SPECIAL ARTICLE

Report and Research Agenda of the American Geriatrics Society and National Institute on Aging Bedside-to-Bench Conference on Urinary Incontinence in Older Adults: A Translational Research Agenda for a Complex Geriatric Syndrome

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The American Geriatrics Society, with support from the National Institute on Aging and other funders, held its ninth Bedside-to-Bench research conference, entitled "Urinary Incontinence in the Older Adult: A Translational Research Agenda for a Complex Geriatric Syndrome," October 16 to 18, 2016, in Bethesda, Maryland. As part of a conference series addressing three common geriatric syndromes—delirium, sleep and circadian rhythm disturbance, and urinary incontinence—the series highlighted relationships and pertinent clinical and pathophysiological commonalities between these conditions. The conference provided a forum for discussing current epidemiology, basic science, and clinical and translational research on urinary incontinence in older adults; for identifying gaps in knowledge; and for developing a research agenda to inform future investigative efforts. The conference also promoted networking involving emerging researchers and thought leaders in the field of incontinence, aging, and other fields of research, as well as National Institutes of Health program personnel. **J Am Geriatr Soc 2017.**

Key words: aging; urinary incontinence; bladder; voiding dysfunction; epidemiology; mechanisms; interventions

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This article was published online on 4 December 2017. An error was subsequently identified. This notice is included in the online and print versions to indicate that both have been corrected 15 December 2017.

DOI: 10.1111/jgs.15157

Urinary incontinence (UI) occurs in nearly 40% of women aged 80 and older, in 10% to 35% of older men, and in up to 80% of long-term care residents.[1–4] The effect of UI on older adults reaches far beyond impairment of quality of life. In a recent evaluation of persons hospitalized with serious illness, more than half of the participants rated bladder and bowel incontinence as conditions worse than death (the most undesirable condition of those queried).[5] Older adults with UI are at greater risk of depression, social isolation, and falls.[6–8] Incontinence is also associated with loss of independence and ultimately institutionalization.[9,10] As a multifactorial geriatric syndrome, UI in older adults occurs when multiple interacting contributing conditions, including multimorbidity (particularly in the setting of cognitive or mobility impairment), changes in lower urinary tract (LUT) function associated with aging, and medications, overwhelm the individual's capacity to remain continent.[11]

Treatment options for UI have expanded over the past two decades, but even with increasing options for treatment and emerging prevention strategies, UI continues to be underreported and undertreated, with many affected individuals failing to report symptoms and many providers ignoring the problem entirely.[12–14]

Despite the effect of UI on health and independence in the context of aging, gaps persist in our understanding of its underlying pathophysiology, particularly with regard to overactive bladder (OAB), an important contributor to UI in older adults. Unanswered questions remain regarding the most beneficial treatment strategies for frail older adults and those living with multiple chronic conditions. Furthermore, questions about UI are generally not included as part of frequently used data sets, such as the National Institutes of Health Toolbox, designed to encourage assessment of common geriatric syndromes in studies involving older adults. Thus, the current situation provides many

0002-8614/17/$15.00

opportunities to improve the lives of older adults and to advance the science of aging by overcoming these knowledge gaps and barriers to progress.

UI AND COMMON PATHWAYS

This U13 conference series focused on three common geriatric syndromes, delirium, sleep and circadian rhythm (SCR) disturbance, and UI, with the goal of identifying common shared risk factors and pathophysiological mechanisms to direct future research efforts. Risk factors common to all geriatric syndromes include older age, decline in functional independence, impaired mobility, and impaired cognition.[11] Associations between UI, delirium, and SCR appear to be bidirectional. For example, delirium is recognized as a precipitating risk factor or cause of potentially reversible UI. Conversely, anticholinergic drug treatments for urinary symptoms associated with UI have been linked to cognitive decline, particularly in persons with dementia.[15] Also, urinary symptoms associated with UI, particularly nocturia, are frequently related to SCR disturbance in older adults,[16,17] and nocturia may exacerbate wakefulness after sleep onset in those with insomnia disorder.[16] Conversely, individuals with sleep disturbance, such as sleep apnea or restless leg syndrome, are more likely to report nocturia.[18,19]

At the U13 conference, a transdisciplinary group of invited experts provided short overviews of the current state of UI science within three broad domains: overlap with other common geriatric syndromes and conditions reflecting potential common pathways, mechanisms of bladder and LUT function from the perspective of basic science and studies in humans, and interventions including models of care delivery. Summaries of these overviews for each domain and the resulting collective vision regarding future research priorities follow.

Common Pathways for UI and Other Geriatric Syndromes—Macro Level

Specific chronic diseases, as well as certain disease categories, such as neurological and cardiovascular diseases, are associated with UI.[20] Diabetes mellitus and obesity are 2 chronic disease states that are strongly associated with UI.[21,22] Metabolic syndrome is also an important precursor to diabetes mellitus and vascular diseases, but there is less evidence that it is a UI risk factor.[23,24] Diabetes mellitus, which may result in neurological and vascular impairments, is associated with twice the risk of UI in population-based studies.[25,26] Obesity is also associated with UI, including stress and urgency UI subtypes, in epidemiological studies and clinical trials.[22,27,28] There is evidence from several clinical trials that weight loss in persons with diabetes mellitus and obese women decreases the severity of UI symptoms.[27,29,30]

Diabetes mellitus and vascular disease progression over time may have a direct effect on UI and other LUT symptoms (LUTS) as contributors to impaired bladder detrusor muscle function and control.[31] Early in diabetes mellitus and vascular disease states, decreases in blood flow may contribute to impaired detrusor muscle control, contributing to symptoms of OAB and UI,[32] although declines in bladder structure and control in later-stage diabetes mellitus and vascular disease can lead to sensory and motor dysfunctions, with associated symptoms including underactive bladder, urinary retention, and resulting incontinence.[33] At the level of the LUT, detrusor muscle fibrosis, changes in innervation, neurotransmitter responsiveness, and alterations in urethral composition and control may all contribute to LUTS. The complicated relationship between diabetes mellitus, metabolic syndrome, obesity, and vascular disease and UI and other LUTS needs further exploration of mechanisms related to bladder functional changes over time, bidirectional relationships between disease and bladder symptoms, and the relationship between disease-specific interventions (e.g., weight loss, physical activity) and bladder function.

Persons with neurological diseases and concomitant UI have poorer quality of life and a larger economic burden than those without UI.[34] Some common neurological diseases with accompanying high rates of UI are Alzheimer's disease, stroke, Parkinson's disease, normal-pressure hydrocephalus, multiple sclerosis, spinal cord injuries, lumbar spinal stenosis, and motor neuron diseases. Depending on the location and extent of the neurological lesions, the type and severity of UI may vary.[35] For example, suprapontine lesions may result in complete loss of voluntary bladder control from lack of sphincteric control despite a normal micturition reflex. Cervical lesions typically result in detrusor-external sphincter dyssynergia, whereas thoracolumbar lesions may be associated with detrusor overactivity (DO) or detrusor areflexia (DA), which contribute to LUTS, including UI. Sacral lesions are often associated with DA or detrusor underactivity (DU), although loss of bladder compliance and DO are also possible. Not all people with neurological disease have bladder dysfunction, and individuals with UI may also have subtle neurological factors contributing to bladder symptoms. Despite these generalizations, incomplete understanding of the relationship between the central nervous system and LUTS contributes to the weak association between symptoms and function among individuals in clinical studies.

Although there is ample evidence that many chronic diseases are risk factors for UI, much less is known about the associations between multimorbidity, frailty, and UI, which are highly prevalent in older adults and share similar clinical outcomes, such as high rates of institutionalization, impaired quality of life, and mortality.[20,36,37] Current evidence from observational studies, clinical cohort studies, and clinical trials suggests that frailty is common in older women with UI.[38–40] Although less is known about prevalence of multimorbidity in older adults with UI, older adults with multimorbidity may be more likely to receive better overall quality of care compared to those without multimorbidity.[41] However, when older adults with multimorbidity also experience common geriatric syndromes, such as UI, the quality of care declines.[42] Multiple factors from the individual and the provider perspective complicate treatment of UI in older adults with multimorbidity and frailty. These factors may include, but are not limited to, polypharmacy, drug-drug interactions, limited mobility, competing demands from disease burden, and cognitive decline. Few clinical trials or clinical practice guidelines include specific recommendations on the treatment of UI in older adults with multimorbidity and frailty.[40,43–45]

Collection of data on multimorbidity and frailty in existing longitudinal studies, clinical trials, and clinical care could inform the many existing gaps, guide clinical practice guidelines, and ultimately improve care.

Knowledge is lacking about the effect of upper urinary tract (kidneys, ureters) aging on LUT function (bladder, urethra). In general, aging kidneys alter fluid balance through several mechanisms. Creatinine clearance may decline in older adults in the absence of known kidney disease and other comorbidities.[46] Fluid balance is also affected through decreases in the ability of aging kidneys to respond to antidiuretic hormone, leading to water loss and low urine osmolality.[47] Sodium wasting may occur through low aldosterone levels in older adults. Through these physiological changes that occur with age, older adults may also have higher rates of urine production at night because antidiuretic hormone secretion decreases specifically at night and atrial natriuretic hormone levels are higher. Nocturnal polyuria is defined as more than one-third of 24-hour urine production occurring at night.[48] Predisposing factors for nocturnal polyuria include older age, chronic kidney disease, fluid shifts in extremity edema while recumbent, and osmotic diuresis. Diuretic-induced polyuria contributes to urinary symptoms and may affect adherence to diuretic treatment.[49] The intersection of high urine production at night, nocturia, and impaired sleep is an important area in which more evidence to inform clinical practice guidelines are needed.

In addition to delirium and insomnia, falls and mobility problems are associated with higher rates of UI. One study suggested that urgency UI and stress UI are associated with slow gait speed and poor balance.[50] Another small study reported that bladder sensations of a strong desire to void may decrease gait speed and stride length in older women without UI.[51] In other studies, nocturia with incontinence increased rates of falls.[6] Presence of white matter hyperintensities within key brain regions overlapping with white matter tracts known to be involved in bladder control may be responsible for declines in mobility and micturition sensations.[52] Once completed, the INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINe in the ElderlY (INFINITY) trial will demonstrate whether more-intensive treatment of high blood pressure reduces white matter hyperintensities and decreases overall burden of disease while delaying functional decline in mobility and incontinence.[53] Such trials targeting brain white matter hyperintensities could help inform future prevention studies addressing these and other shared risk factor pathways.

Cellular and Molecular Mechanisms of UI and Common Pathways—Micro Level

Control over urine storage and voiding is based on a series of carefully coordinated steps, including accurate afferent information regarding bladder volume, reception and integrative processing of this information within the central nervous system, ability to make appropriate decisions, a situationally appropriate efferent neural data stream, ability of end organs involved in LUT control (bladder, urethra, pelvic floor) and mobility (brain, muscle, cardiovascular system) to respond, and ability to engage in socially appropriate toileting behavior (Figure 1, Supplementary Video S1).

The stream of afferent activity reporting on bladder capacity originates with the transduction of the mechanical stresses induced by bladder volume to an afferent nerve signal. The demonstrated linkage of afferent activity to volume-induced wall stresses[54] and observations of bursts of bladder afferent activity accompanying small waves of pressure associated with non-voiding contractions[55] are indicative of the relationship between bladder wall

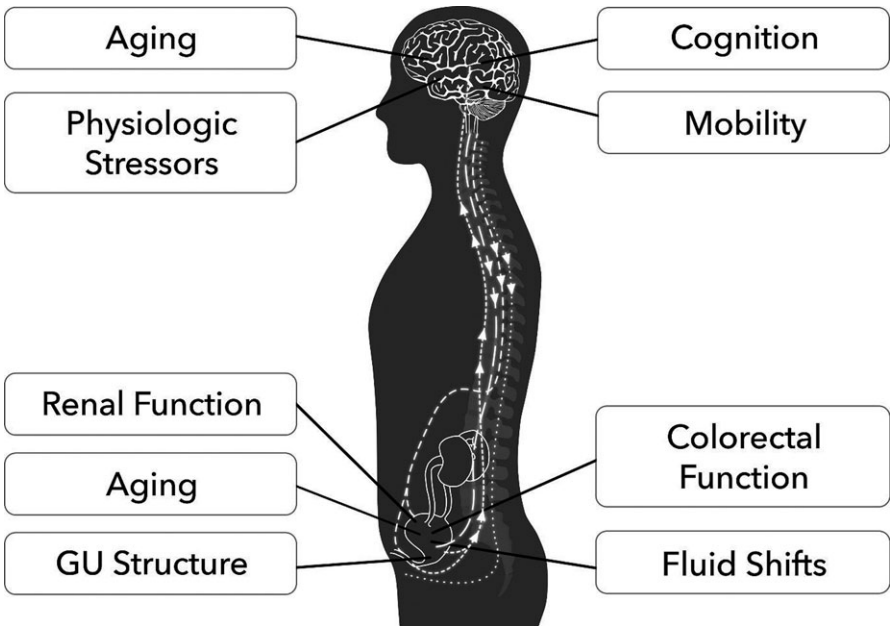

Figure 1. Factors contributing to urinary continence in older adults. Maintaining continence requires adaptive reserve in the bladder and pelvic tissue capabilities, central nervous system control networks, and perceptual processes within the individual's social context. GU = genitourinary. An interactive figure is available at https://adobe.ly/2hDBjvY and as Supplemental Video S1.

biomechanics and afferent responses to bladder volume. Tension in the bladder wall, and thus the relationship between afferent activity and volume, can vary from a minimal value established by the extracellular matrix in the absence of muscle activity to a maximal value due to unsuppressed myocyte activity superimposed on the extracellular matrix.[56] Sympathetic autonomic input normally suppresses detrusor activity, placing afferent sensitivity to bladder volume under central control.

The urothelium has been recognized as a contributor to bladder signaling, rather than acting simply as a passive barrier.[57] Changes associated with aging of the urothelium include increases in the presence of inflammatory cells, P2X3 receptor expression, lipofuscin accumulation, and markers of oxidative stress.[58–61] More-recent findings (unpublished data) regarding the urothelial extracellular matrix include loss of organization, collagen and elastin fiber breakage, thickening, and clumping, contributing to loss of elasticity and greater stiffness.[62] Collagen fibers within the mucosa (urothelium, lamina propria) are normally finer and more organized in a wavy distribution than the larger-diameter fibers in the detrusor smooth muscle and respond differently to stretch. It is likely that these morphological differences reflect functional differences involving mucosal as opposed to muscular responses to bladder distension.

The influence of aging on regulation of volume sensory transduction, transmission, reception, and processing following the tension-induced initiation of the transduction cascade is incompletely understood.[63] Sympathetic modulation of detrusor myocyte activity–induced tension points to the possibility of ongoing sympathetic-mediated central regulation of bladder volume sensitivity. Similar forward-feedback brain regulation of sensory input through end-organ control has been described in other systems such as hearing, permitting adaptive responses aimed at integrating sensory stressors with physiological needs and capabilities. Indirect evidence (power spectral analysis of bladder pressure vs volume waveforms) has indicated increasing influence of brain control over bladder volume sensitivity in an aging mouse cystometric model.[64] Although this could be a pathology of aging, the uniformity of the effect of aging and of the effect within age groups suggests this could be an adaptive mechanism.

Afferent signaling about bladder volume results in activation of the periaqueductal grey in the brainstem. White matter hyperintensity disease (WMD) is associated with loss of the prefrontal cortex–periaqueductal grey long tract connection. Loss of prefrontal inhibition of periaqueductal grey could contribute to urge incontinence. Of interest is the finding that WMD burden in brain areas relevant to urinary control is associated with greater severity, but not necessarily prevalence, of urinary symptoms,[52] indicating the effect of WMD—and perhaps aging—on urinary perceptual processes as a contributor to symptom bother, possibly independent of objective functional changes.

Although intimately involved in the relationship between bladder volume and afferent signaling, the structural and intramural regulatory systems of the bladder are involved with specific responses to efferent activity. Tension in the bladder wall due to chronically high detrusor pressures and overdistended bladder volumes results in hypoperfusion, hypoxia, and activation of oxidative stress mechanisms. A lumbar central pattern generator (lumbar spinal coordinating center) contributes to hind limb control during locomotion in quadrupeds and is probably phylogenetically preserved in humans.[65] This same region communicates with the bladder and the striated muscle component of the urinary sphincter mechanism (external urinary sphincter)[63] and is therefore implicated in the reflexic relationship between bladder volume and voiding. During urine storage, these regions could contribute to detrusor inhibition and sphincter resistance to opening. As a pattern generator, this region could provide the pulsatile sphincteric action observed during voiding in some animal models (mouse, rat) and in dyssynergic human voiding observed in fetuses and infants, dysfunctional voiding in older adults, and in the extreme, neurological injury or disease. The common feature in humans showing this pattern would appear to be loss of suppression related to prefrontal control over synergic pontine voiding, although this remains to be demonstrated. As a contributor to impaired voluntary control and inefficient voiding, loss of normal control over this central pattern generator offers a possible contributor to incontinence in older adults.

Current and Emerging Treatment Modalities for UI

Behavioral therapy for UI encompasses a wide array of strategies, including lifestyle modification, changes in voiding habits, and learning skills to maintain continence. Thus, behavioral therapy is inherently multicomponent and can be individualized depending on the most pertinent individual contributing conditions. Pelvic floor muscle exercise–based behavioral therapy for stress and urgency UI is well studied in women and men.[66,67] Although there is growing evidence of the effectiveness of behavioral therapy in populations with neurological disease such as those with stroke, Parkinson's disease, or multiple sclerosis, larger, controlled trials are needed.[45,68–70] Behavioral therapy requires that individuals maintain motivation and practice to achieve results, which typically occur gradually over several weeks. Evidence suggests that people achieve clinically significant reduction in urgency UI with a self-help booklet describing behavioral therapy, although many perceive greater improvement after receiving instruction from a clinician.[67]

Despite the recommendation that behavioral therapy be the initial treatment approach for UI, many people are not offered treatments. Barriers to broad implementation of behavioral treatments include lack of provider knowledge of behavioral principles and techniques and of a viable reimbursement mechanism for the time needed to teach the behavioral skills. Thus, future research goals include optimizing behavioral training for UI to augment long-term efficacy and improving implementation in order to offer behavioral therapy more broadly. Several studies have evaluated alternate delivery methods to provide behavioral therapy to treat UI, including self-help booklets, Internet-based training, and group classes.[71–73]

UI is usually part of a constellation of urinary symptoms. The symptom complex of urgency (with or without incontinence), identified as OAB,[74] has been equated with

inappropriate detrusor-driven bladder pressurization (DO). More recently, symptoms of impaired voiding have been identified as underactive bladder (UAB),[75] analogously suggestive of insufficient detrusor-driven bladder pressure. These etiological models have contributed to the pursuit of therapies aimed at correcting detrusor dysfunction. For OAB, these initially took the form of nonspecific anticholinergic agents and, in more recent decades, agents aimed at bladder-specific muscarinic M3 receptors.[76] A significant problem with this etiological model is the lack of clear interdependence between symptoms (OAB, UAB) and function (DO, DU) demonstrated during urodynamic assessment.[77–83] An emerging therapeutic model, which may be particularly relevant for older adults, addresses abnormal generation of bladder volume sensory afferent activity due to abnormal focal tensions in the bladder wall or activation of atypical sensory pathways as an etiological pathway for urinary storage symptoms such as OAB and UAB.[84–87]

New therapeutic targets for OAB symptoms include the urothelium, the detrusor, and spinal signaling. Targets of recent investigations have included phosphodiesterase inhibition, purinergic receptors, potassium channel openers, the cannabinoid system, spinal signaling (e.g., gabapentin), and transient receptor potential V1 channel antagonists. Antagonists of the purinergic P2X3 receptor, which are involved in bladder afferent signaling, result in larger voided volumes with less urinary frequency in a rodent model.

PDE5 inhibitors, which the Food and Drug Administration (FDA) has approved for erectile dysfunction, have been associated with reduction in LUTS in men using these agents for their approved purpose.[88–90] Inhibition of fatty acid amine hydrolase, which is a cannabinoid degrading enzyme, similarly leads to depressed bladder afferent signaling with an increase in bladder capacity.[91] Inhibition of aberrant (c-fiber) bladder afferent-induced spinal signaling with gabapentin has been tested in individuals with spinal cord injury but has not been formally evaluated for symptoms of incontinence in individuals without spinal cord injury.[92] A previous study of cannabis in individuals with multiple sclerosis suggested a reduction in urgency UI that was no seen with placebo, although there were no differences in the primary outcome of spasticity.[93] Transient receptor potential channels are found in urothelial cells, bladder afferent nerves, and detrusor smooth muscle cells. An antagonist of transient receptor potential V1 receptors found on substance P and calcitonin gene-related peptide–containing nerves suppressed capsaicin-induced increase in nerve discharge and intravesical pressure without affecting voided volume or maximal voiding pressure in a rodent model,[94] although a phase I clinical trial in humans showed a mean increase in body temperature of up to 1.3°F with the highest administered dose.[95]

Medication-based approaches to influencing central control of bladder function have not been efficacious or have resulted in unacceptable side effects such as sedation. There are no pharmacological treatments for UAB. Functional phenotyping of individuals with OAB, UAB or UI, aimed at establishing mechanisms of pathophysiology, may reveal strategies for personalized therapy or combination therapy designed to optimize treatment goals and minimize side effects.

Third-line treatments for OAB and UI include neuromodulation and chemodenervation. Implantable sacral neuromodulation has been available for refractory urgency UI since 1998 and approved by the FDA for urgency, urge incontinence, and urinary retention. The exact mechanism of action is unknown, but stimulation of the S3 nerve root is thought to reduce bladder afferent signaling and increase relaxation of bladder smooth muscle. Although use in older adults has increased, younger populations are still more likely to receive an implantable stimulator. In one long-term study of Medicare beneficiaries over 10 years, 11% opted for explantation of the device over a mean follow-up of 60 months.[96] Cohort studies have not shown age-dependent differences in efficacy of implantable neuromodulation.[97] Studies in individuals with neurological disease such as Parkinson's disease, stroke, and multiple sclerosis have had mixed results.

Percutaneous tibial nerve stimulation was approved in 2000 for urgency UI and is now approved for use in refractory OAB. Because percutaneous tibial nerve stimulation is minimally invasive and can be administered in an outpatient setting, it may be more feasible in older adults with multiple chronic conditions. Small studies also suggest potential efficacy in older adults with neurological disease[98] or those in residential care.[99]

A recent study compared acupuncture with tolterodine for OAB symptoms in women and showed similar improvements between the groups at 4 weeks, although longer-term studies are needed.[100] The FDA has approved chemodenervation with onabotulinum toxin A for OAB symptoms since 2013. Onabotulinum toxin is presumed to block presynaptic release of acetylcholine, leading to irreversible relaxation of bladder smooth muscle until the toxin is cleared (typically about 6 months). There is greater risk of requiring clean intermittent catheterization after the procedure in persons who have urinary retention at baseline. Ultimately, with all of these approaches, shared decision-making is important to develop a treatment strategy that aligns with the person's preferences and goals of care.

For most geriatric syndromes, single-component interventions are typically less effective, with the evidence supporting multicomponent interventions to reduce incident disease.[101,102] Especially in light of the evidence regarding the association between mobility impairment, changes in neural control of bladder function, and incontinence, the development of novel multicomponent interventions for older adults with multimorbidity and UI deserves renewed attention.[50,52,103] The Multiphase Optimization Strategy is one published strategy for optimizing multicomponent interventions during sequential experiments in order to gain understanding of single-component interventions before implementing a randomized controlled trial.[104] A team science approach with input from multiple disciplines including behavioral scientists and implementation science experts may facilitate development of multicomponent interventions more rapidly.

From Bench to Bedside and Beyond

In addition to discussion of research priorities focused on better treatments, attendees also discussed the urgent need

Table 1. Recommendations for Future Research Priorities and Direction

Category	Example
Regulatory pathways and resilience (causes, mechanisms, pathways)	Defining how aging and specific chronic diseases influence resilience—the ability of regulatory pathways to maintain lower urinary tract homeostasis, normal voiding and continence in older adults when challenged with common stressors (e.g., bladder filling, ischemia, oxidative stress, infection, altered microbiome)
Linkages with other geriatric syndromes (relationships between syndromes)	Bidirectional relationships between urinary incontinence and other geriatric syndromes at the level of shared risk factors and mechanisms or responses to treatment
Designing effective treatments (translation and testing)	Overcoming obstacles to design and testing of single- and multicomponent interventions
Individualizing treatment approaches	Targeting specific treatments to define subpopulation of individuals with voiding disorders or incontinence (e.g., precision medicine)
Help-seeking and uptake of conservative treatments (concerns with implementation and translation to clinical research)	Overcoming barriers to incontinence diagnosis, as well as dissemination and implementation of relevant science
Continence promotion and prevention of lower urinary tract symptoms (predictors, progression, prevention)	Develop deeper understanding of potentially modifiable factors involving individual, caregiver, or environment that contribute to enhanced risk of incontinence in late life
Design and methods considerations	Promote inclusion of secondary outcome measures pertaining to incontinence in large epidemiological studies and clinical trials through advancement of relevant research methods and addition of genitourinary parameters to National Institutes of Health Toolbox

to develop strategies to disseminate existing evidence broadly to the community. Evidence-based practice change models are available to guide best practices for the implementation and dissemination of new models for continence care.[105–107] These models often begin with a practice change leader who creates a sense of urgency about the clinical problem and engaging multiple stakeholders to partner in developing a solution.[108,109] Determination of the core components of a successful quality improvement program is necessary to allow for adaptation and facilitate dissemination.[110]

Investigators have also begun to evaluate the delivery of behavioral therapy to prevent LUTS for populations at risk of developing UI. One study that evaluated a single preoperative visit to teach pelvic floor muscle–based behavioral therapy for continent men preparing for radical prostatectomy for adenocarcinoma of the prostate showed that only 5 men needed to be treated for at least one to achieve postprostatectomy continence.[111] Other studies have evaluated group therapy models in the clinical setting or in community-based settings as preventive strategies for incident UI.[112,113]

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Several overarching research themes were generated during conference planning, presentations, and related discussions. Table 1 includes recommendations and ideas for future research directions that were subsequently synthesized and prioritized. Appendix 1 includes broader discussion of each of the research priorities.

ACKNOWLEDGMENTS

Multiple authors were engaged in the preparation of this paper through service on the Writing Group and the Planning Committee and as presenters. The following key identifies how an author was engaged with this paper: Writing Group (1), Planning Committee (2), Presenter (3).

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Conflict of Interest: Jerry Blaivas: Cofounder, board member and chief scientific officer of Symptelligence, LLC, a medical informatics company that develops software and owns patents relating to LUTS, incontinence diagnosis, clinical decision-making, and phenotyping.

Kathryn Burgio: Grant funding from NIA.

William C. de Groat: Research contract from Astellas Pharmaceutical Company to conduct animal research. Consultant for Bayer Pharma AG, NeuSpera Medical, and Amphora Medical.

Catherine DuBeau: Receipt of honoraria as member of American Geriatrics Society Beers Criteria Review Panel.

Ariel Green: Co-investigator on grants that receive funding from the NIA and the Gordon and Betty Moore Foundation.

Tomas Griebling: Grant funding through the NIA and the Donald W. Reynolds Foundation, neither directly associated with work on this project.

Derek Griffiths: Occasional consulting for University of Pittsburgh and for Laborie Medical.

Alison Huang: Research grants from Pfizer, Inc. awarded through the University of California, San Francisco to conduct research unrelated to this material.

Theodore Johnson: Consultant within past three years for Astellas (unrestricted continuing medical education, use of mirabegron in older adults), Medtronic (UI treatment in long-term care), and Vantia (development of quality-of-life instrument for nocturia).

John Lavelle: Member Scientific Advisory Board Dignify Therapeutics.

Alayne Markland: NIH Grant U01DK106858 and Department of Veterans Affairs funding.

Neil Resnick: NIH grant funding to investigate incontinence since 1982.

Marcel Salive: Employee of the NIA/NIH, which provided a grant for the conference.

Phillip Smith: Research funded by an institutional grant and NIH/NIA Grant 5K76AG054777–02.

Camille Vaughan: Spouse is a full-time employee of Kimberly-Clark Corp.

Adrian Wagg: Monies received personally or for institution for research grants, participation, speaker honoraria, or consultancy from Astellas, Pharma Pfizer Corp, SCA AB.

Jean Wyman: Salary support from National Institute of Diabetes and Digestive and Kidney Diseases, NIH Grant.

The NIA funded this conference (NIA 5U13AG0-39151–02). Additional funding for the conference was provided by Allergan, Astellas, and Medtronic. We thank Marie A. Bernard, PhD, Nancy Lundebjerg, MPA, Francesca Macchiarini, MS, PhD, and all conference participants. We appreciate the excellent administrative support provided by Anna Mikhailovich and Alanna Goldstein, MPH, and the detailed program evaluation provided by Julie Robison, PhD. Views expressed in this article are those of the authors and do not necessarily represent the views of the NIH or other affiliated organizations.

Author Contributions: All authors contributed to this paper.

Sponsor's Role: None.

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APPENDIX 1

RESEARCH PRIORITIES EMERGING FROM AGS/NIA U13 BEDSIDE-TO-BENCH CONFERENCE ON URINARY INCONTINENCE IN OLDER ADULTS

Regulatory Pathways and Resilience (causes, mechanisms, and pathways)

Studies are needed to define how aging and specific chronic diseases influence resilience - the ability of regulatory pathways to maintain lower urinary tract homeostasis, normal voiding and continence in the older adults when challenged with common stressors. Clinically relevant challenges may include mechanistic (e.g. bladder filling, ischemia, oxidative stress, infection, altered microbiome) or symptom-based stressors (e.g. urgency). Knowledge of such resilience mechanisms is needed in order to develop interventions designed to promote normal voiding and continence. More studies are also need to develop a deeper understanding of associations and mechanistic links between specific stimuli at the level of urine constituents, bladder wall, and receptors and associated symptoms. Efforts should also focus on elucidating the mechanisms behind these processes, as well as examining what changes normally occur in the urinary tract with aging and how such changes can be better identified.

Linkages with other Geriatric Syndromes (relationships among syndromes)

A better understanding is needed regarding bidirectional mechanisms that link UI and other lower urinary tract symptoms (nocturia) to other geriatric syndromes, including cognitive impairment, falls, sleep disorders, frailty, depression, falls, and physical activity. There is knowledge to be gained by studies examining how the treatment of one condition affects another. For example, how does the treatment of sleep disorders (such as sleep apnea or insomnia) affect UI; and how does the treatment of UI impact sleep? Furthermore, more needs to be learned regarding the pathophysiology of overactive bladder, which may help to develop more effective treatments for UI.

Designing Effective Treatments (translation and testing)

The T1 translational pipeline involved in translating increased understanding of the mechanisms of aging and disease into the design of effective treatments must be strengthened and sped up. Clear potential exists for identifying therapeutic targets within regulatory pathways, including individual molecules, networks of molecules, and defined pathophysiologic mechanisms. Intervention development may produce single or multi-component treatments for complex older adults and should not exclude often overlooked populations, such as men, nursing home residents, the oldest old, dementia patients, and those with

neurological conditions, refractory OAB, UAB, or mild UI. The value of research could be enhanced by expanding on earlier observations that interventions focused on non-genitourinary targets (e.g., physical function, falls, and vascular risk factors) might improve UI.[114] To this end, designs that allow innovation in how interventions are implemented to promote discovery (as was the case when Tai Chi was identified as a fall prevention strategy) need to be pursued.

Individualizing Treatment Approaches

Due to the complexities of the regulatory pathways and the many mechanisms leading to UI and other LUTS, there is tremendous variation between individuals in the etiology and manifestation of lower urinary tract dysfunction. Moreover, such inter-individual variability increases with aging. This results in a need to better individualize treatment programs, at times consisting of multiple varying components. Research is needed to establish strategies for determining the most effective and appropriate single or multi-component treatment approaches for individual older adults, especially in the context of frailty or multi-morbidity. As providers attempt to individualize treatments, phenotype-specific treatment protocols will be needed, for example, for urgency or detrusor overactivity. Targeting interventions to specific types of patients or populations has potential to optimize efficacy as well as efficiency. Further, as individualized approaches to treatment are developed, the value of qualitative research into goal setting and how to approach the patient's goals to ultimately achieve patient-centered outcomes must not be neglected.

Help-Seeking and Uptake of Conservative Treatments (implementation and T2 translation issues)

The majority of people with UI do not seek treatment and a large proportion of those who do, lack access to state-of-the-art conservative therapies, especially behavioral treatments. Therefore, a better understanding of the facilitators and barriers to these processes and interventions to promote treatment seeking is needed. Help-seeking research might examine issues of stigma and public awareness, as well as specific factors associated with help-seeking. Implementation science and health services research are needed to extend beyond the usual focus on individual patients, to include a focus on providers and practice patterns (including referral patterns), health system factors (including reimbursement), and strategies to optimize the availability and uptake of conservative treatments. It is important to pursue the dissemination of increased knowledge about incontinence at both the patient and provider level and therefore help providers screen for UI and implement non-pharmacologic therapies. A geriatric incontinence toolkit could be developed and disseminated to primary care providers.

Continence Promotion and LUTS Prevention (predictors, progression, and prevention)

Although a large literature exists on risk factors for UI in some populations, there is still a need for work on modifiable factors, especially individual behaviors (e.g., toileting, voiding habits, lifestyle), that influence the risk of developing or worsening UI. Knowledge in this area could inform specific prevention intervention strategies to promote sustained continence in the context of aging. While examining individual level factors has been the traditional approach, it is also important to consider exogenous factors, such as the role of caregivers and other interpersonal and societal factors potentially involved in the etiology of UI. Understanding risk and protective factors could help identify at-risk target populations, such as those with diabetes, neuro-degenerative disease, multi-parity, early symptoms, or hospitalization, for educational or skill-based prevention interventions. Furthermore, the field of UI prevention could benefit from more of a life course perspective, not just prevention in later years.

Design and Methods Considerations

Investigative efforts should include determining the most clinically-relevant and meaningful outcomes and outcome measures for incontinence trials in older adults, potentially driven by patients. To that end, investigators of studies examining outcomes related to aging need to also include questions related to urinary symptoms. Finally, for studies examining the effects of age, stratified analyses may help reveal more about the impact of interventions and how they work in the oldest old.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Writing Group, Planning Committee, Presenter List

Video S1. Video of the interactive version of Figure 1.

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