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

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Abstract

The American Geriatrics Society (AGS), with support from the National Institute on Aging (NIA) 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 (SCR) 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, clinical, and translational research on urinary incontinence in older adults; for identifying gaps in knowledge; and for the development of 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.

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INTRODUCTION

Urinary incontinence (UI) occurs in nearly 40% of women over the age of 80, in 10–35% of older men, and in up to 80% of long term care residents^{1–4}. The impact of UI among older adults is far-reaching beyond impaired quality of life. In a recent evaluation of persons hospitalized with serious illness, bladder and bowel incontinence were rated as conditions worse than death by more than half of the participants (the most undesirable condition among those queried)⁵. Moreover, older adults with UI are at an increased risk of depression, social isolation, and falls^{6–8}. Incontinence is also associated with loss of independence and ultimately institutionalization in some studies^{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 function associated with aging, and medications, overwhelm the individual's capacity to remain continent¹¹. Treatment options for UI have expanded over the past two decades; however, even with increasing options for treatment and emerging prevention strategies, UI continues to be underreported and undertreated with many afflicted patients failing to report symptoms and many providers ignoring the problem entirely^{12–14}.

Despite the negative impact 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 NIH Toolbox, designed to encourage assessment of common geriatric syndromes in studies involving older adults. Thus, the current situation provides many opportunities to improve the lives of older adults and to advance the science of aging by overcoming these knowledge gaps and barriers to progress.

URINARY INCONTINENCE 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 pathophysiologic mechanisms to direct future research efforts. Risk factors common to all geriatric syndromes include older age, decline in functional independence, impaired mobility, and impaired cognition¹¹. 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 among persons with dementia¹⁵. 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 disorder¹⁶. 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/lower urinary tract function from a basic science and T1 translational perspective, and interventions including models of care delivery. Summaries of these overviews for each domain follow and the resulting collective vision regarding future research priorities.

Common Pathways for UI and Other Geriatric Syndromes – Macro level

Specific chronic diseases along with other disease categories, such as neurologic and cardiovascular diseases, are associated with increased rates of UI.²⁰ Diabetes and obesity represent two chronic disease states that are strongly associated with UI.^{21,22} Metabolic syndrome also represents an important precursor to diabetes and vascular diseases, but less data exist showing it is a known UI risk factor.^{23,24} Diabetes, which may result in neurologic and vascular impairments, is associated with a two-fold increase in UI from population-based studies.^{25,26} Obesity is also associated with increased rates of UI, including both stress and urgency UI subtypes, in epidemiologic studies and clinical trials.^{22,27,28} Further, there is evidence from several clinical trials that weight loss in persons with diabetes and among obese women improves the severity of UI symptoms.^{27,29,30}

Diabetes and vascular disease progression over time may have direct impact on UI and other LUTS as contributors to impaired bladder detrusor muscle function and control.³¹ Early in diabetes and in vascular disease states, decreases in blood flow may contribute to impaired detrusor muscle control, contributing to symptoms of overactive bladder and/or UI.³² However, declines in bladder structure and control in later stage diabetes and vascular disease can lead to both sensory and motor dysfunctions, with associated symptoms including underactive bladder, urinary retention and resulting incontinence.³³ At the level of the lower urinary tract, increased detrusor muscle fibrosis, changes in innervation, neurotransmitter responsiveness and alterations in urethral composition and control may all contribute to lower urinary tract symptoms (LUTS). The complicated relationship of diabetes, metabolic syndrome, obesity, and vascular disease to UI and other LUTS needs further exploration of mechanisms related to bladder functional changes over time, bi-directional relationships between disease and bladder symptoms, and the relationship of disease-specific interventions (such as weight loss and physical activity) on bladder function.

Among persons living with neurologic diseases, those with concomitant UI experience greater impairments in QOL and a larger economic burden compared to those without UI.³⁴ Some common neurologic diseases that have increased rates of UI include Alzheimer dementia, stroke, Parkinson disease, normal pressure hydrocephalus, multiple sclerosis, spinal cord injuries, lumbar spinal stenosis, and motor neuron diseases. Depending on the location and the extent of the neurologic lesion(s), 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, while 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); however, loss of bladder compliance and DO are also possible. Not all patients with neurologic disease have bladder dysfunction and patients with UI may also have subtle neurologic factors contributing to bladder symptoms. Despite these generalizations, incomplete understanding of the relationship between the central nervous system and LUT contributes to the poor association of symptoms with function in the individual patient.

While there is ample evidence that many chronic diseases are risk factors for UI, much less is known about the associations among multi-morbidity, frailty, and UI. Multi-morbidity, frailty, and UI are highly prevalent among older adults and share similar clinical outcomes, such as increased 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 among older women with UI.^{38–40} While less is known about multi-morbidity prevalence among older adults with UI, older adults with multi-morbidity may be more likely to receive better overall quality of care.⁴¹ However, when older adults also experience common geriatric syndromes, such as UI, the quality of care declines.⁴² Treatment of UI in older adults with multi-morbidity and frailty is complicated by multiple factors from the patient and the provider perspective. 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 among older adults with multi-morbidity and frailty.^{40,43–45} Collection of data measuring multi-morbidity 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 impact of upper urinary tract (kidneys and ureters) aging on LUT function (bladder and urethra). In general, the aging kidney impacts 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 aging kidney's ability to respond to anti-diuretic hormone (ADH), leading to water loss and decreased urine osmolality.⁴⁷ Sodium wasting may occur through decreased aldosterone levels in older adults. Through these physiologic changes that occur with age, older adults may also have increased rates of urine production at night via decreased rates of ADH secretion specifically at night and lower rates of atrial natriuretic hormone. Nocturnal polyuria is defined by more than a third of the 24-hour urine production occurring at night⁴⁸. Predisposing factors for nocturnal polyuria include advanced age, chronic kidney disease, fluid shifts in extremity edema while recumbent, and osmotic diuresis. Diuretic-induced polyuria contributes to urinary symptoms, and may impact adherence to diuretic treatment.⁴⁹ The intersection of increased urine production at night, nocturia, and impaired sleep represents an important area where more evidence to inform clinical practice guidelines are needed.

In addition to delirium and insomnia, falls and mobility problems are associated with increased rates of UI. One study suggested that urgency UI and stress UI are associated with decreased gait speed and 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 INFINITY (INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINE in the ElderLY) trial will demonstrate whether more intensive treatment of elevated blood pressure reduces white matter hyperintensities and decreases overall burden of disease while delaying functional declines 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 & Common pathways – Micro level

Control over urine storage and voiding is predicated on a series of carefully coordinated steps. These include accurate afferent information regarding bladder volume, the 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 in mobility (brain, muscle, cardiovascular system) to respond, plus the ability to engage in socially appropriate toileting behavior (Figure 1, 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 stresses⁵⁴ and observations of bursts of bladder afferent activity accompanying small waves of pressure associated with non-voiding contractions⁵⁵ are indicative of the relationship of bladder wall biomechanics to afferent responses to bladder volume. Tension in the bladder wall, and thus the relationship of afferent activity to volume, can vary from a minimal value established by the extracellular matrix (ECM) in the absence of muscle activity, to a maximum due to unsuppressed myocyte activity superimposed on the ECM⁵⁶. Detrusor activity is normally suppressed by sympathetic autonomic input, 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 barrier⁵⁷. Published 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 presented (*Birder et al., unpublished*) regarding the urothelial extracellular matrix include loss of organization, collagen/elastin fiber breakage, thickening, and clumping, contributing to loss of elasticity and increased stiffness⁶². Collagen fibers within the mucosa (urothelium/lamina propria) are normally finer and more organized in a wavy distribution than the larger diameter fibers within the detrusor smooth muscle, and demonstrate different responses to stretch. These morphologic differences likely 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 over bladder volume sensitivity. Similar forward-feedback brain regulation over sensory input via end-organ control has been described in other systems such as hearing, permitting adaptive responses aimed at integrating sensory stressors with physiologic needs and capabilities. Indirect evidence (power spectral analysis of bladder pressure vs. volume waveforms) has suggested increasing influence of brain control over bladder volume sensitivity in an aging mouse cystometric model⁶⁴. Although this could be a pathology of aging, the uniformity of both aging impact and 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 (PFC)-periaqueductal grey (PAG) long tract connection, contributing to loss of voluntary control over storage vs. voiding. Loss of prefrontal inhibition of PAG could contribute to urge incontinence. Of interest is the finding that WMD disease burden in brain areas relevant to urinary control is associated with increased severity, but not necessarily prevalence of urinary symptoms⁵², pointing to the impact of WMD – and perhaps aging – on urinary perceptual processes as a contributor to symptom bother, possibly independent of objective functional changes.

While intimately involved in the relationship of 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 increased detrusor pressures and/or over-distended bladder volumes result in hypoperfusion, hypoxia, and activation of oxidative stress mechanisms. A lumbar central pattern generator (Lumbar Spinal Coordinating Center, LSCC) contributes to hindlimb control during locomotion in quadrupeds and is likely phylogenetically preserved in humans⁶⁵. This same region communicates with bladder and the striated muscle component of the urinary sphincter mechanism (external urinary sphincter, EUS)⁶³, and is therefore implicated in the reflexic relationship of bladder volume and voiding. During urine storage, these regions could contribute to detrusor inhibition/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 fetal life/infants, dysfunctional voiding in older adults, and in the extreme, neurologic injury/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 both impaired voluntary control and inefficient voiding, however, 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}. While there is growing evidence for behavioral therapy in populations with neurologic disease such as those with stroke, Parkinson disease, or multiple sclerosis, larger, controlled trials are needed^{45,68–70}. Behavioral therapy requires that individuals maintain motivation and practice in order to achieve results, which typically occur gradually over several weeks. Evidence suggests patients achieve clinically significant reduction in urgency UI with a self-help booklet describing behavioral therapy, although many patients perceive greater improvement after receiving instruction from a clinician⁶⁷.

Despite the recommendation that behavioral therapy be the initial treatment approach for UI, many patients are not offered treatments. Barriers to broad implementation of behavioral treatments include lack of provider knowledge of behavioral principles and techniques and 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 suffered by the individual. The symptom complex of urgency (with or without incontinence), identified as OAB⁷⁴, has been equated with inappropriate detrusor-driven bladder pressurization (detrusor overactivity, DO). More recently, symptoms of impaired voiding have been identified as “underactive bladder (UAB)”⁷⁵, analogously suggestive of insufficient detrusor-driven bladder pressure. These etiologic 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 receptors⁷⁶. A significant problem with this etiologic 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 either abnormal focal tensions in the bladder wall and/or activation of atypical sensory pathways as an etiologic pathway for urinary storage symptoms such as OAB and UAB^{84–87}.

New therapeutic targets for OAB symptoms include the urothelium, 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 (TRP) V1 channel antagonists. Antagonists of the purinergic P2X3 receptor, which are involved in bladder afferent signaling, result in larger voided volumes with decreased urinary frequency in a rodent model.

PDE5 inhibitors, FDA approved for erectile dysfunction, have been associated with improved lower urinary tract symptoms in men using these agents for their approved purpose^{88–90}. Inhibition of fatty acid amine hydrolase, which is a cannabinoid degrading enzyme, similarly lead to depressed bladder afferent signaling with an increase in bladder

capacity⁹¹. Inhibition of aberrant (c-fiber) bladder afferent-induced spinal signaling with gabapentin has been tested in spinal cord injury (SCI) patients, but has not been formally evaluated for symptoms of incontinence in the non-SCI population⁹². A previous study of cannabis in multiple sclerosis patients suggested a reduction in urgency UI compared to placebo although there were no differences in the primary outcome of spasticity⁹³. TRP channels are found in urothelial cells, bladder afferent nerves, and detrusor smooth muscle cells. An antagonist of TRPV1 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 model⁹⁴. However, a phase I clinical trial in humans showed a mean increase in body temperature of up to 1.3° F with the highest administered dose⁹⁵.

Medication-based approaches to influence central control of bladder function thus far have resulted in low efficacy or unacceptable side effects such as sedation. Currently there are no pharmacologic treatments for UAB. Functional phenotyping of patients with OAB/UAB/UI, aimed at establishing mechanisms of pathophysiology, may reveal strategies for personalized therapy or combination therapy aimed at optimizing treatment goals and minimizing 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, FDA approved for urgency, urge incontinence, and urinary retention. The exact mechanism of action is unknown; however, stimulation of the S3 nerve root is thought to reduce bladder afferent signaling and increase relaxation of bladder smooth muscle. While use in older patients has increased, younger populations are still more likely to receive an implantable stimulator. In one long-term study of Medicare recipients over 10 years, 11% of patients opted for explantation of the device over a mean follow-up period of 60 months⁹⁶. Cohort studies have not shown age-dependent differences in efficacy of implantable neuromodulation⁹⁷. Studies in patients with neurologic disease such as Parkinson disease, stroke and multiple sclerosis, have shown mixed results.

Percutaneous tibial nerve stimulation (PTNS) was approved in 2000 for urgency UI and is now approved for use in refractory overactive bladder. Because PTNS is minimally invasive and can be administered in an outpatient setting, it may be more feasible in an older population with multiple chronic conditions. Small studies also suggest potential efficacy in older adults with neurologic disease⁹⁸ or those in residential care⁹⁹.

A recent study compared acupuncture to tolterodine for overactive bladder symptoms in women and showed similar improvements between the groups at 4 weeks, although longer term studies are needed¹⁰⁰. Chemodenervation with onabotulinum toxin A has been FDA-approved for overactive bladder 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 increased 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 patient preferences and goals of care.

For most geriatric syndromes, single intervention studies are typically less effective, whereas evidence supports multicomponent interventions to reduce incident disease^{101,102}.

Especially in light of the evidence regarding the association of mobility impairment and changes in neural control of bladder function with incontinence, the development of novel multicomponent interventions for older adults with multi-morbidity and UI deserves renewed attention^{50,52,103}. The Multiphase Optimization Strategy is one published strategy for optimizing multicomponent interventions, while gaining understanding of single intervention components prior to a randomized controlled trial¹⁰⁴. 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 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 in order to allow for adaptation and facilitate dissemination¹¹⁰.

Investigators have also begun to evaluate the delivery of behavioral therapy to *prevent* lower urinary tract symptoms for populations at risk of developing UI. One study evaluated a single pre-operative visit to teach pelvic floor muscle-based behavioral therapy for continent men preparing to undergo radical prostatectomy for adenocarcinoma of the prostate and showed only 5 men needed to be treated in order for at least one to achieve post-prostatectomy continence¹¹¹. Other studies have evaluated group therapy models either in the clinical setting or in community-based settings as preventive strategies for incident UI^{112,113}.

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

Ultimately, 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. Supplementary Appendix S2 includes broader discussion of each of the research priorities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

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Honoraria		X		X		X		X		X		X		X
Speaker Forum		X		X		X		X		X		X		X
Consultant		X		X		X		X		X		X	X	
Stocks		X		X		X		X		X		X		X
Royalties		X		X		X		X		X		X		X
Expert Testimony		X		X		X		X		X		X		X

Board Member	X		X		X		X		X		X		X	
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Personal Relationship	X		X		X		X		X		X		X	
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Grants/Funds	X		X		X		X	X			X			X
Honoraria	X		X		X		X		X		X			X
Speaker Forum	X		X		X		X		X		X			X
Consultant	X		X		X		X		X		X		X	
Stocks	X		X		X		X		X		X			X
Royalties	X		X		X		X		X		X			X
Expert Testimony	X		X		X		X		X		X			X
Board Member	X		X		X		X		X		X			X
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Grants/Funds	X		X		X		X		X		X		X	
Honoraria	X		X		X		X		X		X			X
Speaker Forum	X		X		X		X		X		X			X
Consultant	X		X		X	X			X	X				X
Stocks	X		X		X		X		X	X				X
Royalties	X		X		X		X		X		X			X
Expert Testimony	X		X		X		X		X		X			X
Board Member	X		X		X		X		X		X			X

Patents	X		X		X		X		X		X		X	
Personal Relationship	X		X		X		X		X		X		X	
Elements of Financial/ Personal Conflicts	Author 22 Mary H. Palmer		Author 23 Neil Resnick		Author 24 Marcel Salive		Author 25 Phillip Smith		Author 26 Stephanie Studenski		Author 27 Camille Vaughan		Author 28 Adrian Wagg	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation	X		X		X		X		X		X		X	
Grants/Funds	X		X		X		X		X		X		X	
Honoraria	X		X		X		X		X		X		X	
Speaker Forum	X		X		X		X		X		X		X	
Consultant	X		X		X		X		X		X		X	
Stocks	X		X		X		X		X		X		X	
Royalties	X		X		X		X		X		X		X	
Expert Testimony	X		X		X		X		X		X		X	
Board Member	X		X		X		X		X		X		X	
Patents	X		X		X		X		X		X		X	
Personal Relationship	X		X		X		X		X		X		X	
Elements of Financial/ Personal Conflicts	Author 29 Leslie Wolfson		Author 30 Jean Wyman											
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation	X		X											
Grants/Funds	X		X											
Honoraria	X		X											
Speaker Forum	X		X											
Consultant	X		X											
Stocks	X		X											
Royalties	X		X											
Expert Testimony	X		X											
Board Member	X		X											
Patents	X		X											

Personal Relationship	X	X
* Authors can be listed by abbreviations of their names.		
For all “Yes” responses provide a brief explanation here:		
The following individuals do not have a conflict of interest:		
Peter Abadir		
Karl-Erik Andersson		
Tamara Bavendam		
Lori Birder		
Ananias Diokno		
Matthew Fraser		
Patricia Goode		
Francine Grodstein		
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Figure 1. Factors Contributing to Urinary Continence in Older Adults

Maintaining continence requires adaptive reserve within 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 online as Supplemental Video S1.

Table 1**Recommendations for Future Research Priorities and Direction**

Category	Example
Regulatory Pathways and Resilience (causes, mechanisms, and 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 the older adults when challenged with common stressors (e.g. bladder filling, ischemia, oxidative stress, infection, altered microbiome)
Linkages with other Geriatric Syndromes (relationships among syndromes)	Bidirectional relationships between urinary incontinence and other geriatric syndromes at the level of shared risk factors/mechanisms or responses to treatment
Designing Effective Treatments (translation and testing)	Overcoming obstacles to the design and testing of single and multi-component interventions
Individualizing Treatment Approaches	Targeting specific treatments to define subpopulation of patients with voiding disorders or incontinence (e.g. Precision Medicine)
Help-Seeking and Uptake of Conservative Treatments (implementation and T2 translation issues)	Overcoming barriers to incontinence diagnosis, as well as dissemination and implementation of relevant science
Continence Promotion and LUTS Prevention (predictors, progression, and prevention)	Develop a deeper understanding of the potentially modifiable factors involving the patient, caregiver or environment that contribute to an enhanced risk of incontinence in late life
Design and Methods Considerations	Promote the inclusion of secondary outcome measures pertaining to incontinence in large epidemiological studies and clinical trials, through the advancement of relevant research methods and addition of genitourinary parameters to NIH Toolbox