their bodies is empowering. Action is key: WHF focuses on small steps to get women the right care faster. Persistence matters, and perceptions need to change. For example, it is culturally acceptable to talk about breast and bone health—similarly, it should be acceptable to discuss bladder health. WHF creates a community to bring women together—through mechanisms such as fitness initiatives and senior programs—to adopt its messages. The messages are designed to be organic, easy to understand, put into practice, and ignite dialogue by creating conversations that are fun. For example, the WHF uses a “Be Fit, Be Sexy, Be in Control” marketing effort to empower women to take action. One effort, entitled “Sex, Chocolate, and Your Pelvic Floor,” inserted medical conversations into a “girlfriend” discussion. WHF also appreciates health campaigns, such as Michelle Obama's Let's Move campaign or other general healthy lifestyle campaigns.

WHF convenes consumers, providers, public health officials, industry, advocacy, research, and fitness experts to generate engaging and empowering educational opportunities. WHF wish list includes the incorporation of pelvic health into middle and high school health curricula, full insurance coverage of physical therapy, and wide use of pelvic floor physical therapists and experts in bladder and pelvic floor disorders. WHF also promotes better screening for fibroids and the addition of pelvic health questions in annual screening. Women always are encouraged to discuss their symptoms with a doctor or nurse. The overarching goal of WHF is to empower women to strive for pelvic health and engage in prevention efforts to accomplish that objective.

Discussion

A participant asked about the opportunity related to familial conditions, as educating one patient can help additional family members. Ms. Lavender explained that the strategy of the WHF is to provide information that can flow “upstream.” For example, the WHF is developing a “board book” about potty training that will be read to a young girl by her mother, thus educating two women about healthy urinary habits. Ms. Lavender acknowledged that understanding the genetic contribution to the conditions is important; had she known the risk factors, she might have chosen a different path for her own health. Dr. Hebert-Beirne agreed that the opportunity for sharing information within the mother-daughter dyad is huge, as women tend to promote healthy behaviors for their kin. In her work with a Mexican-American community in Chicago, the topic of bladder and bowel health is “sneaked” into other conversations. Since women make 80% of the health care decisions for the family, empowering the woman has an automatic “trickle-down effect.”

An attendee asked how curriculum change can be implemented at the middle and high-school level, which can be a challenge. Ms. Lavender replied that the WHF is an approved vendor for the Illinois Coalition of Public Health and school system because it promotes an uncontroversial message—bladder

and bowel health and hygiene are important, but not contentious, topics. She acknowledged that accomplishing curriculum changes at any level is difficult, but conveying the message of bladder health is important to reduce healthcare costs. Dr. Hebert-Beirne added that the unfortunate proximity of the bladder to the vagina does create barriers to discussing bladder health. Time is another issue—the pilot program replaced gym and health classes in the school. Top-down mandates are important to shape the healthcare-seeking behavior of young girls.

The participants discussed the use of menstrual pads instead of incontinence pads as a coping mechanism for UI. Dr. Bavendam explained that, conceptually, constantly wearing a pad might increase the risk of bacterial infections and, anecdotally, replacing menstrual pads with incontinence pads helps in some cases. The fibers in menstrual pads are designed to absorb blood, and chronic use of menstrual pads might increase the risk of dermatitis and vaginitis because moisture is not pulled away from the body. A different participant asserted that a new polymer in menstrual pads does whisk the blood away from the surface. Another attendee stated that case-control studies found no association with menstrual pads and the risk of UTIs.

In response to a question, Dr. Bavendam explained that bladder health questions are not presented systematically when women receive annual checkups with their PCPs. Some individual practitioners may insert relevant questions into their own questionnaires.

A participant noted that school nurses do not have enough time to educate students about bladder health, given the need to discuss such topics as smoking cessation and sexual education. Female sport coaches, however, tend to be receptive to providing this education (e.g., ensuring that young women understand which pelvic floor muscle group to exercise). Focusing efforts to empower coaches will be beneficial, especially as the prevalence of UI increases in high-impact sports. Ms. Lavender noted that as the assistant trainer for Girls on the Run, she discussed pelvic floor exercises. Many women athletes leak urine. Ms. Lavender agreed on the importance of educating other “megaphones,” such as coaches and community health workers. The entire bladder health curriculum does not need to be delivered; relevant tools and information can be provided to women who are being educated about prediabetes, senior health, or other related topics. Tracking the outcomes of these educational programs is difficult, but important.

An attendee commented that messages can be extended beyond an individual by addressing the family. Saudi Arabian members of the International Urogynecological Association have indicated that educating younger women results in reaching their mothers and grandmothers as well with the messages.

Mr. Shields asked the speakers to comment on examples of successful campaigns. Dr. Hebert-Beirne noted that in the curriculum for middle and high school youth, one homework assignment is for the student to ask her mother and grandmother about experiences with menstruation. That conversation sets the stage to later discuss issues of incontinence. As young women are empowered to take better care of their bodies, they can influence older members of their family. Ms. Lavender noted that focus groups of Hispanic and African American women illuminated the cultural difficulty of sharing experiences related to UI. Younger women tend to be more open to sharing; older Latinas were the most resistant to discussion bladder health. She asserted that social media efforts warrant time and effort. For example, the “blue waffle” campaign was highly effective. Girls are comfortable talking about their periods, and it would be great to get them excited about bladder health as well.

A participant remarked that teaching adolescents about bladder health—including topics of frequency, urgency, and pain—is important, but often the young women cannot practice what is taught (e.g., they cannot urinate during the school day). Dr. Bavendam acknowledged that many students do not urinate during the day due to limited time, safety concerns, or lack of restroom cleanliness. This behavior likely contributes to future UI, but evidence is needed to convince school administrators to improve the situation. Dr. Amanda Clark added that teachers often are urogynecological patients, and they also cannot visit the restroom during the day. Ms. Lavender reiterated that messages of bladder health must be woven

into sexual education and other subjects. She noted that her own daughter experienced recurrent UTIs and now practices healthy bladder habits to avoid the painful UTIs.

An audience member commented that the level of bladder health literacy within the American population is low. Americans do not know how much water they should drink, for example. Creating a curriculum requires a foundation of basic facts. Dr. Bavendam agreed that it was a good place to start; sufficient evidence is required to identify and promote healthy behaviors.

An attendee noted that prolapse and mesh slings are examples of overmedicalization of pelvic-floor disorders. She commented on the importance of balancing public awareness and prevention with overmedicalization. Dr. Bavendam acknowledged that it was a great concept.

In response to a question about the WHF curriculum, Ms. Lavender explained that the pilot curriculum was conducted in three urban high schools and the manuscript is awaiting publication. The curriculum, will hopefully be applied more broadly in the future. A version of the training may be provided to community health workers in collaboration with the Illinois Coalition for Public Health.

A participant relayed the challenge of female military personnel being unable to urinate for up to 15 hours during the day for months at a time because of safety concerns. Dr. Bavendam referenced a recent publication addressing LUTS in women recently separated from military service (Bradley et. al). She agreed that it is an important population to study.

SESSION 2: PREVENTION AND EPIDEMIOLOGY

Basics of Prevention Research

Denise Simons-Morton, M.D., Ph.D., M.P.H., Morton Consulting, Bethesda, MD

Dr. Simons-Morton provided examples from the cardiovascular disease (CVD) field as a model for studying the natural history of disease and levels of prevention. She noted that there is a lot to study, and not every topic can be studied at once. The natural history of disease progresses from birth to death, from no risk factors to risk factors, to clinical disease. Levels of prevention along the path include primordial prevention of risk factors, primary prevention to treat risk factors and prevent disease, and secondary prevention to identify and treat disease early.

Dr. Simons-Morton covered some basic concepts used in this research field. Confounders are factors or characteristics associated with the outcome and exposure of interest, but it is not clear whether that factor or the exposure caused the outcome. An example is the relationship between age, high blood pressure, and stroke. Older people experience more strokes as well as higher blood pressure, and people with high blood pressure have more strokes. By controlling for age in the analyses or study design, it is possible to evaluate whether high blood pressure is associated with strokes. Causality is evidence that an exposure or intervention causes a chronic disease or outcome. Several elements are not dependent on study design, including biologic plausibility and consistency of findings. Types of evidence that are dependent on the study design include strength of association, biological gradient (e.g., dose-response relationship), temporality (e.g., the cause precedes the effect), specificity of association (e.g., control for confounders), and experimental evidence. The availability of these types of evidence varies between observational studies (case-control and cohort studies) and RCTs. For example, in an RCT, the intervention is the exposure, and confounding is controlled through randomization. Sufficient evidence from observational studies is needed to warrant conducting RCTs, which provide the highest level of evidence but are difficult and expensive.

Dr. Simons-Morton described basic features of case-control studies, observational cohort studies, and RCTs. A case-control study analyzes past (or current) exposures compared in people with and without the disease. It is important to evaluate exposures that occur prior to the disease, and potential confounders are

controlled by matching and in the analysis. Exposure level or prevalence is compared in cases versus controls.

The purpose of an observational cohort study is to identify factors associated with disease onset. After eligibility, naturally occurring exposure to the factor of interest is measured, and the outcomes are compared in groups of exposed versus not exposed. The groups differ in many characteristics that might influence the outcomes, which are controlled for in the analyses.

The purpose of an RCT is to test the effects of an intervention and provide experimental evidence of causality. Eligible participants are assigned randomly to intervention or control groups; the design controls for confounding. Interventions are delivered and outcomes are compared between groups. An intention to treat analysis is necessary for this type of study to assure that the groups being compared are similar in all characteristics except the intervention. Importantly, random assignment is not the same as random selection.

A research question for a RCT must include four components: Population, intervention or exposure control group or comparison, and outcome. An example research question would be to investigate in pregnant women whether episiotomy is associated with future SUI. For example, a case-control study could investigate the rate of prior episiotomies in women with SUI compared with no SUI.

Dr. Simons-Morton described several cohort studies that helped inform CVD prevention efforts. The Framingham Heart Study, which is still ongoing, was initiated by the National Heart, Lung, and Blood Institute (NHLBI) in 1948. This study identified high blood pressure, blood cholesterol, obesity, smoking, diabetes, and physical inactivity as risk factors for CVD. Other studies followed a similar model in various population groups, including the Jackson Heart Study in African Americans. RCTs addressing hypertension include the Hypertension Detection and Follow-up Program, Action to Control Cardiovascular Risk in Diabetes (ACCORD), and the Dietary Approaches to Stop Hypertension trials.

Studies of CVD have addressed many factors along the natural history disease progression to identify environmental influences and evaluate interventions. Along the efficacy-effectiveness continuum are efficacy RCTs, which are performed under ideal circumstances to deliver controlled interventions, and effectiveness studies performed under more typical circumstances with feasible interventions. The results from both types of trials, as well as observational epidemiological studies, inform the translation of research to medical practice.

Dr. Simons-Morton summarized that the natural history of disease is studied to determine causal relationships. Research questions ask about the effect of exposures or interventions on many outcomes. Observational studies provide some causal evidence and can develop hypotheses for experimental testing, and RCTs provide the highest level of evidence and, if designed to do so, can provide high generalizability to real-world settings.

Epidemiology Contribution to Understanding LUTS

Karin Coyne, Ph.D., M.P.H., Evidera, Inc., Bethesda, MD

Dr. Coyne emphasized that the strong need for integrated research includes preclinical research to confirm biological plausibility, RCTs, and population-based epidemiologic research. Also important is the consideration of the patients' voice to ensure that what is important to them is captured.

Epidemiology studies the distribution and determinants of health conditions or events among populations and the application of that study to control health problems. Causality is a factor (e.g., characteristic, behavior, or event) that directly influences the occurrence of a disease. Reducing such a factor among a population should reduce the occurrence of the disease. An association is the statistical relation between two or more events. Koch's postulates, articulated in 1890, laid the foundation for the study of temporal

relationships between multiple risk factors. LUTS, for example, are associated with major comorbidities, such as depression, decreased cognition and vision, diabetes, obesity, and CVD. Teasing apart the complex relationships is not easy, however, as LUTS can result in decreased physical activity and thus contribute to increased obesity, a major public health issue, it is important to get started.

Issues to consider when reviewing epidemiologic research in LUTS include the study design (e.g., cross-sectional, longitudinal, retrospective), method of data collection, questions asked and responses used, and statistical methods. Longitudinal studies can establish causality, but are costly and lengthy. Cross-sectional studies are relatively quick and can have large samples and are thus highly generalizable. They are useful for hypothesis generation, but they cannot be used to assess causality. Retrospective studies can interrogate large databases, such as claims data, to evaluate questions quickly with enhanced generalizability, however determining causality is not possible with such analyses.

Standard approaches for data collection include in-person visits, telephone interviewing, and Web-based surveys, each with benefits and drawbacks. The web-based Epidemiology of LUTS (EpiLUTS) study, for example, collected data from 20,000 individuals in 2 weeks. Framing the question is very important, as the way a question is asked can influence the response, and the responses offered can affect the results received. Providing a gradient of responses allows identification of subtle changes in disease remission that might go unnoticed with a binomial yes/no response.

Dr. Coyne described the differences in results from the EpiLUTS, EPIC and National Overactive Bladder Evaluation (NOBLE) studies that primarily investigated OAB. Discrepancies in the results, including OAB prevalence rates, were attributed to the method of data collection, questions asked, and response options provided.

A variety of statistical approaches for epidemiological data were discussed. Logistic regression with LUTS subgroups can be applied to find associations between comorbid conditions and LUTS variables, and multivariable odds ratios can be calculated to identify lifestyle factors that influence UI incidence. Other statistical approaches include cluster analysis, which sorts similar objects into groups, and latent class analysis, which is the categorical variable analog to factor analysis. As an example, cluster analysis of symptoms identified six groups of LUTS in the EPIC study.

Dr. Coyne advocated for thinking outside the box and considering additional methodologies to study LUTS prevention. Large databases are available for secondary data analyses, natural language processing can be applied to electronic health record (EHR) systems, and social media approaches (e.g., crowdsourcing, patient-based forums) are other options. Future directions from the Boston Area Community Health (BACH) survey include evaluating the relationship between LUTS and diet, obesity, depression, and CVD. Integrated research that includes all components (e.g., patient voice, population-based, and clinical research) is critical in designing a pathway to LUTS prevention.

Discussion

An audience member commented that LUTS is a collection of symptoms based on a patient's report. He asked for comments regarding strategies to link biology to symptoms. Dr. Coyne explained that the LURN network is designed to address that question by relating phenotypes to symptoms. LUTS is multifactorial and the symptoms cannot be related to a specific disease (e.g., UUI can be linked to OAB or other diseases). UTIs are well-defined by a high bacterial burden; other LUTS are not as distinctly defined. Dr. Bavendam agreed that there is a lot to learn, and hopefully the LURN will provide much-needed evidence.

A participant questioned whether society and industry are ready to fund the issue of LUTS and take it seriously. Heart disease is the number-one cause of death; by comparison, no one dies of LUTS. The participants heartily agreed that yes, society, industry, and individuals are ready to address the challenge of LUTS. Dr. Robert Star, Director of NIDDK's Division of Kidney, Urologic, and Hematologic Diseases

(KUH), declared that the NIDDK is ready to address LUTS; the purpose of this conference is to figure out the best way to address the topic. What studies are needed to build the evidence base required to design communications and messages and be translated into practice? He asserted that the purpose of the two epidemiological talks was to study how other fields addressed (at the time) intractable problems with a scientific approach.

In response to another question, Dr. Simons-Morton explained that the NIH embraced heart health with the initiation of the Framingham study at the NHLBI. All of the trial examples listed in her presentation were initiated at the NHLBI. She asserted that the NIDDK can provide the same leadership to the field of urology.

An audience member noted that although the CVD field has many observational studies and RCTs, few long-term, population-based observational studies and treatment RCTs exist in the field of urology. He solicited insight for identifying risk factors established in observational studies, given the cautionary note about relying on epidemiology studies for risk-factor evidence. Dr. Morton acknowledged that although RCTs provide the strongest level of evidence, action must be taken based on the best existing evidence while additional evidence is being generated. The Institute cannot wait for perfect evidence. Observational studies can be used to inform educational initiatives as additional evidence is being collected.

A participant noted that for years, IC was addressed by psychologists. In PubMed 20 years ago there were 50 articles about IC; now there are 2,500 publications, reflecting a tremendous growth in knowledge. Identification of urine biomarkers common to several inflammatory conditions (e.g., OAB and IC) is a current priority.

A participant observed that female leaders in elevated governmental positions can assist in promoting funding to address women's health issues. A multipronged effort is needed.

A question was raised by an audience member as to whether data collected through social media impart a bias. Dr. Coyne explained that social media techniques are employed for exploratory studies that generate new hypotheses and perspectives.

In response to a question, Dr. Morton clarified that obesity is related to cholesterol levels, particularly low-density lipoprotein.

A participant commented that frequency and presence of symptoms are measured, but the biological mechanisms underlying the symptoms are not assessed. She asserted that the bother associated with the symptoms drives treatment, and those data are not readily available. The LURN network studies might facilitate comprehensive, evidence-based prevention efforts. Dr. Coyne agreed and noted that the outcomes of prevention studies must be symptom-based because symptoms are reported. Dr. Bavendam reminded participants that the MAPP network addresses pelvic pain, and the LURN network is focused on the treatment of LUTS from a broader perspective.

SESSION 3: RESEARCH INSIGHTS

Urinary Incontinence (UI) Prevention Study

Ananias Diokno, M.D., Oakland University William Beaumont School of Medicine, Royal Oak, MI

Dr. Ananias Diokno discussed the Medical, Epidemiological, and Social Aspects of Aging (MESA) Prevention Study, which was funded by the NIA over a decade ago to study the prevalence of UI. The results of the study, published in 2004, indicated a baseline prevalence of 38 percent in women older than 60 years, with an annual incidence of 22 percent and annual remission of 11 percent. Previous research funded by the NIDDK had demonstrated that behavioral modification (e.g., pelvic-floor exercises) is effective in treating SUI, UUI, and mixed UI (MUI). Based on these studies, Dr. Diokno's research group

investigated the prevention of UI with a group behavioral modification program (BMP). The prospective RCT enrolled older women to determine whether a BMP provided to groups of ambulatory post-menopausal continent women 55 to 80 years old living in a community would reduce the incidence of UI, increase the strength of the pelvic floor muscles, and improve voiding control.

The group BMP provided two 1-hour sessions, including a 1-hour lecture on anatomy, physiology, innervation of bladder, fluid intake, voiding frequency, and types of UI. The second hour addressed healthy bladder habits, a discussion of the voiding diary, and instructions on pelvic muscle training. The outcome measures at baseline and quarterly for 1 year included a MESA Incontinence Questionnaire measuring the number of UI episodes; a 3-day voiding diary measuring UI episodes, type, and volume of urine loss, and a digital test for pelvic floor muscle strength. Phased mailings and geriatric program requests were used to recruit a total of 359 participants for the intent-to-treat protocol.

Following the training, the participants were quizzed to ensure they understood the lessons. At the end of 1 year, 37 percent of the treatment group exhibited absolute continence compared to 28 percent of the control group, while 56 percent of the treatment group experienced same or better continence compared to 41 percent of the control group. Results from the pelvic floor muscle strength testing indicated that 33 percent of the treatment group had increased the strength of the muscle. The voiding diary results indicated that the BMP group significantly reduced the UI episode frequency and increased the interval between voiding. The results of this study, which was the first prospective RCT of UI prevention among older women in the community, indicated that group BMP followed by brief follow-up instruction is effective in maintaining continence, improved pelvic muscle strength, and voiding control. Furthermore, BMP effects are durable for at least 12 months.

Dr. Diokno outlined several items for consideration for future preventive studies, including characteristics of the population to be studied (e.g., age, risk factors, predictors); the definition of continence/LUTS (e.g., frequency, quantity, QOL); and preventive measures assessed (e.g., public education, bladder health, bladder training, pelvic floor muscle exercise). Dr. Diokno relayed lessons learned concerning the recruitment strategy, choice of outcome measures, study cost, and need to establish consensus to standardize issues related to prevention.

Community-Based UI Research

Cara Tannenbaum, M.D., Université de Montréal, Montreal, QC

Dr. Cara Tannenbaum described the importance of conducting community research across the lifespan of women. Leakage in young female athletes (46%), postpartum women (21%), healthy mature women (35–50%), and nursing home residents (more than 50%) has important consequences for self-esteem, mental health, sexual function, and social engagement. The various populations should be targeted differently, through such mechanisms as well-baby programs and sports teams, to prevent geriatric issues.

Dr. Tannenbaum presented a case study of a 74-year-old woman who is depressed and isolated from social gatherings because of her fear of leakage. Importantly, this woman has not sought care. Her comorbid conditions are primarily reversible risk factors, including type 2 diabetes mellitus (T2DM; control blood sugar), venous insufficiency (wear elastic stockings to prevent leg swelling), and chronic pain due to osteoarthritis (physical therapy to increase mobility). Furthermore, her numerous medications could be influencing UI through such mechanisms as water retention and muscle relaxation. The woman's behavior, including consumption of three cups of tea per day and lack of pelvic floor muscle exercises, also influence her risk for UI.

A Canadian survey demonstrated that 47 percent of women ages 55–95 experience incontinence. Of those with urine leakage, the majority never sought treatment, considering it to be a “normal part of aging.” Secondary prevention efforts to target this population include interventions that detect and treat preclinical pathological changes and thereby control disease progression. Primary prevention, by contrast, seeks to prevent the onset of specific diseases, while tertiary prevention seeks to soften the impact caused by the disease on the patient's function, longevity, and QOL. Health education is key—practitioners think that education works, but evidence-based medicine and health care resource allocation now demands that it be proven effective. Education of patients like the woman in the case study is designed to increase knowledge and change beliefs about incontinence, causing the adoption of new behaviors to proactively address reversible risk factors for incontinence and/or seek care, which ultimately will result in improved health outcomes (e.g., reduced incontinence and depression, and increased social participation).

The research pipeline has six phases—discovery, feasibility, efficacy, effectiveness, implementation, and sustainability—that address specific questions ranging from safety to distribution. Dr. Tannenbaum described a Canadian community-based participatory research effort for LUTS that spans the research pipeline. The What Older Women Want health survey conducted in 2004 indicated the need for intervention. In the discovery phase, a community-based health education intervention on incontinence and an evidence-based self-management tool for incontinence were developed. The intervention was based on several behavioral theories. Constructivist learning theory addresses the erroneous belief that incontinence is a normal part of aging and something that patients learn to live with. The elicitation of cognitive dissonance (e.g., if a 98-year-old woman was cured of incontinence, then it can't be a normal and irreversible part of aging) is an effective technique. The health belief model applies perceived health threats to lead to behavior change. Fear and ego are two excellent motivators. Constructivist learning and cognitive dissonance work on the ego, while the health belief model works on fear. Components of successful self-management include the dissemination of evidence-based knowledge to help with decision making and active self-monitoring.

Two different theory-based educational interventions for incontinence were analyzed. The educational incontinence workshop applied constructivist learning to combat myths and provide information on etiology and treatment. This intervention was delivered in a 1-hour workshop. The evidence-based self-management intervention applied the theory of self-management in 1-hour group workshops with a customized self-management tool to empower women and address risk factors (e.g., weak pelvic floor muscles, obesity, fluids). The feasibility of the two interventions was assessed in the second phase of the research pipeline. A 2-hour interactive workshop demonstrated that after 6 months, 85 percent of the women had been mobilized to change their lifestyle behaviors or seek treatment. The evidence-based self-

management tool targets six risk factors (weak pelvic floor muscles, high caffeine intake, high body mass index [BMI], constipation, functional impairment, and smoking) and provides associated change strategies. Outcomes at 3 months demonstrated that incontinence was reduced by 50 percent, and 23 percent of women had addressed their body weight.

To determine which approach generated the greatest reduction in incontinence, the Continence Across Continents RCT was designed, with the control group receiving a lecture on other health issues. The hypothesis for this phase 3 efficacy trial was that group intervention combining education (knowledge) and self-management (skills) would be most effective in reducing symptoms of incontinence. A representative sample for the study was acquired by searching for community partners in the United Kingdom. Randomization occurred after enrollment, and incontinence was assessed with the Patient Global Impression of Improvement (PGI-I) scale at 3 months post-intervention. More than 65 percent of subjects in the combined intervention group experienced improvement, compared to 11 percent of the control group. The secondary outcomes were assessed to determine the extent of attitude and behavior change. Results indicated that beliefs were changed and risk-reducing behaviors were readily implemented, suggesting that it is relatively easy to activate women to take charge of their health.

Phase 4 of the research pipeline addresses effectiveness, and an international trial will determine whether the continence promotion intervention decreases stigma, falls, and dependency. These research studies continue to build stakeholder capacity to address implementation (phase 5) and sustainability (phase 6). Dr. Tannenbaum reiterated the take-home messages for LUTS prevention efforts: Women are ready, willing, and able to receive information on improving bladder health and act on it; interventional community-based research on LUTS in women is feasible and can be rigorously conducted; it is best to seek out a representative study population, rather than a “worried well, volunteer” population; and stakeholders are needed for implementation and sustainability.

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A Community-Engaged Research Approach to Reducing Obesity: Implications for Preventing and Treating UI

Carolyn M. Tucker, Ph.D., University of Florida, Gainesville, FL

Dr. Carolyn Tucker presented the results from studies suggesting that reducing obesity can help prevent and treat UI. Several studies have shown that obesity is an established independent risk factor for UI, and several weight-loss intervention studies have demonstrated that weight loss is associated with reductions in UI in women and men. The PRIDE Study (a randomized clinical trial study) found that overweight and obese women, who participated in a 6-month behavioral weight-loss intervention involving diet, exercise, and behavioral modification, found a 8-percent weight loss and a 47-percent reduction in UI episodes.

Shortcomings of studies linking obesity and other factors to UI in women include the absence or under-representation of racial/ethnic minority women as research participants, a lack of community engagement, and use of culturally insensitive research approaches. Intervention studies to prevent or treat UI have typically not included physicians as interventionists, and have not included a focus on provider cultural sensitivity. Studies targeting health-promoting behaviors associated with preventing and reducing obesity and/or UI have not assessed and addressed the motivators of and barriers to these behaviors.

Dr. Tucker provided justification for an approach to reducing obesity that is anchored in Health Self-Empowerment (HSE) Theory.^{1,2} HSE Theory asserts that health-smart (health promoting) behaviors (e.g., healthy eating and physical activity) are influenced by health motivation; health self-efficacy; health self-praise; health knowledge/responsibility; and coping skills for managing stress, anxiety, and depression—

which often are associated with overeating and reduction in physical activity. HSE Theory also asserts that health-smart behaviors influence primary health outcomes such as waist-to-hip-ratio and BMI, which in turn influence secondary outcomes such as blood pressure and levels of fasting blood glucose, cholesterol, and triglycerides.

Obesity and UI can be prevented and reduced by fostering health-smart behaviors, which are behaviors over which each individual has some control. Social and environmental variables linked to obesity (e.g., poverty, low education level, culture, and lack of access to healthy foods) are typically intractable; thus, individuals, families, and communities must be empowered to engage in health-smart behaviors under whatever conditions that exist in their lives.

Between 2011 and 2012, the prevalence of obesity in the U.S. was 35.1%.³ However, obesity prevalence differs by race/ethnicity and sex, both of which are associated with differences in socio-economic power. Specifically, for example, obesity is most prevalent among non-Hispanic black adults (47.8%) in general and non-Hispanic black women in particular (56.7%)—groups that have lower socio-economic power compared to non-Hispanic white adults. Thus, HSE Theory has potential for guiding research to prevent obesity and UI, particularly when this research includes non-Hispanic black women and other minority women.

The community-engaged research approach to reducing obesity led by Dr. Tucker is anchored in HSE Theory and is culturally sensitive and assessment based. This approach began with a focus group study involving African American, Hispanic/Latino, and non-Hispanic white adult and child community members for the purpose of identifying the motivators of and barriers to health-smart behaviors for each age group within each race/ethnicity.^{4,5} The focus groups included disproportionately high percentages of community members with low household incomes. The identified motivators and barriers from the focus groups were used to construct a pilot *Motivators of and Barriers to Health-Smart Behaviors Inventory* (MB-HSBI) for adults and an MB-HSBI for youth. A subsequent national study was conducted to finalize each inventory and assess its reliability and validity.^{6,7} Results of this national study concluded that the internal consistencies and the convergent, discriminant, and concurrent validity of both inventories are good. Both the final MB-HSBI for adults and the final MB-HSBI for youth are available in Spanish and English. These inventories can be used as pre-post assessments to evaluate the impact of any health promotion intervention that targets health-smart behaviors or as an assessment tool for “customizing” health promotion interventions for a particular individual, family, or community, thus making these interventions culturally sensitive.

HSE theory and identified common motivators of and barriers to health-smart behaviors were used to develop the 6-week Health-Smart Behavior (HSB) Program—an intervention to promote health and modify and prevent obesity. The HSB Program, which is delivered by trained community members called Health Empowerment Coaches, involves (a) structured assessment of each program participant’s motivators of and barriers to health-smart behaviors (such as choosing water rather than drinks containing sugar); (b) individual and family goal-setting based on the assessed motivators and barriers; (c) viewing and discussing segments of a Health-Smart DVD that features culturally diverse experts and lay community members sharing strategies for overcoming barriers to health-smart behaviors/lifestyles, (d) reviewing and discussing sections of a Health-Smart Resource Guide that features supplemental information and activities that parallel the Health-Smart DVD; (e) community-based physical activities led by community members; and (f) panels of health professionals who anonymously answer health and overweight/obesity-related questions from program participants. During the group discussions, program participants share (i.e., teach each other) health promoting strategies and participating parents are trained to be health promotion coaches for their children. Research to assess the effects of the HSB Program revealed statistically significant reductions in BMI and blood pressure and increases in healthy eating and physical activity.⁸

Dr. Tucker described several implications of her culturally sensitive, assessment-based, community-engaged research approach to reducing obesity for preventing UI in women. Specifically, research is

needed to assess the views of racial/ethnic minority, low-income, and other women with UI regarding the cognitive, emotional, physical, psychological, and other correlates of UI; the motivators of and barriers to discussing UI with providers; the motivators of and barriers to the behaviors/lifestyles that promote bladder health; the motivators of and barriers to engaging in UI prevention/intervention research; recommendations for preventing and overcoming UI; and desired culturally sensitive provider behaviors that promote women patients' comfort, trust, and feelings of being respected. Ideally, an assessment tool based on these assessed views of women with UI should be developed and used to obtain data to inform interventions to prevent UI in racial/ethnic minority women and other women. Research is needed to assess the independent effects that providers trained to be culturally sensitive have on their minority women patients' levels of comfort with discussing bladder health and with participating in provider-involved research and interventions to prevent UI. The HSB Program holds much potential for promoting bladder health and preventing UI among racial/ethnic minority women and other women at risk for UI (e.g., women diagnosed with obesity and/or diabetes). Racial/ethnic minority women and other women ideally should be trained to implement the HSB Program at health care sites and other community settings such as churches and YMCAs. Research is needed to assess the long-term effects of the HSB Program on UI prevention among women at risk for this condition. Finally, racial/ethnic minority women, women with low incomes, and other women who have experienced UI must be included as research partners in all aspects of this needed research, as these women are the "true experts" on preventing and treating UI among women racially and socioeconomically similar to themselves.

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Discussion

A participant commented on the importance of formalizing and prioritizing the primary risk factors. Dr. Bavendam agreed, and noted that prioritization would occur during the following day's breakout sessions.

In response to a question, Dr. Diokno said that it is currently voluntary for physicians to ask women ages 65 and older about UI symptoms. Starting next year, physicians will be penalized for failing to ask about LUTS and referring patients. It could become a question for all ages of patients.

A participant noted that the two interventions presented were conducted in older women. He asked if any studies existed to evaluate the effectiveness of interventions in younger women with regard to prevention of LUTS. Dr. Diokno explained that one study evaluated a behavioral modification program in pregnant women, but no existing studies address prevention in a younger population. Dr. Tannenbaum agreed that most of the studies have monitored prevention efforts, such as pelvic floor exercises, in pre- and postpartum women. Some studies have looked at middle-aged diabetic and obese populations. Social determinants and young children are popular topics in public health. It might be helpful to frame the NIDDK's LUTS campaign in terms of bed wetting, which has been associated with obesity. One idea is to perform an intervention to determine whether decreased obesity can reduce UI. Epidemiological studies are hypothesis-generating and important, but intervention studies must be conducted.

SESSION 4: GETTING STARTED

LUTS Risk Factors

Emily Lukacz, M.D., M.A.S., University of California, San Diego, La Jolla, CA

Dr. Emily Lukacz presented existing evidence for the biological risk factors for UI. She noted that the progression of LUTS encompasses elements of genetics (e.g., predisposition), exposures (e.g., vaginal delivery, obesity), and time. Understanding risk factors is important in helping women make informed decisions about behaviors, childbirth delivery methods, and so forth. It is important to study women who do and do not develop LUTS to understand the contributions to disease manifestation.

LUTS include urinary urgency, frequency, nocturia, hesitancy, dribbling, feeling of incomplete emptying, retention, slow flow; urinary incontinence (e.g., SUI, UUI, MUI, overflow, unconscious); UTIs (lower, recurrent, multidrug resistant); and IC/painful bladder syndrome (PBS; e.g., urgency, frequency, bladder pain, dysuria, dyspareunia). Of these symptoms, it is important to assess which are the most important to women.

Several studies have investigated the genetics of LUTS. Symptoms seem to cluster in families, and a genetic predisposition for a vitamin D receptor variant was identified in men. The Norwegian Epidemiology of Incontinence in the County of Nord-Trøndelag (EPINCONT) study, twin studies, and studies of connective tissue disorders identified genetic associations with UI. The association of race/ethnicity to LUTS was investigated in the BACH study, which demonstrated no differences. Several studies, including the Nurses' Health Study, uncovered a lower prevalence of UI in African Americans. The association of genetics and race/ethnicity to UTI and IC/PBS identified specific genetic variants and expression data that might be associated with the development of those conditions.

Increased urinary frequency is well-defined in pregnant women; frequency and nocturia increases with each trimester as a result of hormonal changes, and most symptoms resolve after delivery. UI occurs in up to 50 percent of pregnant women, with pregnancy symptoms predicting later UI. Several studies have examined the impact of the mode of delivery on SUI and UUI. The EPICONT study indicated an increased prevalence of SUI, but not UUI, with vaginal delivery. Pregnancy increases the risk of UTI, but might be protective of IC/PBS.

Association of a patient's medical history also must be considered in the development of LUTS. Obesity is the leading risk factor, as obese children are 1.9-fold more likely to experience symptoms of OAB. Prevalence of UI increases with increasing BMI, and weight loss results in decreases in SUI. Diabetes is associated with UI independent of obesity as well as UTIs, as bacteria thrive in a diabetic environment. Hysterectomies, chronic coughing, high-impact activities, and osteoporosis are also associated with the risk of developing UI.

The association of menopause to the development of LUTs is unclear. Up to 70 percent of women report an onset of UI with menopause, and post-menopausal oral hormone-replacement therapy increases the

risk of UI. Recurrent UTI increases with menopause, as decreases in vaginal estrogen result in an increased pH and higher coliform colonization.

Age is a clear risk factor for LUTS, but one that cannot be modified. Adjusted analyses suggest that age alone does not result in LUTS. Twenty percent of elderly women experience UTI, which comprise 5 percent of all emergency room visits. Causes might include menopause, comorbid conditions, or exposure to antibiotics. Twin studies suggest that IC/PBS decreases with age.

Dr. Lukacz presented several priorities for the prevention of LUTS. She asserted that it is important to define LUTS that are important to the patient and focus on preventing those conditions. Identifying women at risk through genotyping and phenotyping is a goal, and prevention efforts should be targeted to high-risk populations. It is important to prevent and treat obesity and other chronic illnesses. The UTI burden could be minimized by characterizing the normal urogenital host defense and identifying prevention strategies in high-risk populations.

Discussion

A participant noted that opposition exists to addressing the mode of delivery on UI symptoms. Many patients remark that they would have opted for a C-section had they known the risks, but many physicians consider C-section rates too high already. Dr. Lukacz noted that there have been several attempts to reduce the rate of C-sections. She suggested developing an online model to evaluate the risks, such as age and BMI. The patient can then make an informed decision regarding the percent risk of complication.

An attendee clarified that UTIs are associated with obesity in isolation from diabetes.

An audience member asked whether any of the identified risk factors warrant clinical trials. Dr. Lukacz asserted that a measurable, objective (or validated subjective) outcome measure is required. At this point, only UTIs meet this criterion. An important consideration for LUTS outcome measures is the importance to the patients. UTIs are the easiest topic to study, followed by UI for which several validated outcome measures exist. Patients at high risk of UI due to obesity or pregnancy would yield significant results. A participant countered that women self-manage LUTS through incontinence pads and fluid control. She asserted that these women, although they do not seek formal treatment by a physician, are bothered by their symptoms and should be treated.

Landmark Studies: Can They Inform?

Lisa Begg, Dr.P.H., R.N., Office on Women's Health, Washington, DC

Dr. Lisa Begg discussed several NIH studies that can inform the discussion of LUTS prevention, including the Women's Health Initiative (WHI; funded by the NHLBI), the Study of Women Across the Nation (SWAN; led by the NIA), and the Action for Health in Diabetes study (Look AHEAD; led by the NIDDK). Possible approaches to studying LUTS can be drawn from NHLBI cohort studies. The NHLBI has guidelines whereby new investigators can potentially develop manuscripts using the WHI data, and/or submit applications for ancillary studies. Data are available from questionnaires, laboratory tests, other clinical tests, adjudicated outcomes based on medical record review, and genetic analyses. Existing data includes some data elements related to incontinence and prolapse. Several cohort study databases (e.g., WHI, Framingham Heart Study, MESA) have been linked with Medicare claims data; urologic diagnosis and procedure codes would be available. There is also the possibility of adding questions to studies in the questionnaire-development phase.

Proposals for observational studies could include new questionnaire or laboratory analyses, and a medical record review of self-reported conditions could be considered. Proposals for pragmatic clinical trials could leverage the study infrastructure for recruitment and data collection. Large prevention trials involving interventions delivered by mail, phone, or Internet, could be considered.

The WHI collected self-reported data from 161,000 women ages 50–79. Limited analyses of self-reported UI and pelvic organ prolapse have been conducted. More than 27,000 women were randomized to estrogen-plus-progestin or estrogen-alone. Results indicated that self-reported UI was higher in the hormone therapy group than in the placebo group. After stopping hormone use, UI remained higher although it was slightly attenuated. The study is ongoing, and a post-intervention follow-up through September 2010 indicated that 81.1 percent of surviving subjects are still participating in the study. A WHI ancillary study assessed the effects of menopausal hormone therapy on the incidence and severity of symptoms of SUI, UUI, and MUI in healthy postmenopausal women.

SWAN is a multi-site longitudinal, epidemiologic study designed to examine the health of women, ages 40–55 at entry. The study is examining the physical, biological, psychological, and social changes during the menopausal transition and beyond. The study began in 1994, and 3,302 participants joined SWAN through seven designated research centers. SWAN participants represent five racial/ethnic groups and a variety of backgrounds and cultures. UI symptoms, including frequency and type, are assessed annually on self-administered questionnaires. Results indicate a prevalence of 47 percent monthly UI, comprised of SUI, UUI, and MUI. The incidence of UI was calculated as 11 percent monthly. UI prevalence was the highest in Caucasian women and lowest in Hispanic women.

The Look AHEAD and UI substudy were designed to compare, in overweight and obese persons with T2DM, the long-term health effects of an intensive lifestyle intervention designed to produce weight loss with a less intensive program of diabetes education and support delivered over up to 13.5 years. Weight loss intervention focused on reduction in calories, increase in physical activity, and behavioral modification. The study hypothesis investigated the incidence rate of the first post-randomization occurrence of a composite outcome—including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke—over 11.5 years in the lifestyle intervention compared to diabetes support and education. Overweight individuals with T2DM on any treatment were enrolled, and one-third of the subjects were minorities. The UI substudy indicated that moderate weight loss reduced the incidence, but did not improve the resolution rates of UI at 1 year among overweight/obese women with T2DM. Weight loss interventions should be considered for the prevention of UI in overweight/obese women with diabetes.

The WHI, SWAN, and Look AHEAD studies are just several resources that can inform the discussion of LUTS prevention. Exploring resources in existing databases provides a cost-efficient way to obtain new data.

Discussion

Dr. Lukacz asked what proportion of the original WHI and SWAN study populations would be available to study. Dr. Begg replied that approximately 81 percent of the WHI participants remain in the study. She agreed to investigate the matter and communicate the actual numbers to Dr. Lukacz. Dr. Begg noted that the NHLBI has set up an ancillary research system to leverage the larger studies. Ancillary studies to SWAN have not extended beyond the Principal Investigator network, but it is possible. While there is no longer a set-aside funding for SWAN, the study will compete for future funding. She said that she would defer to the NIDDK for information regarding Look AHEAD. Dr. Begg emphasized the importance of maximizing the benefit of existing resources, especially in this era of limited budgets.

In response to a question, Dr. Begg explained that the CDC's National Health and Nutrition Examination Survey (NHANES) is ongoing, and the published data are readily available on the Internet. The NHANES provides an excellent data set with nationally applicable results generated from strict statistical methods. She acknowledged the usefulness of HHS resources, such as the NHANES.

Dr. Roberts indicated that another database that could be mined for information is the National Ambulatory Medical Care Survey deployed by the National Center for Health Statistics.

Evidence We Need—New Thinking on New Knowledge

Richard Roberts, M.D., J.D., University of Wisconsin, Belleville, WI

Dr. Richard Roberts acknowledged that evidence can change the world and transform lives, as evident by Albert Einstein, Marie Curie, and Charles Drew. Although each made important contributions to science, not one of them is remembered for conducting a RCT. An iterative process exists between screening, diagnosis, treatment, clinical practice, performance measures, outcomes that matter to patients, evidence, and guidelines. Patient-oriented evidence that matters to individuals (e.g., death, disability, distress, dollars) differs from disease-oriented evidence (e.g., biometric measures, disease-specific mortality, significance, theories). Previous studies have indicated the perils of intermediate targets. For example, hormone replacement therapy reduces cholesterol but increases the death rate.

Dr. Roberts discussed how fields outside of health care deal with evidence. Law requires 100-percent certainty for a conviction beyond a reasonable doubt and 51-percent certainty for “a reasonable degree” in some trials. Engineering requires accuracy of six standard deviations, or less than 3.4 defects per million opportunities. By comparison, medicine applies a certainty of two standard deviations (i.e., $p < .05$) to conclude that a result is statistically significant. In the hierarchy of evidence, an individual randomized trial is the best, but it can be difficult to generalize from those studies. In descending rigor, evidence is generated from meta-analyses of RCTs, RCTs, systematic reviews of observational trials, observational studies, physiologic studies, and unsystematic clinical observations. RCTs provide a trade-off between efficacy and effectiveness as the trial size and treatment complexity increase.

A review of clinical evidence indicated that of 49 highly cited studies, 45 claimed that the intervention was effective. Sixteen percent of those studies, however, were contradicted by subsequent studies; 16 percent found effects stronger than those of subsequent studies; 44 percent were replicated; and 24 percent remain unchallenged. Dr. Roberts suggested that the current state-of-the-science included the wrong researchers, questions, subjects, settings, and answers. He noted that only the most symptomatic patients tend to be enrolled in academic studies; thus, these patients are not representative of the general population. Clinical trials tend to be commercially driven and results are generated in highly selected populations. The use of exclusion criteria in the selection of study subjects may improve the precision of the study's findings, but reduces its relevance given the sizable and growing proportion of people with multiple co-morbid conditions. It is important to reevaluate the current paradigm to ensure that studies reflect the general population.

The average PCP visit involves a discussion of three to eight issues on average. The total relative complexity, as well as complexity density, is the greatest in primary care. It is challenging to encourage PCPs to add more questions to a survey (e.g., for UI symptoms) because there are already so many questions being asked. Dr. Roberts noted that noncommunicable diseases are expected to comprise 73 percent of deaths in 2020, exceeding the communicable disease burden. The top four noncommunicable diseases are cancer, CVD, chronic respiratory disease, and diabetes. Dr. Roberts encouraged the community to consider how LUTS relates to these four conditions to attract the most funding. He also detailed the importance of considering the real-life impacts of an intervention, focusing on the outcomes that matter to patients. For example, the ACCORD study effectively reduced the levels of hemoglobin A1c (HbA1c), but the intensive glucose control resulted in a greater risk of death.

Old science is reductive, univariate, short-term, performed at academic health centers, and relies on RCTs and expert outcomes. New science utilizes “big data” efforts (e.g., EHRs) and is integrative, multivariate, complex, long-term, and practice-based (e.g., research networks). Comparative effectiveness research also is important. Ultimately, all elements of clinical care must be deliberated in planning a prevention effort, including policy, physician, and patient considerations. Evidence, context, and values all influence clinical judgment.

Discussion

A participant commented that Dr. Roberts presented a helpful framework, but there was similarity between data collection and customer surveys. Dr. Roberts clarified that some research questions are best answered by RCTs—they are necessary, not sufficient. Approximately 90 percent of physicians in the United States use EHRs, which provides a tremendous opportunity to mine the data set. “Big data” will not answer all questions, but the analysis can adjust for multiple comorbidities. Dr. Roberts encouraged the participants to keep their minds open, as future research programs are likely to be integrated, multi-institutional projects comprised of RCTs, as well as big data studies and community engagement efforts.

In Search of a Healthy Bladder

Carolyn Sampsel, Ph.D., R.N., National Institute of Nursing Research, NIH, Bethesda, MD

Dr. Carolyn Sampsel introduced the objectives of her talk, including a review of the impact of stigma associated with UI and other LUTS, a consideration of women’s treatment preferences, and guidance on plotting a pathway to LUTS prevention. Stigma is an attribute that discredits an individual, reducing him or her from a whole and usual person to a tainted, discounted one. Stigma of UI and LUTS is linked to depression, anxiety, strained relationships, low self-esteem, and poor body image, which can result in discomfort disclosing UI symptoms to a health care provider. The level of embarrassment is greater for UI than for cancer or depression, and fewer than 50 percent of individuals experiencing fecal incontinence or UI reported their symptoms to their health care providers without being prompted.

LUTS has a health disparity component. African American and Hispanic populations are more likely to perceive themselves as stigmatized and are more reluctant to seek help for a stigmatized condition. They experience a greater sense of shame and worry about what others might think. Regarding a difference in gender, the few studies that compare male and female difference in seeking treatment for LUTS indicate that men are more likely to seek treatment. Men and women are raised differently, which affects their comfort levels with seeking help. Dr. Sampsel explained that girls constantly receive messages about modesty and their body’s not being something to celebrate. When Georgia O’Keefe’s paintings of flowers drew criticism for resembling female genitalia, for example, her exhibit was banned in several locations despite having received critical acclaim. Because women receive messages about being uncomfortable with their bodies, they might perceive the treatment of LUTS as less valuable to society.

Consensus Panel Recommendations released in 2007 indicated that health care providers are well-positioned to initiate discussion about UI, including symptoms of frequency, volume, bother, and desire for treatment. Provider education about the issue is necessary, but not sufficient. Women must be alerted that LUTS are reportable information. The Public Health Initiative concluded that some medical conditions cause UI and can be treated, UI does not need to be part of aging, lifestyle changes and behavioral interventions can prevent UI in many cases, and it is important to discuss the symptoms with a health care provider.

Many women continue to use protective padding for UI rather than seek treatment. As pads are not a reimbursable expense, some low-income women use toilet paper instead. Pharmaceutical advertisements indicate adverse effects—such as dry mouth, nausea, and constipation—and surgical treatments can result in adverse outcomes such as perioperative complications and voiding difficulties. Surgical treatment should not be the first-line treatment. Dr. Sampsel recommended that treatment begin with the least invasive method with the lowest risk of adverse outcomes. In general, this means that behavioral approaches are followed by pharmacological and, ultimately, surgical approaches. Women express a preference for less invasive interventions that do not require medication or surgery. Telephone screening for the Translating Unique Learning for Incontinence Prevention (TULIP) study, for example, generated an overwhelmingly positive response.

Dr. Sampsel encouraged the participants to move beyond the usual way of thinking; many approaches beyond RCTs can be used to study LUTS prevention. The National Association for Continence demonstrated positive outcomes in spousal relationship quality when women practiced pelvic floor exercises. It is important to keep the interventions fun to increase adherence and facilitate beneficial results.

Dr. Sampsel described the history of the NIH's Clinical and Translational Science Awards (CTSA) initiative, which was designed to speed the translational trajectory so that discoveries move more rapidly into the mainstream, where they can benefit the health of the public. When Dr. Elias Zerhouni introduced the NIH Roadmap in 2003, he explained that in order to effectively address the complex health issues faced by our citizens, science needed to develop “new ways of combining skills and disciplines.” In 2010, NIH Director Dr. Francis Collins emphasized the need for multidisciplinary cooperation to advance health. Under his leadership, in 2012 the NIH established the National Center for Advancing Translational Sciences (NCATS) to further advance the goals of the CTSA. The Public Trust Initiative, established in 2004, influenced the CTSA commitment to community engagement with a goal of listening to and learning from the public while ensuring the public's access to and understanding of biomedical research. As of 2014, there are 62 funded CTSA sites across the country. As the participants discuss the pathway to LUTS prevention, consideration should be given to studies that will enhance the final translation of discoveries into real-world practice, including the adoption of health-promoting treatments and prevention prescriptions by clinicians and an uptake of prevention behavior by the public.

Dr. Sampsel emphasized the importance of ensuring community involvement in all phases of research. She presented several guidelines in developing a pathway to LUTS prevention: Design interventions that can easily scale up to permit delivery to more women. Partner with stakeholder communities to ensure development of accessible and acceptable interventions. Include cost and effectiveness for sustainability. Move expeditiously to pragmatic clinical trials to test real-world effectiveness.

Discussion

A participant noted that physicians face time constraints that limit their ability to promote behavioral interventions. Prescribing medicine is quick, but educating patients about diet or Kegel exercises takes much longer. She suggested that research efforts focus on how to protect the physician's time with the patients. Dr. Sampsel agreed, noting that behavioral interventions are not incorporated readily into clinical practice. The Gladiolus study is testing a group intervention with many patients together, and a DVD is being developed. The idea is that a clinician can provide the DVD during an annual exam when discussing the importance of preventative behavioral modifications. The patient can watch the DVD at home and then discuss any questions during the next visit. The DVD also could be accessible online for education efforts. Dr. Bavendam referenced Dr. Tannenbaum's self-care model that required no physician intervention. A participant noted that different practices place greater value on behavioral interventions, and she has helped many women with LUTS. She noted that the International Consultation on Incontinence (ICI) recommends that behavioral interventions be performed by a knowledgeable provider.

SESSION 5: CONTRIBUTORS TO HEALTHY BLADDER FUNCTION AND OR RISK FACTORS FOR LUTS

Anatomy

John DeLancey, M.D., University of Michigan Medical Center, Ann Arbor, MI

Dr. DeLancey provided an analogy of the symptoms of LUTS with the symptoms of "cough," both of which have a wide range of manifestations that can be attributed to multiple causes. It is important to understand the cause of LUTS symptoms related to the anatomy of the lower urinary tract. To illustrate, dysfunction in the bladder is primarily a storage problem, whereas problems in the urethra are generally structural problems related to voiding. Both the bladder and urethra have efferent and afferent components that must work in concert for proper functioning. The bladder has epithelium lining the inside with the detrusor muscle surrounding the epithelium; problems with the bladder are primarily in dysfunction of the detrusor muscle, a smooth muscle, which may contract at inappropriate times or may not relax appropriately to allow urine storage. The urethra is comprised of an epithelium, a rich submucosal vasculature, smooth and striated muscles, and autonomic and somatic innervations; problems with the urethra include inadequate closure, improper timing of muscle contraction, and abnormal sensations. The urethra is surrounded by the muscles of the vagina, which are associated with urethral damage in approximately 10 percent of women during natural childbirth. An area of research that has been largely ignored is the urethral epithelium and the vascular plexuses inside the muscles that fill and empty in that area and are responsible for providing a hermetic seal inside the urethra.

Dysfunction in the urethral support system is the primary cause of SUI. The support system is comprised of a sphincter system and the fascial and levator muscles that surround and support the sphincter. A study to test the null hypothesis that there is no difference between women with and without SUI was conducted. The Research On Stress Incontinence Etiology (ROSE) found that maximum urethral closure pressure (MUCP) was demonstrably lower in women with SUI than in those women in the control group who were continent. Racial differences also were compared in the Establishing the Prevalence of Incontinence (EPI) telephone survey study. Results of EPI showed a twofold higher level of incontinence in White women than in Black women. A further study of a subset of 400 women from the EPI study found that Black women have a 22-percent higher MUCP than White women, suggesting this may account for the lower rates of incontinence among Black women. Another result suggested by the EPI study is that women with UUI have comparable MUCP scores to women with SUI. These two studies confirm the need to conduct studies on incontinence with continent controls.

Histological staining comparing young (21 years) and old (70 years) women show significantly diminished numbers of striated muscle cells in old women. There is less difference over time in nulliparous than parous older women, thus suggesting that childbirth may be the cause of the loss of striated muscles. In addition, a study of MUCP comparing nulliparous, continent primiparous, and

primiparous women with SUI found few differences between the nulliparous and continent primiparous women, but significant differences between the continent primiparous and primiparous women with SUI. It is not clear whether childbirth resulted in incontinence or whether congenitally weaker urethral muscles caused the incontinence. Longitudinal studies are needed to address this question. A study to address this question was conducted in nulliparous women that found a wide range of MUCP values in nulliparous women, which could indicate which women may become incontinent due to damage to the urethra during childbirth.

Discussion

Dr. Robert Star asked if there is a test to measure MUCP. Dr. DeLancey replied that engineering students say they could develop a test using iPhone technology for approximately \$75. The tests being used today were developed in the 1960s and are outdated. We need to develop new tests that include metrics consistent with current research. Dr. Toby Chai followed up with a question regarding what needs to be done to improve measurement tools, since these tools are not adequate for what we currently know about incontinence. Dr. DeLancey noted that capabilities in metrics on incontinence have improved in the past decade and will continue to improve in the future.

Dr. DeLancey observed that MUCP captures measurable information to assign risk, but it does not specify the types of interventions needed. Lower MUCP values could be used to counsel women on whether to have natural childbirth or cesarean birth. There is no evidence that physical exercise or available pharmaceutical interventions improve urethral function. Stem cell injections have shown some promise, but this is not prevention. There also is no effective strategy for reducing age-related loss of urethral function.

An audience member asked about the differences between MUCP values among White and Black women. In response, Dr. DeLancey said that the study showed that Black women could have lots of detrusor muscle contractions without urine leaking. In investigations of the amount of intraurethral pressure consciously generated during times of need, Black women were able to generate higher pressures than White women. This finding suggests that for a Black woman to have urgency incontinence, she would have to have stronger detrusor contractions before leaking; it also suggests that Black women may be treated with anticholinergic agents more effectively than White women. These findings need to be tested in trials.

A participant noted that in the EPI study, women with SUI and UUI had low MUCP values and asked if the mechanism was the same in both situations. Dr. DeLancey replied that in studies of these conditions, it is difficult to separate the two conditions because they appear similar and often exist in tandem in individuals. It seems logical to shift our thinking to physiology first and then to look at the symptoms. There does not appear to be discrete physiology.

Initial Conditions, Feet, and Symmetry

Niall Galloway, M.D., Emory University School of Medicine, Atlanta, GA

Dr. Galloway presented information that suggests human anatomical anomalies are suggestive of future pelvic health and can be used by the clinician in patient assessment. The bladder, vagina, rectum, and anus rest on and are contained within the pelvic floor and are formed together in the embryo. Embryonic development in the perineum contains symmetry, similar to the human face and appendages. An overlooked aspect of embryonic development is the significant role of apoptosis and its importance in molding the human form. For example, during embryonic development, humans pass through a stage where a tail is formed; programmed cell death is responsible for absorption of the caudal segments and this can lead to anomalies in humans such as an anus without an opening.

Ano-rectal, genito-urinary and pelvic floor variations and anomalies reflect failure of nervous system and neural crest cells, which have a critical role in tissue growth and development and in shaping caudal body segments. In animals with a tail, this does not happen because the nerves must extend past the anus to the tip of the tail. There are great variations in the form and function of the human pelvic floor structures, with fully formed structures being more versatile. Common signs of sacral neurogenic deficits can be observed by the physician, such as surgical scarring and hair patches. Less obvious, but more common anomalies include sacral lipoma, hemangioma, dimple, pigmentation, crease anomalies, or asymmetries.

The sacral nerves also innervate the feet and toes, and if the feet are not well formed and versatile, the pelvic floor cannot be fully formed and versatile. For example, if the medial toes are well formed but the lateral toes and metatarsals are hypoplastic, there is likely to be pelvic floor and intrinsic sphincter weaknesses. In addition, if the gluteal muscles are not well formed or asymmetric the pelvic floor muscles will not be complete in form or fully versatile in function. For physicians using neuromodulation, understanding asymmetry is important for placing the device. A study of bilateral lead placement in asymmetric patients, most (13 of 19) favored the less versatile side; this was statistically significant. This study suggests that neuromodulation should be directed to treat the less versatile and less fully-formed side of the asymmetrical patient. In a study of men incontinent or continent after prostatectomy, sacral neurogenic deficit scores were determined based on gluteal mass, abduction of toes, anal grip strength, 2-point discrimination, and presence/absence of peno-scrotal web. Results of the study showed that the lower the score, the higher the risk of incontinence after radical prostatectomy.

Clinical deficits are the sum of both congenital and acquired losses. Clinicians need to assess initial conditions and recognize variations among patients. The impact of acquired loss will be different among individuals, and the severity of problems will reflect the sum of both congenital and acquired deficits.

Discussion

Responding to questions from the audience, Dr. Galloway noted that symmetry is important: It is associated with balance and health. All people are genotypically different, and there are racial differences in the initial abnormalities. Some conditions are more prevalent in one racial/ethnic group than another, such as spina bifida more prevalent in the white population. Another risk factor is diabetes in the mother, which implies that we as a society may be looking at a future increase in congenital abnormalities.

A participant asked if the MRI is a useful tool for identifying abnormalities; Dr. Galloway stated that it would be better to use observation first, but there is a role for technology. In response to another question, Dr. Galloway noted that some nonconventional tests can be used in the laboratory, such as bilateral EMG recordings during cystometry to detect pelvic floor asymmetry.

Musculoskeletal System

Diane Borello-France, Ph.D., P.T., Duquesne University, Pittsburgh, PA

Dr. Borello-France provided evidence from published literature that highlights the importance of the musculoskeletal (MS) system in pelvic health, focusing on comorbidities; the relationship between UI, breathing disorders, gastrointestinal symptoms, and back pain; and the impact of high-intensity sports. Comorbidities include obesity and respiratory disease, which increase pressure on the pelvic floor, and pain, arthritis and fibromyalgia, which lead to impaired mobility and constipation from medicines prescribed for these conditions. Studies on UI, breathing disorders, gastrointestinal symptoms, and back pain suggest that a failed MS system may explain the interrelationship between disorders. In a study on elite Danish athletes, 52 percent reported UI; another study on nulliparous athletes found greater bladder descent and larger hiatal area compared to controls.

A recent review describing the integrated continence system identified modifiable risk factors for UI, including motor control factors, MS factors, and behavioral factors. Each of these can affect the structural systems needed for continence, including the urethral support system, the intrinsic urethral closure system, and the lumbopelvic stability system. The lumbopelvic stability system promotes effective load transfer from the upper body through the lumbopelvic system during movement. Results from published literature propose that a failed lumbopelvic stability system leads to lower back pain, pelvic pain, and SUI. Numerous muscles control effective closure of the urethra, including those that limit intersegmental motion, intrapelvic motion, and control compressive forces. Deficits in the motor control, MS, and behavior factors can lead to UI. For example, slumping posture when sitting increases pressure on the pelvic floor muscle, which becomes less active than when sitting with correct posture. Studies have shown that women with SUI had less activity than continent women. Improving posture could be one strategy for preventing UI, especially in women with higher risks of UI. Studies also have found that standing posture is important for pelvic health. Another study found associations between levator pain and dyspareunia in women with interstitial cystitis. Reducing muscle spasm and stiffness improved bladder symptoms in a large proportion of the women studied. These findings further illustrate the importance of healthy muscle function in bladder health.

Numerous studies have shown the association between motor coordination deficits, such as in balance activities and standing rapid-arm movements, and urinary incontinence. In other studies comparing women with and without lower back pain, researchers found greater bladder base elevation and trunk muscle activation needed for balance in those without pain. In addition, a study in men found quicker activation of internal oblique and muscles in single-leg stance tasks in those without sacroiliac joint pain compared to those with sacroiliac joint pain. The significance for prevention is that impaired balance, bladder symptoms, and back pain may share underlying mechanisms. Particularly, the inability to activate the pelvic floor, abdominal and back muscles may lead to ineffective load transfer and increases in intra-abdominal pressure, which affects bladder health. This failed mechanism of load transfer may also explain the multiple complaints in women seeking treatment for LUTS.

Bowel Function

Clare Close, M.D., Close Pediatric Urology, Henderson, NV

Dr. Close reviewed bowel problems from childhood through adulthood. Studies of children in the first grade in the United States and Australia indicate that signs of LUTS are present in approximately 15 percent of girls; this percentage is approximately the same as what is seen in women over age 18 years. This suggests that urinary problems in childhood predict adult overactive bladder. A research area that pediatricians should be addressing is bowel function in children with urinary symptoms. Sonographic studies show that in these children, the bowel is distended, putting pressure on the bladder. Studies have shown that constipation in children is associated with enuresis and UTIs. A subsequent study showed that 50 percent of children with enuresis were constipated; treatment for constipation in these children was shown to alleviate enuresis and reduce the incidence of UTIs. Similar studies in the 27 percent of elderly adults who report constipation have shown the same result. It must be recognized that subjective recall of bowel behavior does not accurately reflect constipation status in either adults or children. Objective self-collected data obtained through tools such as the Bristol Stool Chart may more accurately reflect bowel behaviors but this may not correlate with fecal loading in the rectum.

Increased fecal loading and the resulting rectal distension is a chronic disease in many children and adults. This condition, diagnosed by plain film or sonography, results in a sensation of bladder filling at smaller volumes and reduced maximum bladder capacity. Bladder changes that occur in rectal distension include early sensation of bladder fullness, urinary frequency and urgency, small functional bladder capacity, daytime frequency of urination, and nocturnal enuresis. A study in children with constipation using abdominal radiography measured cecal diameter, rectal stool length, and total colonic stool length, and found that 70 percent of children with LUTS had distended rectums and associated symptoms. There

is a need to conduct similar studies in adult women, especially to determine if rectal distension correlates with constipation as defined by accepted criteria.

Urologists need to raise awareness in the scientific community and among patients on the associations of bowel function, such as fecal loading and rectal distension, and urinary symptoms. Simple solutions can work for many patients, including drinking more water and improving diet for bowel health. This is especially true in the school setting because of the number of students who often are restricted from frequent visits to sources of water and bathrooms. Another research need is better identification of young girls who are at risk for bladder problems and follow-up studies that extend into adulthood. Those young girls who have unhealthy habits (holding, constipation, or poor diet) and the presence of pelvic floor pathology should be assessed to see if structural bladder changes persist into adulthood.

Sexual Activity

Betsy Foxman, Ph.D., University of Michigan, Ann Arbor, MI

Dr. Foxman presented information on the association between sexual behavior and UTIs, noting that, urinary symptoms associated with UTIs have both infectious and noninfectious causes. Approximately 20 percent of women with classic UTI symptoms (e.g., dysuria, frequent urination, urgency, suprapubic pain, and hematuria) have negative urine screens for infectious agents. A controlled study of women with UTI symptoms or no symptoms found that more than one-half of the women with UTI symptoms did not have a positive bacteria culture. This suggests that women with positive bacteria screens may have had symptoms not caused by the bacteria.

Significant data exist on the role of sexual behavior and UTI. Results from a population-based study found that the risk of UTI increased with sexual activity. Bacteria screenings the morning after sexual activity found that many women had high levels of urinary bacteria, which were spontaneously cleared within 24 hours. Clinical studies have shown that post-coital prophylaxis reduces the incidence of UTIs. Bacteria can infect the urinary tract during sexual activity and move from the vagina or rectum into the bladder and can be transmitted from a sex partner. Host immune responses and urination help remove the bacteria from the urinary tract; however, bacteria can colonize for long periods of time before causing symptoms. A potential marker of inflammation, LL-37, is higher in women with UTI symptoms than in women without UTI symptoms. Data from the EPIC study found that women with LUTS are less likely to engage in or enjoy sexual activity, and they have more bladder pain than women without LUTS.

Research gaps include the role of sexual activity on LUTS in women with noninfectious etiology, and it is not clear when UTIs should be treated. It is likely that there is significant overtreatment for UTI, which poses a problem due to the rise of antibiotic-resistant bacteria. Data from several studies comparing cure rates in women treated with antibiotics or placebo show that lower UTIs (bladder) in women are generally self-limited. In addition, because antibiotics act to reduce inflammation, it is not clear whether the cure rates are because of the anti-bacterial action or anti-inflammatory action of antibiotics. A pilot study comparing antibiotics with the anti-inflammatory agent ibuprofen found no significant difference in dysuria after seven days with either treatment.

Asymptomatic bacteriuria is common and increases with age, though bacteriuria does not predict symptoms, which suggests that the innate immune response is being activated by another factor. Because studies show sexual activity decreases with age and asymptomatic bacteriuria increases with age, there are compelling reasons to gain a better understanding of asymptomatic bacteriuria. Another research gap is the understanding of the conditions that exist to allow bacteria to move from the bladder to the kidney (acute pyelonephritis). Although the perception in the clinical community is that bladder infection must be treated because the risk of acute pyelonephritis is high if untreated, this belief is not borne out by the evidence. The actual risk is approximately 1 or 2 per 1000. The occurrence of a first UTI among healthy women increases the risk of a second UTI within 6 months by 24 percent; similarly, a first incidence of

pyelonephritis also increases the risk of a second incident. This suggests that a research gap exists on the factors predicting both the development of UTIs and pyelonephritis.

Discussion

A participant commented that because so much is known about the immune system, it would make sense to conduct research to better understand the host response. Dr. Foxman agreed, because we do not know why some people's immune system self-limit bacterial infection and others' do not.

In response to a question, Dr. Foxman noted that a study was conducted to investigate bowel function and no difference in the occurrence of UTIs was found in women with or without constipation, defined as small, hard stools that are difficult to pass.

A participant first observed that there is a movement among some professional organizations to better understand the noninfectious causes of LUTS—such as differentiating between vulvar-vaginal atrophy from the genital-urinary syndrome of the menopause, both of which have low states of estrogen as their cause—then wondered how this fit with the knowledge gaps identified for LUTS. Dr. Foxman replied that it is difficult to get accurate information on urinary symptoms; for example, some women who report urinary symptoms have a yeast infection. The role of estrogen has to be ruled out, but there has been a high dropout rate in recent studies on estrogen because many treated women could not tolerate estrogen replacement. An area that could use more research in aging women is related to microbiotic replenishment to improve the pH and vaginal secretions that influence the microbiota of the vaginal cavity.

Are Fats Bladder Friendly?

Barbara Shorter, Ed.D., R.D., CDN, Long Island University Post and Smith Institute for Urology, Brookville, NY

Dr. Shorter reported on the role of dietary fats in LUTS. There is limited information on nutrition and LUTS. Obstacles to gaining the information include variations in disease definitions and the lack of diagnostic criteria and tools, high treatment costs, and the effects of mixed symptoms and comorbidities. In addition, a lack of follow-up regarding LUTS treatment is critical to the lack of understanding. Researchers have identified urinary markers of inflammation for urinary conditions, especially for IC, including elevated levels of interleukin 6, histamine, C-reactive protein, nerve growth factor, and prostaglandins. These inflammatory markers also are seen in such common diseases as heart disease, cancer, arthritis, diabetes, irritable bowel syndrome, fibromyalgia, and overactive bladder. We now know that chronic inflammation is not synonymous with infection, but is associated with excessive production of pro-inflammatory substances (i.e., certain eicosanoids), and pro-inflammatory substances are a result of overconsumption of particular polyunsaturated fatty acids (PFAs). Among the dietary PFAs, many are essential for maintaining cell membranes, which control what goes in and out of the cell. The two types of PFAs are omega-6 fatty acid (O-6FA) and omega-3 fatty acids (O-3FA). O-6FA is the most common form found in diets, especially in liquid vegetable oils, spreads, and processed foods; O-3FA is limited in the diet and found in cold-water, fatty fish. Consumers generally consume 20 times more O-6FAs than O-3FAs. These fatty acids are metabolically and functionally distinct and have oppositional physiological roles. Of significant importance is that O-6FAs increase inflammation and O-3FAs decrease inflammation. Biochemical pathways of the omega fatty acids show that the anti-inflammatory effects of O-3FAs occur through down-regulation of inflammatory markers, although it is not directly involved in either stimulation or inhibition. This needs further examination to determine if it is possible for O-3FAs to be used as adjuvant therapy to regulate inflammatory responses.

Among the monounsaturated fats, olive oil has been found to lower blood cholesterol and provide powerful antioxidants and anti-inflammatory factors. People who regularly consume olive oil in place of other fats have lower rates of heart disease, diabetes, colon cancer, and asthma. Lesser amounts of

monounsaturated fats are found in canola oil, peanut oil, nuts, and avocados. Thus, this is another comestible that is worthy of investigation to determine its effects on bladder symptoms.

Regarding supplementation of O-3FAs, the FDA has stated that 3 grams/day (g/d) is Generally Regarded as Safe (GRAS), although it is important to understand that supplements are not regulated by the FDA. Other agencies and professional bodies have recommended 1 g/d of O-3FA for secondary prevention of myocardial infarction and 2–4 g/d for lowering blood triglycerides; a patient taking these supplements should take them under the care of a physician. It also should be noted that research shows that eating whole foods is more beneficial than taking supplements.

Research using a validated patient survey has identified known bladder irritants that have been used in the treatment of patients with IC and overactive bladder. Irritants identified through the survey included coffee (both caffeinated and decaffeinated), tea, carbonated, and alcoholic beverages; certain fruits and fruit juices; artificial sweeteners; spicy foods and tomato products.

Discussion

A participant asked if some nuts are bad, or if some are better than others. Dr. Shorter replied that there are “good” nuts and “better” nuts. Because nuts are energy dense, it is important to consume only reasonable amounts of nuts.

In response to a question about the possible development of IC from an untreated bladder infection, Dr. Shorter noted that there are many theories about the development of IC, and some research is investigating this area.

Environmental Factors and Voiding Behaviors

Mary H. Palmer, Ph.D., RNC, University of North Carolina at Chapel Hill, Chapel Hill, NC

Dr. Palmer discussed the environmental factors related to voiding behaviors, including what is known and what areas need further research. Voiding occurs in a social context, especially in areas of employment. Toilet accessibility in public spaces is challenging, with issues of “potty parity,” closure of public toilets, and disability issues restricting access. In the United States, the Occupational Safety and Health Administration issued guidelines in 1998 for employers, delineating the number of toilets per worker and sanitary standards. Many workers face stressful environments that restrict available access to toilets, based not on availability but on other factors. This applies to teachers, telephone operators, nurses, workers paid by production quotas, and deployed women in the military, as well as women prisoners. Studies of work productivity and women with overactive bladder have identified absenteeism, higher number of days of disability, and a negative impact on career, job choices, and retirement decisions in these women. Multiple studies also have focused on retirement homes and hospitals and the unfriendly toilet environment posed in these settings for the elderly, which often leads to increases in UTIs.

There also are cultural and language barriers for those trying to access public toilets, whether in public byways, airplanes, or commercial enterprises. The home also introduces environmental challenges, especially for those with disabilities or the elderly. Many older homes have a toilet only on one floor or level, which presents barriers or safety issues for people with problems with mobility, balance, gait, or vision. Even in accessible environments, perceptions and social norms may be barriers. A study of school-aged girls found that 25 percent never use the school bathroom; other studies indicate that teachers often discourage regular toilet use, which causes students to wait until breaks or until arriving home after school. In the workplace, peer pressure on those taking frequent toilet breaks is common. In addition, in jobs that require special clothing, such as HAZMAT suits, taking a toilet break is a cumbersome process.

A significant behavior reported from studies is that less than one-half of incontinent women report this to their physician, citing feelings of shame, embarrassment, and apprehension about how health care

providers may respond. Underlying these behaviors is knowledge. Studies show that women lack knowledge about UI and pelvic floor disorders, with evident racial and ethnic differences. This is true even in women with high health literacy scores. A study of attitudes among women with UUI and SUI during the transition to menopause shows they have lower self-esteem and feelings of control, and they often keep a change of clothes at work in case they leak. In addition, hovering behavior—which places undue stress on the pelvic floor muscles—is common among women in public toilets. A study of women’s toilet behavior among nurses from the United States and China found similarities in both cultures about their concern for cleanliness in public toilets, their delay in emptying their bladder during busy times at work, emptying their bladders at home when they do not need to urinate, and waiting to empty their bladders until they can no longer hold urine. Because comorbidities increase with age, it is important to have a better understanding of disease and treatment effects. Studies show that 30 to 50 percent of nursing home residents are continent but there is little understanding of the protective effects of voiding behaviors in this population.

Research gaps in voiding behavior include increasing public awareness as has been done for breast cancer and heart disease; valid and reliable measures of women’s knowledge, attitudes, beliefs, and behaviors related to bladder health across the lifespan; the exploration of the effect of environmental modifications on women’s bladder health; and how to prevent or delay LUTS in women.

Discussion

A participant observed that we often ask children to void before they have the urge. The person then asked if the study of American and Chinese nurses looked at the differences between those women who voided prematurely and those who did not to determine if there was a difference in bladder size. Dr. Palmer replied that the study did not look at that particular factor.

BREAKOUT SESSIONS

BREAKOUT SESSION 1: RISK FACTOR ASSESSMENT AND PRIORITIZATION

Introduction

Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD

Dr. Bavendam introduced the topics for Breakout Session 1 and directed participants to find their assignments listed on their name badge. There were four breakout groups, each defined by life stage: Child–Adolescent, Young Adult (childbearing), Midlife (post-childbearing), and Older Person (≥ 65 years). The groups focused on risk factors assessment and prioritization. The assigned groups were developed with a focus on the balance of scientific/clinical perspective. The NIDDK program research goals for this activity are to establish an evidence base for factors associated with normal or healthy bladder function and to identify behavioral and other risk factors for LUTS.

The task for each group was to develop a high-level list of a broad spectrum of factors that may either contribute to healthy bladder function or be a risk factor for LUTS. Factors that were considered high priority were to be ranked in order of importance. Each breakout group was given a blank grid to assist in developing the priority list. The title of the grid for each group was “Potential Contributing Factors to Bladder Health and LUTS.” The contributing factors were grouped into seven categories:

- bladder/urethral structure and function
- pelvic tissue injury
- musculoskeletal
- “omics” (microbiome, proteome, metabolome)
- comorbidities
- behaviors
- personal factors

The breakout groups prioritized the study of risk factors under each of those categories according to the potential impact on the following clinical conditions:

- bladder infection
- overactive bladder (OAB)
- incontinence
- bladder pain/interstitial cystitis (IC)
- voiding difficulty

Note that not all groups were able to cover all seven categories and all conditions during their discussions.

Breakout Session 1 Report Back

Older Person Group

The breakout group considered the study of skeletal muscle to be important to OAB, incontinence, and bladder pain/IC. Innervation with regard to infections was considered a priority area, as was urothelial function across all of the LUTS.

Regarding pelvic tissue injury, collagen disorders should be studied related to incontinence and voiding issues. Peripheral denervation might play an important role in infections, incontinence, and voiding issues. Abnormal pelvic floor support and function was identified as a high priority across many of the LUTS.

Musculoskeletal issues were identified as a priority to better understand OAB and incontinence. The study of “omics,” specifically urine, vagina, and bowel “omics,” was prioritized related to infections, OAB, incontinence, and bladder pain/IC.

Relating to comorbidities, mental health was identified as a high-priority factor related to infections, OAB, and incontinence. The study of other comorbidities (e.g., obesity, diabetes, and decreased mobility), as well as the study of dietary behaviors, also were given high priority related to infections.

Midlife Group

Risk factors for women change after childbearing age and into midlife. In terms of structure and function, urothelial function was considered a priority related to infections. With regard to IC pelvic pain, innervation also has a role. The breakout group considered pelvic tissue injury as less of a research priority.

In terms of the priorities for bladder function, skeletal muscle was a high priority with regard to incontinence, defined by the breakout group as stress incontinence. The group considered wet and dry overactive bladder together, and voiding issues were narrowed to voiding difficulty and dysfunction to make it easier to conceptualize. With regard to injury, the group decided that there was a role for studying the relationships between intercourse and infections, intercourse and bladder pain/IC, vaginal delivery and stress incontinence, and abnormal pelvic floor support and stress incontinence.

The group members agreed that the musculoskeletal category was related to the personal factors category. They gave high priority to studying women’s pelvic floor awareness and function in regard to many types of LUTS. The group also noted the important role of pelvic floor support as well as core muscle strength and alignment, specifically with regard to stress incontinence. Another identified priority was a better understanding the role that woman can play in improving LUTS.

The breakout group highly prioritized the role of studying the microbiome, metabolomics, and proteomics with regard to infections, OAB, and pelvic pain. This was identified as a high-priority area to identify and understand markers that subsequently can be used to prevent disease.

Certain comorbidities were deemed more important for research than others, including mental health related to bladder pain and voiding issues. Obesity and diabetes are high-priority areas with regard to OAB and stress incontinence. The role of respiratory conditions, such as allergies and chronic obstructive pulmonary disorders (COPD), in bladder pain/IC is a high priority, as is investigating the role of musculoskeletal/decreased mobility on OAB and stress incontinence. The interplay between sexual function/dysfunction and IC should be prioritized, as well as the role of rectal factors in many of the LUTS.

The group agreed with the role of behavioral modification, specifically with regard to OAB and bladder pain, and filling sensations with regard to IC was identified as a priority.

The breakout group’s highest priority area was the role of personal factors and understanding what contributors play a role, specifically with regard to pain. The main take-home messages included the need for predictive biomarkers for all of the “omics,” including the microbiome, and a strong need for women to take an active role in understanding their bodies and risk factors, as well as play an active role in prevention.

Young Adult Group

This breakout group focused on the idea that what women know, do, and care about is very important from the young adult stage through potential later interventions. The question of occupational demands was a high priority related to restroom use restrictions. Epigenetics also was considered a priority to help identify women who are at risk for a difficult delivery during their childbearing years. Musculoskeletal issues were a priority in terms of the pelvic floor, as were studying the parameters important in muscle function. Metabolomics was identified as a priority along with the epithelial-host response. The study of rectal factors, including evacuation and bowel function, was a priority across several LUTS. The role of physical activity as related to voiding issues also was considered important. This group considered what women would do for bladder health to be a priority across all of the LUTS. Specifically, the group was interested in the issues experienced by women and what they consider doing to correct the issues (e.g., physical exercises).

Dr. Bavendam commented on the significant consistency across the different breakout groups. She added that the risk factor categories were intended as a discussion tool.

Child/Adolescent Group

The breakout group engaged in the discussion from the perspective of priority areas that could be funded to investigate young children with the hope of informing research later in life. The group identified many high-priority areas related to behavior, which was appropriate because children represent the beginning of the story. The group was challenged by considering not only children, but also issues that span into child-bearing age for post-adolescents, who are essentially “adult children.”

The group suggested adding a category of attention-deficit hyperactivity disorder (ADHD) to potential contributing factors. Research has indicated that the bladders of children with ADHD function differently. ADHD should be added to the comorbidities category.

Regarding behaviors, it is important to learn a lot more about children’s intake and voiding decisions. Toilet availability is a concern: Some children are stuck in portable school buildings with no bathroom nearby, and the outcome of this situation is not known. Toileting behaviors in adolescents should be addressed, as some data exist for toileting behavior in older women. Physical activity engagement in terms of incontinence and voiding issues should be studied for children who play video games extensively and never get up to use the bathroom. Those data are not available.

Several of the comorbidities are not as relevant for children, but the contribution of obesity and diabetes to LUTS is important. The group added sexual abuse under the category of sexual function, because that is an important issue that is not talked about and for which little data exist. The study of rectal factors is an important priority across all of the LUTS.

The group considered musculoskeletal issues as important, as well as pelvic tissue injury, particularly for young women playing high-impact sports and considering vaginal deliveries. Identifying groups of females at risk for vaginal deliveries would be beneficial.

Regarding bladder/urethral structure and function, the group agreed that the area needs to be defined, but it is not the highest priority.

BREAKOUT SESSION 2: WHAT'S NEXT?

Introduction

Tamara Bavendam, M.D., M.S., NIDDK, NIH, Bethesda, MD

Dr. Bavendam introduced the topics for Breakout Session 2 and indicated that the participants' assignments were listed on their name badge. The four breakout groups were each defined by a topic area of interest to the NIDDK. The breakout group reports, detailing suggestions in the topic areas, will be used by the NIDDK and other sponsors of the meeting to develop a research plan to move the study of LUTS forward. The groups focused on (1) the prioritized topics for assessment in population surveys; (2) an assessment of stakeholders needed to develop partnerships in all aspects of prevention research; (3) the actions that can be undertaken with the current level of evidence; and (4) proposed clinical studies to address research gaps.

Breakout Session 2 Report Back

Each breakout group presented a summary of the key points discussed during the session. The format of the presentations varied according to the preferences of each group.

Population Survey Group

Moderators: *Mary H. Palmer, Ph.D., R.N.C., and Tamara Bavendam, M.D., M.S.*

The purpose of the breakout discussion was to provide proposed topics and designs for a population survey of women that could be used to develop research ideas to improve bladder health for women. The session was titled, "What do Women and Girls Know and Do?"

During the discussion, the group was asked to address the following tasks:

- Discuss and prioritize topic areas to be covered in survey.
- Discuss existing measures for bladder health.
- Identify and prioritize target populations for inclusion in the survey.

Dr. Palmer presented an outline developed by the members of Breakout Group 1 in response to these tasks.

A. Population survey

The following list includes items, captured as questions and/or topics, identified as those needed to be collected in a population survey. Note: discussion did not have sufficient time for prioritization or discussion of survey methodology.

1. Women (note—healthcare providers may also be assessed, likely as a separate survey)
 - a. What do women know and do (attitudes, behaviors)?
 - b. What do women feel about their bladder function?
 - c. Bother/impact
 - d. How concerned are you?
 - e. Misconceptions
 - f. How would you prefer to be informed of normal versus abnormal behaviors and symptoms, treatments, coping mechanisms?
 - g. Where do you go for knowledge?
 - h. Symptomatic versus asymptomatic
 - i. Past beliefs (cultural issues)
 - j. Disclosure: Whom have you told?

- k. Family history issues
 - i. Do you have children younger than 10 years of age?
 - ii. Did others in your family have bladder issues?
- l. Behaviors
 - i. Toileting
 - 1. Situational voiding habits
 - 2. Voiding diary
 - 3. Technique (strain, squat, hover)
 - ii. Bowel diary
 - 1. Situational habits
 - 2. Technique
 - 3. Incontinence
 - iii. Barriers
 - iv. Adaptive
 - 1. How do you control voiding?
 - v. Treatment-seeking
 - vi. Diet and fluid intake
 - vii. Protection
 - viii. Enuresis (bedwetting)
- m. Barriers
 - i. Occupation
 - ii. Veteran status
 - iii. Socioeconomic status
 - iv. Lack of access to toileting
 - v. Lack of access to healthcare
- n. Treatment-seeking behavior
 - i. Whom did you see?
 - ii. Why did you go?
 - iii. What happened?
 - iv. Previous experience/treatment/PT
 - v. Compliance with Recommendations
 - vi. Why do you **not** seek help?
- o. Health history
 - i. BMI
 - ii. Smoking
 - iii. Exercise habits, including pelvic floor muscle exercises
 - iv. Comorbidities
 - v. Reproductive history
 - vi. Sexual trauma
 - vii. Surgical procedure history
 - viii. UTI history
 - ix. Medication history
 - x. Menstrual status/symptoms
 - xi. Menopausal status
 - xii. Bedwetting history in childhood
 - xiii. Injury
 - 1. Spinal cord
 - 2. Bladder
 - 3. Pelvis/perineum
 - 4. Sexual abuse
 - 5. Gynecologic surgery
- p. Economic issues
 - i. Work loss due to condition
 - ii. Productivity

- iii. Lost income
- iv. Activity restriction
- q. Sexuality issues
- r. Activity issues
 - i. Impact or lifting
 - ii. Physical therapy
 - iii. Emotional stress exposure

B. Discuss existing measures for bladder health

1. Bladder diaries
2. Bowel diaries
3. Survey Tools—by age group

C. Identify and prioritize target populations for inclusion in the survey

1. Fourth grade and up (ages 10–12)
2. Few existing tools include bowel issues
 - a. Pediatric Lower Urinary Symptom Form
 - b. Dysfunctional Voiding Symptom Scale
 - c. Bristol Stool Scale
3. Parents of younger children (mothers may differ from fathers)
4. Adolescents
5. Young adults
6. Reproductive age adults
7. Midlife women
8. Older women

Stakeholder Assessment Group

Moderators: *Richard Roberts, M.D., J.D., and Mary Worstell, M.P.H.*

The purpose of this breakout session was to provide information on stakeholder groups relevant to research on bladder health. Discussion points included the following:

- Identify stakeholder groups relevant to a Bladder Health Initiative (BHI), from research to implementation.
- Discuss how to communicate with stakeholders and assess their interest and potential contributions.
- Prioritize the order in which the stakeholder communications/assessments should be performed.
- Define key issues and questions for each stakeholder group.
 - What is “at stake” for individual group/organization?
 - How does a BHI meet/advance the mission of the group/organization?
 - What do they need to get out of participation?
 - What obstacles (e.g., policy, attitude, resources) may affect each stakeholder’s ability to participate?
 - What can NIDDK/BHI do to help overcome these obstacles?

The participants in Breakout 2 developed a list of key stakeholders, grouped by specific areas:

- **Public:** Men should be included in this area because they also experience urinary tract problems.
- **Government agencies:** Center for Disease Control and Prevention, Department of Defense, Environmental Protection Agency.

- **Private companies/industries:** Insurance, pharmaceutical, marketing, and communication companies.
- **Health care providers and professionals:** Focus on first-line groups such as nurses, including school nurses, and long-term care providers, as well as caregiver associations.
- **Advocacy groups:** ADA and other groups that can advocate for health care.
- **Employer groups:** Occupational health care groups.
- **Education and school bodies:** Approach with issues for students and teachers.
- **Faith communities:** Would help with stigma and cultural issues.
- **General:** Media groups can spread the word; we would need to develop clear messages.

Participants in this breakout group also commented on the need to overcome the barrier of the stigma of urinary problems. Stakeholders need options for ways that they can help.

Taking Action Group

Moderators: *Jennifer Hebert-Beirne, Ph.D., M.P.H., and Carolyn Sampelle, Ph.D., R.N.*

The purpose of this breakout was to provide suggested actions that are congruent with the vision statement of preserving and improving bladder health for women. Specific tasks for this group included the following:

- Develop a prioritized list of actions identifying key stakeholders for implementation.
 - Are there essential provider groups that need to be involved?
 - Should a team science model be used?
 - Are there essential community groups to include?
 - What is the best way to incorporate community perspectives?
- Identify the activity that will have the most impact on each life-stage population segment.
- Recommend a realistic timeline for implementation of activities.
 - Given the current state of the science, is there a case for early conduct of a pragmatic clinical trial to accelerate the translational trajectory?
 - What critical data are needed to support scaling up interventions in order to benefit the broadest segment of the population?

Breakout Group 3 had a wide-ranging discussion about the actions for identifying key stakeholders, such as clinicians, nurse practitioners, physical therapists, public health professionals, and epidemiologists. There was consensus that the method needs to be a broad team science approach. The group produced a detailed list of actions per life stage, with a focus on pelvic health throughout the lifespan. Although it is not possible to institute a long-term study at this time, it may be possible to use data from existing studies, such as the Health eHeart study, which would allow the collection of data in a low-cost manner. Another option is to begin a study in young children and follow them throughout their lives. The following is the list produced by the breakout group. The issues and items below each issue are not prioritized.

- Awareness to what?
 - Targeted strategies
 - Decision makers
- Measurement issues (clarification and standards)
 - Increase use of biometrics
 - Family/community-based programs
 - Cost utility study
 - PFO/bladder health economics studies to determine cost
- Link bladder health to major health concerns
 - Violence

- Obesity
- Sexually transmitted infections

Thoughts

- Make it inclusive
- Have broad stakeholder involvement from the beginning
- Take knowledge to action (Community Partnerships to Advance Research, Clinical and Translational Science Award) and in participatory research setting
- Advantages are identified, including familial issues

List of Actions

- Raise awareness and support
 - Bladder Health Week
 - Importance of participating in research (especially for racial/ethnic minorities and low-income groups in the United States)
 - Use life course (infant—child—adolescent—adult)
- Obtain sponsorships/partnerships
 - Media
 - Pharmaceutical companies
 - Insurance companies
- Need cost effectiveness to show that prevention works
- Learn from CTSA regarding racial, low income, and minority groups for enrollment

Key Stakeholders

- LUTS clinicians, pediatricians, geriatricians (M.D., N.P., P.T., L.P.N.)
- Basic science
- Urban planning
- Patients
- Schools
- Churches
- Patient advisory groups (policy)
- Geographic diversity
- Health educators
- Athletic trainers
- Public health/epidemiologists

Clinical Studies Group

Moderators: *Emily Lukacz, M.D., M.A.S., and Lisa Begg, Ph.D., R.N.*

The purpose of this breakout group was to develop ideas for clinical studies and designs to address the problems identified during the presentations. The following questions were presented to the breakout group:

- What are healthy bladder behaviors for women and girls?
- What are behaviors for women and girls’ pelvic health?

During the discussion, the group was asked to address the following tasks:

- Identify settings and methodologies for answering each of these questions across the female lifespan.
- Define bladder “healthy” populations.
- Develop a prioritized list of needed studies, taking into account feasibility, costs, and ability to inform pilot prevention interventions within 5 years.

Dr. Lukacz reported on the Breakout Group 4 discussion, which produced a grid to illustrate the types of data needed at each life stage and used this information to propose specific clinical studies that could be conducted. In general, the same type of clinical study could be conducted at each life stage, with a few added metrics at each life stage (shown in the grid). There was an emphasis on being able to identify individuals at higher risk for specific conditions for entry in clinical studies. A strong recommendation was made to assess ongoing trials and studies to see if there are data that would be useful in designing new studies, or if it is possible to have the existing studies add metrics that would be useful in the study of LUTS.

Dr. Lukacz presented the table below as a summary of specific issues for pelvic health associated with the life stages.

Life Stage	Specific Issues for Pelvic Health	Research Issues Across All Life Stages
Child	<ul style="list-style-type: none"> • Screening for LUTS • Identify predictors of LUTS 	<ul style="list-style-type: none"> • Behavioral issues (use life cycle of the day) • Water (?) • Real-time data collection
Teen	<ul style="list-style-type: none"> • Prevalence of LUTS • Prevalence of other pelvic health issues 	
Adult	<ul style="list-style-type: none"> • Stem cell research • Examine wellness studies as option (example: Patient Centered Outcomes Research Institute [PCORI]) and innovative data and technology collection • Workplace wellness strategies 	
Older Adult	<ul style="list-style-type: none"> • Home to institutional care 	

Study Specifics

Specific areas needed for clinical studies at each life stage include the following:

Children

A study using collected urine, stool, and blood specimens to investigate biomarkers before and after toilet training should be considered. The time frame should be 5 years, so enough children can be assessed to have valid results.

Young Adults

There is a need for a cross-sectional, longitudinal cohort study similar to that for children. The study should assess the possibility of accessing existing data and whether current trials, such as the AD2/HEALTH study, collect biomarker data on sex, drinking, voiding, and stool behavior. If not, it is important to see if these factors can be added to an existing study or conduct a new study. There is a need to collect LUTS parameters from this type of study.

There needs to be a study to define “normal” and “abnormal” and what is important for prevention. Any study should investigate differences in populations. A study is needed to investigate what affects pelvic floor health, such as posture, core strength, musculoskeletal system, and other factors. The study should determine physical measures before and after an intervention, and include comorbidities, personal behavior, and BMI throughout the lifespan.

Midlife

A potential prospective randomized clinical trial is needed in high-risk populations. It should run for 5 years. Risk factors should include obesity, multiple births, and others developed in the design.

Older

Functional limitations should be added to the core measures from other age groups to a clinical trial, including motivation. A caregiver intervention trial should be considered. This could be a clustered, randomized trial comparing independent, ambulatory seniors with those who are codependent. It could be conducted in a senior care center.

MEETING SUMMARY: KEY MESSAGES

Robert Star, M.D., Director, Division of Kidney, Urologic, and Hematologic Diseases, NIDDK

Dr. Star recognized that the LUTS community is engaged and ready to move forward to address this important health issue. During the meeting, the participants identified numerous opportunities that warrant research attention. The challenge is choosing those opportunities that are ready to move forward in an organized manner, given the current budget restraints. He asked if the biology is sufficiently understood to inform subsequent clinical studies.

Patients are in dire need of prevention strategies, but first it is necessary to make a model that integrates information on structure, function, behavior, environment, and other factors, and then the model must be tested. One concern is that many real-time measures are lacking, especially measures that identify patients at the greatest risk—across the lifespan—who can benefit from interventions. With knowledge of informative subgroups, it will be easier to design clinical studies to answer important questions.

There is a great need for publically available educational information so that patients can have a better understanding of their condition. The education program should be evidence based and culturally sensitive. This is an area where the LUTS community can learn from other groups and perhaps leverage activities with other groups.

NIDDK will review the information presented at the meeting, and look for collaborators. Dr. Star reminded the participants that NIDDK Director, Dr. Rodgers, had indicated his commitment for moving the LUTS field forward. A funding announcement will be developed and issued on this topic in the near future.