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14. ABSTRACT

Growing research into interstitial cystitis/bladder pain syndrome (IC/BPS), a prevalent, debilitating urologic condition characterized by pain perceived to derive from the bladder, suggests a potential role for the diverse microbial communities of the urinary tract in disease development and progression. To explore the pathophysiology of IC/BPS, we will examine the relation of these urinary bacterial and fungal communities and their impact on the bladder urothelium to patient symptomatology, phenotypes, and treatment outcomes, culminating in an investigation of how these microbial communities could guide diagnosis, classification and treatment decisions for these patients. The novel application of large-scale systems biology approaches to the urinary tract and the integration of these data with detailed clinical phenotyping will facilitate profound advances in the approach to and understanding of this condition and will serve as the foundation for additional studies developing new preventative and therapeutic approaches.

15. SUBJECT TERMS
Interstitial Cystitis, Bladder Pain Syndrome, Microbiome, Urobiome, Fungi, Machine Learning

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a. **Updated Curriculum Vitae**

b. **Ackerman AL**, Torosis M, Jackson NJ, Caron AT, Kaufman MR, Lowder JL, Routh JC. The Persistency Index: a novel screening tool for identifying myofascial pelvic floor dysfunction in patients seeking care for lower urinary tract symptoms. Am J Obstet Gynecol. 2023 Aug 24:S0002-9378(23)00587-2. doi: 10.1016/j.ajog.2023.08.017. Online ahead of print. PMID: 37633575

c. Dallas KB, Chiang JN, Caron AT, Anger JT, Kaufman MR, **Ackerman AL**. Development and Validation of a Machine Learning Algorithm to Classify Lower Urinary Tract Symptoms. medRxiv 2022.12.25.22283168; Preprint. doi: 10.1101/2022.12.25.22283168. *In submission.*

1. **INTRODUCTION:**

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating, incurable chronic condition whose central feature is intrusive pain attributed to the bladder in the absence of other demonstrable pathology, such as urinary tract infection (UTI). This is a diagnosis of exclusion; thus, patients diagnosed with IC/BPS likely encompass multiple disease phenotypes reflecting different pathologies with overlapping symptomatology. With this kind of heterogeneity, it has been challenging to advance our understanding of IC/BPS disease mechanisms or improve care and management. The similarity of IC/BPS symptoms to UTI suggests a microbial involvement, and modern, sensitive microbial detection methods have further implicated the hypothesis that IC/BPS-associated microbes interact with the bladder to perpetuate a chronic inflammation responsible for the painful symptoms of IC/BPS. However, while alterations in urinary bacterial community diversity are evident in IC/BPS, the differences observed thus far have provided little diagnostic utility or insight into disease mechanisms. Assuming multiple etiologies for the symptoms of IC/BPS patients, we hypothesize that perturbations in microbial communities associated with IC/BPS will only become meaningful in concert with objective clinical phenotyping identifying more homogenous disease phenotypes. We seek to better define these IC/BPS phenotypes utilizing an expanded set of questionnaires focused on the symptomatic domains implicated in our Discovery award. In addition, we will create novel indices to quantitate the salient features of each phenotype for use in clinical care and research assessment. Previously, we generated a simple PCR-based tool to assess urinary microbial biomarkers for their potential as a diagnostic test which demonstrated good clinical potential to identify unique IC/BPS phenotypes. We also will further optimize this PCR-based assay to develop a rapid, scalable tool for the diagnosis and phenotyping of IC/BPS patients. We will also examine the utility of this microbial profiling assay in guiding treatment decisions, which may dramatically improve IC/BPS care. Lastly, we will explore *in vitro* the host-microbe interactions that influence development of bladder-specific pain. We will study the virulence, invasiveness, and inflammatory potential of patient-derived primary microbial isolates and their impact on urothelial activation and gene expression. Together, these goals combine clinical phenotyping, microbial community profiling, and *in vitro* disease modeling to define clinical manifestations, microbial patterns, treatment responses, and molecular etiologies of IC/BPS phenotypes. This approach will allow the development of clinically useful disease measures and testing paradigms and promote a more comprehensive understanding of how IC/BPS pathogenesis is associated with variations in commensal and pathobiont microorganisms.

2. **KEYWORDS:**

Interstitial Cystitis, Bladder Pain Syndrome, Microbiome, Fungi, Clinical Microbial Isolates, Host-Pathogen Interactions, Urobiome, Clinical Phenotyping, Biomarkers, Predictive Algorithms, Machine Learning

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**
  - The Major tasks of the project as specified in the SOW are listed below and described in greater detail in the table below. The targeted timeline and current progress are specified for each subheading.

1. *Patient Recruitment and Sample Accrual*
2. *Deep Clinical Phenotyping of IC/BPS Subjects*
3. *Bacterial And Fungal Community Profiling*
4. *Validation Of Microbial Markers as Prognostic Indicators*
5. *Exploration Of Host-Microbe Interactions Related to IC/BPS*
6. *Probe Fungal Antagonism of Lactobacilli in Urothelial Co-Cultures*

Aim 1: **To evaluate the diagnostic accuracy and prognostic utility of a novel microbial biomarker panel to better define IC/BPS phenotypic and clinical characteristics.**	**Target Timeline (Mo.)**	**Actual Progress**
Major Task 1: PATIENT RECRUITMENT AND SAMPLE ACCRUAL		
<u>Subtask 1.</u> Ethical Study Review 1.1. Local IRB Approval 1.2. HRPO/ACURO Approval	1-3	Completed
<u>Subtask 2.</u> Sample Accrual 2.1. Identification of Appropriate Patient Candidates 2.2. Collection of Patient Urine and Clinical Data 2.3. Initial Sample Processing and Aliquoting 2.4. Cataloging of Patient Clinical Information	3-12	In Progress (35% Complete)
<u>Subtask 3.</u> Patient Follow-up/Post-Treatment Assessment 3.1. Assignment of Subjects to Standardized Treatment Pathway 3.2. Collection of Post-treatment Urine, Clinical Data, and Response Outcomes 3.3. Secondary Sample Processing and Aliquoting 3.4. Clinical Database Management and Secure Archiving	6-18	In Progress (25% Complete)
Major Task 2: DEEP CLINICAL PHENOTYPING OF IC/BPS SUBJECTS		
<u>Subtask 1.</u> Definition of IC/BPS Phenotypes Using Machine Learning 1.1. Unsupervised Clustering of Clinical Data to Define Subgroups 1.2. Detailed Description of Salient Features of Each Subgroup 1.3. Determination of Discriminatory Factors as Potential Prognostic Markers	9-15	1.1, 1.2: Completed 1.3: In Progress (90% Complete)
<u>Subtask 2.</u> Development of Novel IC/BPS Phenotypic Indices 2.1. Definition of New Clinical Measures to Quantitate Unique Symptomatic Domains Using Discriminatory Factors in 1.3. 2.2. Determination of Face and Construct Validity 2.3. Validation of Proposed Measures on Independent Population	15-24	In Progress (80% Complete)
Major Task 3: BACTERIAL AND FUNGAL COMMUNITY PROFILING		
<u>Subtask 1.</u> Microbial Profiling by Next-Generation Sequencing 1.1. DNA Extraction from Urine and Quality Control Assessment 1.2. Library Creation and Next Generation Sequencing (ITS1, 16S) 1.3. Bacterial and Fungal Taxonomic Assignment of OTUs	12-20	Not Yet Started (0% Complete)
<u>Subtask 2.</u> Validation of Community Profiling by qPCR 2.1. Primer Design and Validation 2.2. Assessment of qPCR Assay Validity and Reliability 2.3. Determination of Test-Specific *Diagnostic* Thresholds	12-24	In Progress (95% Complete)

<u>Subtask 3.</u> Bioinformatics/Biostatistical Analysis 3.1. Description of Control and IC/BPS Microbial Populations 3.2. Confirmatory Reanalysis of Populations Altered in IC/BPS 3.3. Correlation of Microbial Population Features with Urinary Phenotypes defined in Major Task 2. 3.4. Validation of qPCR correlations with NGS findings	18-26	In Progress (20% Complete)
Major Task 4: VALIDATION OF MICROBIAL MARKERS AS PROGNOSTIC INDICATORS		
<u>Subtask 1.</u> Correlation of qPCR Microbial Biomarker Assay with Symptomatically-Defined Phenotypes 1.1. Statistical Correlation of qPCR Assay with Phenotypic Classifications Defined in Major Task 1 1.2. Iterative optimization of qPCR Assay with additional taxa defined in Major Task 3 as needed 1.3. Determination of Test-Specific *Phenotypic* Thresholds	18-26	In Progress (20% Complete)
<u>Subtask 2.</u> Determination of Potential of qPCR Microbial Biomarker Assay to Predict Patient Responses to Standardized IC/BPS Treatments 2.1. Statistical Correlation of Baseline qPCR Assay with Treatment Responses to IC/BPS Therapies 2.2. Correlation of individual taxa with improvements in specific symptomatic domains 2.3. Assessment of Intraindividual Changes in Microbial Composition Related to Symptomatic Improvements	22-30	Not Yet Started (0% Complete)
***Aim 2:* To examine host-microbe interactions influencing the development of bladder-specific pain.**		
Major Task 5. EXPLORATION OF HOST-MICROBE INTERACTIONS RELATED TO IC/BPS		
<u>Subtask 1.</u> Generation of Primary Clinical Microbial Isolate Library 1.1. Growth of bacterial and fungal clinical isolates using a wide range of media and growth conditions 1.2. Expansion and Purification of Isolates By Serial Propagation 1.3. Identification and Characterization by Sequencing and Microscopic Examination 1.4. Cataloging of Isolates Against Symptoms of Originating Subject	3-12	1.1, 1.2: Completed 1.3, 1.4: In Progress (70% complete)
<u>Subtask 2.</u> Examination of Virulence of Primary Candida Strains 2.1. Examine adhesion and cytotoxicity of Candida clinical isolates in urothelial co-cultures 2.2. Investigate invasive potential of Candida isolates in a genitourinary, epithelial model 2.3. Assessment of Candida Strain filamentation potential 2.4. Statistical Correlation of Virulence with Symptoms in Originating Subject	12-30	2.1, 2.2, 2.4: In Progress (80% Complete) 2.3: Completed
<u>Subtask 3.</u> Analysis of impact of Candida isolates on urothelial cells 3.1. Measure cytokine production by urothelial cells following co-culture with clinical isolates 3.2. Targeted qPCR-based examination of expressional changes in implicated inflammatory, activation, and nociceptive pathways 3.3. Examine global urothelial transcriptional changes following co-culture with clinical isolates 3.4. Statistical Correlation of Inflammatory and Transcriptional Changes with Symptoms in Originating Subject	12-30	In Progress (75% Complete)
Major Task 6. PROBE FUNGAL ANTAGONISM OF LACTOBACILLI IN UROTHELIAL CO-CULTURES		

<u>Subtask 1</u>. Assess Primary Lactobacillus Strain Effect on Candida Virulence 1.1. Exclusion, Displacement, and Competition Experiments to Assess Inhibition of Candida Adhesion by Primary Lactobacilli Strains 1.2. Examine Impact of Primary Lactobacillus Strains on Candida Filamentation 1.3. Assess Inhibition of Candida-mediated Cytotoxicity in Urothelial Co-culture of Unique Primary Lactobacillus Strains	18-22	In Progress (15% complete)
<u>Subtask 2.</u> Test Pathogenicity of Lactobacillus Strains for Urothelial Cells 2.1. Examine Cytotoxicity of Lactobacillus Strains on Urothelial Monolayers 2.2. Measure Cytokine Production by Urothelial Cells following Co-culture with Clinical Lactobacillus Isolates 2.3. Targeted, qPCR-based Examination of Expressional Changes in Implicated Inflammatory, Activation, and Nociceptive Pathways	20-30	In Progress (5% complete)
Major Task 7. DATA SYNTHESIS		
<u>Subtask 1.</u> Compilation of all data and manuscript preparation 3.1. Statistical Modeling and Integration of Multiple Datasets 3.2. Manuscript Writing and Submission	24-36	In Progress (10% complete)

- **What was accomplished under these goals?**

1. Patient Recruitment and Sample Accrual

***a.* Sample Accrual and Patient Follow-up/Post-Treatment (Task 1.2)**

We continue to hold a specialized pelvic pain clinic to facilitate trial recruitment and management. We continue to recruit subjects and catalog their clinical data. Some subjects have completed all study activities including follow up assessment.

2. Deep Clinical Phenotyping of IC/BPS Subjects

***a.* Definition of IC/BPS Phenotypes Using Machine Learning (Task 2.1)**

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic, debilitating condition with the hallmark of pressure or pain perceived to be originating from the bladder (1). Prevalence estimates suggest that IC/BPS may affect as many as 7% of women and 4% of men (2). While first publicly recorded in 1836 (3) as a syndrome of chronic frequency, urgency, dysuria, and pelvic pain, no objective consensus definition exists (1, 4-7). As a result, the etiology of this syndrome of pain and lower urinary tract symptoms remains unclear. In addition, the lack of clear diagnostic criteria for IC/BPS patients results in a population with heterogenous presenting symptoms that often overlap with other urologic conditions, like overactive bladder (8, 9). Although IC/BPS likely consists of different subtypes of pain representing distinct pathophysiologies, IC/BPS is often studied, diagnosed, and treated as a single entity. Because of this heterogenous population, clinical trials and basic science studies have failed to advance the field in understanding and treating IC/BPS (10-12). We observed similar findings in our analysis of microbial and inflammatory data from patients with IC/BPS; **if analyzed as a single population, no associations of either microbial taxa or inflammatory markers were statistically significant. However, when examined in greater granularity, several different patterns of microbial communities emerge that affiliate with the same diagnosis.** If we begin to consider that this heterogeneous population may represent several unique phenotypes, it becomes clear that better

differentiation of distinct IC/BPS phenotypes is critical to improving our understanding and treatment of this condition.

While multiple IC/BPS phenotypes likely exist, only the presence of Hunner lesions on cystoscopy denotes a disease subgroup recommending a change in treatment (13, 14). Other classification systems for patients without Hunner lesions have been proposed but remain underutilized due to reliance on extensive clinical information, detailed physical exams, or genetic/histopathologic results (15-18). To address the challenge of phenotyping without the burden of excessive evaluation, in the previous reporting period, we evaluated symptomatic patterns in 145 women with IC/BPS without Hunner lesions (19). Using unsupervised machine learning (ML) approaches, patients with bladder pain could be categorized into 3 distinct phenotypes using patient-reported symptomatic questionnaires alone. These 3 unique symptom clusters included: 1) myofascial pelvic pain (MFP) characterized by persistent pelvic discomfort, straining to void, urinary frequency and urge, and a sensation of incomplete emptying, 2) non-urologic pelvic pain (NUPP) exhibiting urethral and vaginal pain not associated with voiding, and 3) bladder-specific pain symptoms (BPS) worsened with bladder filling and relieved by bladder emptying. Importantly, these groups were associated with different responses to common IC/BPS therapies, correlating well with the presumed etiologies. **This classification system did not require physician assessment or exam**, which could provide an objective classification system that could be used by providers of any specialty or skill level. As this was a single-center cohort, however, it is unclear if these symptomatic clusters could be reliably reproduced in other populations.

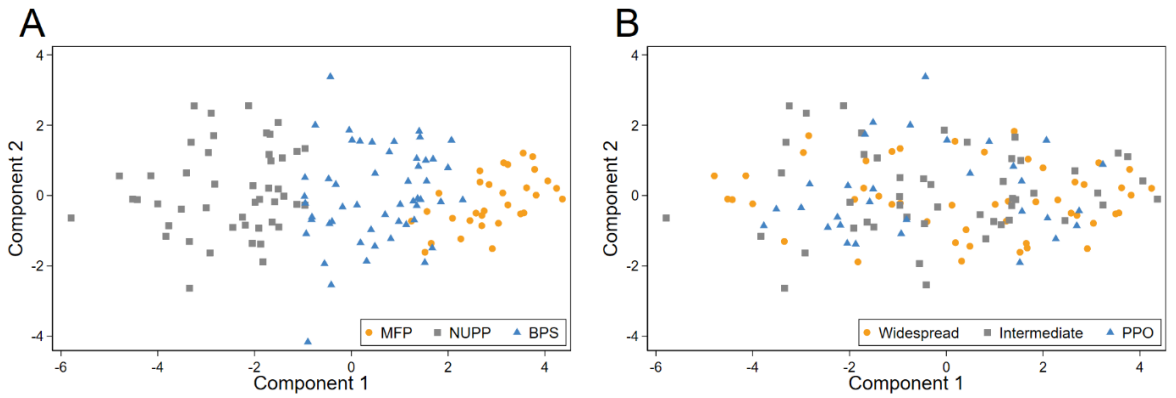


Figure 1. ***Principal component analysis of MAPP cohorts.*** When classified using the ML algorithm (A), MAPP clusters demonstrated good separation. In contrast, when patients were classified into groups based on body map patterns (B), no distinction between groups could be visualized. MFP: myofascial pain; BPS: bladder-specific pain symptoms; NUPP: non-urologic pelvic pain.

The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network recruited a multi-center, national cohort of patients with IC/BPS to understand better the nature of the condition and its subgroups (20). As clinicians have noted that patients with widespread pain present and respond to treatment differently than those with localized pelvic pain, 3 different phenotypes based on pain distribution have previously been proposed for the MAPP cohort: local pain, intermediate pain, or widespread pain, using detailed body mapping of painful regions (21). We therefore validated the findings of our prior pilot study in this larger, more geographically diverse patient cohort and determined the correlation of the pathophysiologic phenotype clusters defined in our pilot study with the widespreadness of pain described by body map phenotyping (**Fig. 1**). During this reporting period, we were able to validate the previously described phenotypic schema in the multi-center, prospectively recruited national IC/BPS cohort of the MAPP Research Network, demonstrating the generalizability to more diverse populations. Patients could again be subgrouped into three groups (**Fig. 2**), in which the myofascial pain (MFP) group demonstrated the most widespread pain, with significant extrapelvic pain sites and the most severe overall painful complaints not related to urologic or pelvic pain. In

contrast, the non-urologic pelvic pain (NUPP) group had the most confined pain and few urinary symptoms. The bladder-specific pain (BPS) cluster defined an intermediate phenotype. In addition, we were able to reduce the number of features needed to classify patients with bladder pain. In the original study,(19) cluster definitions were generated using 5 symptomatic questionnaires comprised of 49 individual features. We independently derived the 3 phenotypes in the MAPP cohort using only 11 features. Despite substantial reduction in features, unsupervised ML classified this independent, multisite cohort into similar symptom clusters with equivalent patterns of urinary and pain symptoms and physical exam findings as the single center cohort. The robust nature of these clusters across cohorts suggests these differences likely reflect true clinical and pathophysiologic differences.

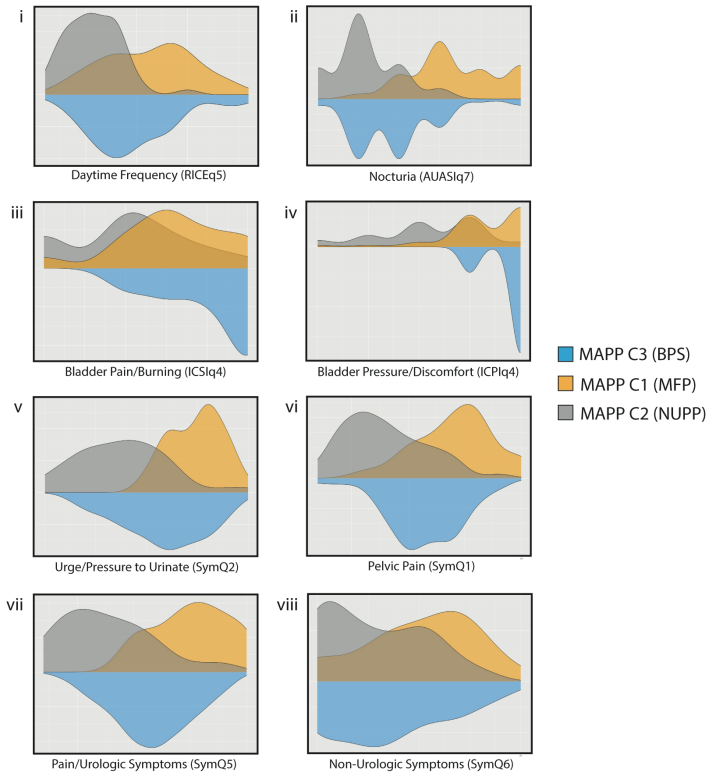


Figure 2. ***Scaled patient scores on a range or painful and urinary complaints for the MAPP cohort clusters.*** Mirrored density plots display the differences in the distributions of patient responses for each cluster for (i) urinary frequency during the day; (ii) nocturia; (iii) bladder pain; (iv) bladder pain, burning, pressure or discomfort; (v) an urge or pressure to urinate; (vi) generalized pelvic pain; combined pelvic pain and urologic complaints (vii); and non-urologic symptoms (viii).

We also compared our classification system with prior MAPP research publications categorizing IC/BPS patients by pain distribution(21) based on the clinical observation that patients with widespread pain behave differently than those with local pelvic pain. This classification schema defined three groups: widespread, intermediate, and local pelvic pain. If widespread pain represents a pathophysiology distinct from localized pain, we would expect differences in symptomatic patterns. The phenotypes defined solely by body mapping, however, revealed few symptomatic differences between groups (**Fig. 1,3**). While the ML clusters described in this study demonstrated poor overlap with these body map clusters, the underlying concept noting differences in widespreadness of pain persisted in the ML model (**Fig. 3**).

Consistent with this hypothesis, a different study subdivided the MAPP cohort according to pelvic floor tenderness, noting that subjects with more severe pelvic floor tenderness exhibited more severe symptoms, a wider distribution of non-urologic pain, and worse quality of life.(22). This group is highly analogous to the C1-MFP group. Despite disparate methods of identification, one using physical exam findings and the other utilizing patient-reported symptoms, the phenotypes are highly similar, supporting the hypothesis that the MFP phenotype represents a different and clinically significant pathology from the BPS subgroup.

Thus, patient-reported symptoms can be utilized to identify distinct subgroups of perceived bladder pain that previously required discriminate pelvic exam and detailed clinical history to differentiate. The characteristic symptomatic patterns were reproducible between a single institution cohort(19) and a multi-center population and recapitulated previous findings relating clinical outcomes to differences in widespreadness of pain and pelvic floor muscle tenderness. This work is currently being considered for publication:

Nettey OS, Gu C, Jackson NJ, **Ackerman AL**. Validation of Distinct Bladder Pain Phenotypes Utilizing the MAPP Research Network Cohort. ***Submitted to International Urogynecology Journal.***

Additional work moving forward will include a deeper dive into the non-urologic, extrapelvic manifestations of these phenotypes to provide insight into the likely etiologies and possible phenotype-specific treatment approaches. We have also incorporated this pain phenotyping schema into a larger classification system for lower urinary tract symptoms, generated from an unselected population of patients with all types of lower urinary tract symptoms LUTS. This independent generation of the same pain phenotypes (BPS, NUPP, and MFP) as those seen with a selected population of pain suggests that these phenotypes are robust. In addition, the machine learnining algorithm derived from this work is capable of distinguishing these phenotypes from other lower urinary tract symptomatic clusters, suggesting these phenotypes represent clinically relevant and reproducible disease subsets. This work is also currently in submission, but is available as a preprint on the Medrxiv preprint server.

Dallas KB, Chiang JN, Caron AT, Anger JT, Kaufman MR, **Ackerman AL**. Development and Validation of a Machine Learning Algorithm to Classify Lower Urinary Tract Symptoms. medRxiv 2022.12.25.22283168; Preprint. doi: 10.1101/2022.12.25.22283168. *In submission.*

b. Development of a novel index to identify myofascial dysfunction, a subtype of IC/BPS (Task 2.2)

Currently, we lack objective, quantitative markers to distinguish the many conditions that fall under the umbrella of LUTS. This aim has sought to define new clinical measures, preferable those that can be used by non-specialist clinicians, to help identify the unique subtypes of IC/BPS and help to tailor treatment. After determining that a large number of subjects under the IC/BPS umbrella expressed more symptoms of urge to void, urinary frequency and pelvic pressure, they may not describe a frank "bladder pain" on evaluation, which could lead to misdiagnosis as overactive bladder (OAB). Urinary urgency, defined as the sudden, compelling desire to urinate, which is difficult to defer, is the hallmark of OAB, however, many patients have difficulty discussing their symptoms and may feel too embarrassed or ashamed to delve into the manifestations of their condition.(23) Further, the words patients use to describe LUTS, especially urgency, can be another obstacle as this term may be interpreted in a variety of ways by

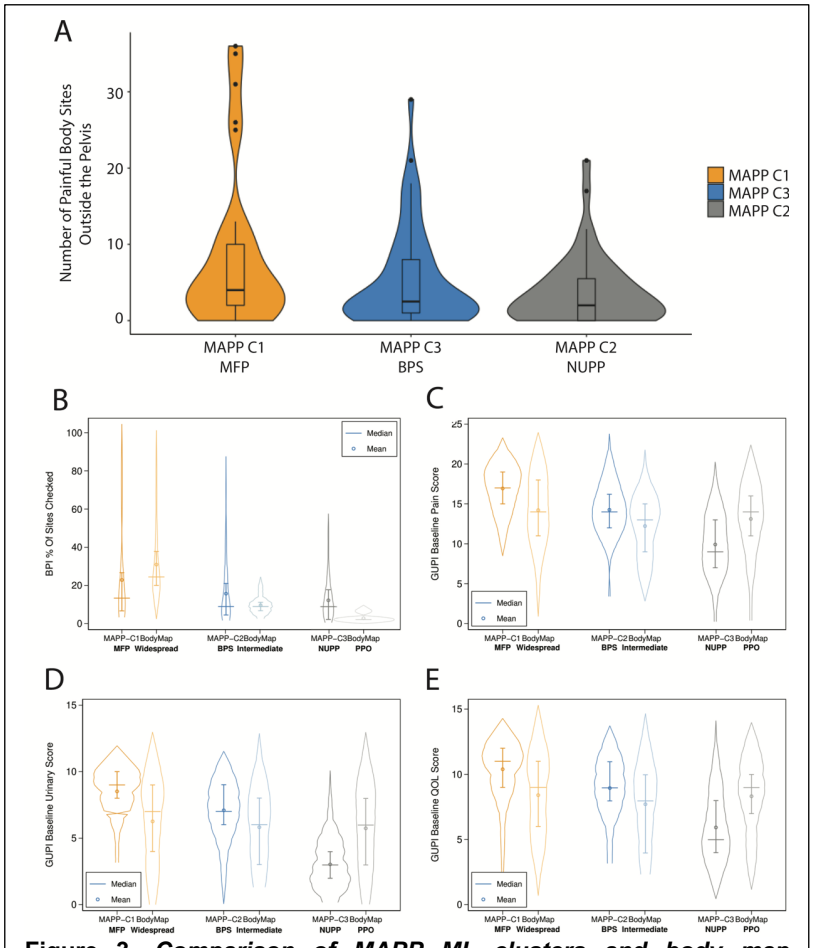


Figure 3. ***Comparison of MAPP ML clusters and body map phenotypes.*** The number of painful body sites outside the pelvis is shown in a violin plot with the median indicated by a bold line, and the box indicating the first and third quartiles. MFP: myofascial pain; BPS: bladder-specific pain symptoms; NUPP: non-urologic pelvic pain.

patients.(24) Thus, diagnosing these conditions is challenging,(25) meaning that urinary syndromes such as OAB often end up including highly heterogeneous groups of patients that lack key symptomatic features associated with these diagnoses. Many patients present with a similar urinary frequency and desire to urinate ("urge") as that expressed by OAB patients, but lack the sudden urge to urinate with little warning ("urgency") that is central to an OAB diagnosis (**Fig. 4**). These patients describe bladder pressure or discomfort, but in the absence of the distinct bladder pain with bladder filling. These patients are highly similar to the myofascial pain subtype of IC/BPS described above. Such patients have been allocated into various categories (e.g., frequency-urgency syndrome), but currently are often labeled as "OAB-dry" to specify this lack of incontinence (or fear of incontinence). While the name suggests this condition represents a less severe form of OAB with incontinence, the absence of true urinary urgency suggests a different pathophysiology. We have hypothesized that this subset of OAB-dry patients represent a similar group of patients as the MFP IC/BPS phenotype. Misdiagnosis of these patients as OAB may lead to inappropriate treatment assignment and overmedication with inappropriate therapies. A recent study of the Lower Urinary Tract Dysfunction Research Network (LURN) cohort revealed that OAB-dry individuals exhibit unique patterns of presenting features that differ from classic OAB subjects, including straining with urination, bladder discomfort, and a feeling of incomplete emptying.(26) The severity of symptomatic bother in these OAB-dry subjects was most closely related to the severity of pelvic floor tenderness on exam, implicating a possible myofascial dysfunction in this LUTS subgroup. We hypothesized that this subgroup represents a similar pathophysiology as the myofascial pain phenotype of IC/BPS.

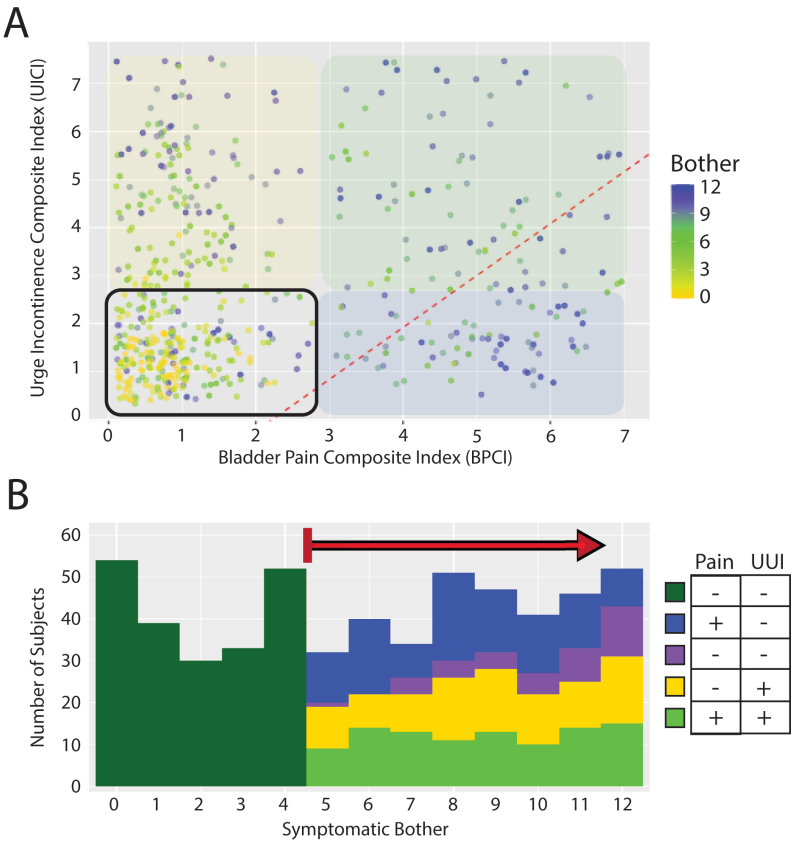


Figure 4. ***A highly bothered subset of patients lacks clear bladder pain or urgency/urge incontinence.*** A) Dot plot of bladder pain and urge incontinence symptomatic scores for all subjects with bother indicated in a yellow to blue gradient. OAB patients with UI (yellow overlay) occupy the upper left quadrant, while IC/BPS patients with BP (blue overlay) are in the lower right quadrant. A substantial population negative for either symptom domain is seen in the left lower quadrant. B) In a test population of 551 subjects with a variety of LUTS, the Bother Index was used to identify those patients dissatisfied with their urinary symptoms but lacking either pain or urgency incontinence (UUI) in purple.

During this reporting period, we engaged in a detailed examination of highly bothered patients with urinary symptoms who lack the frank bladder pain with filling of the BPS phenotype or the urgency/urgency incontinence characteristic of BPS or OAB, but are highly bothered by urinary frequency and bladder pressure. We sought to characterize this poorly described phenotype of LUTS and its association with pelvic floor myofascial dysfunction, hypothesizing that a similar group with myofascial dysfunction as that seen in the bladder pain subgroup (above) may be present within individuals presenting with non-painful LUTS. Detailed qualitative and quantitative analysis identified

a novel, distinct phenotype of urinary symptoms named “myofascial urinary frequency syndrome” (MUFS) present in one-third of individuals presenting with urinary frequency. In addition to a characteristic symptom constellation suggestive of myofascial dysfunction, such as defecatory dysfunction and dyspareunia, MUFS subjects exhibit “persistency”: bothersome urinary frequency resulting from bladder discomfort or pelvic pressure conveying an uncomfortable desire to urinate. On examination, 97% of MUFS patients demonstrated pelvic floor hypertonicity with either global tenderness or myofascial trigger points, and 92% displayed evidence of impaired muscular relaxation, hallmarks of myofascial dysfunction. To confirm this symptom pattern was attributable to the pelvic floor musculature, we confirmed the presence of “persistency” in 68 patients with pelvic floor myofascial dysfunction and evoked pain established through comprehensive examination and electromyography and corroborated by improvement with pelvic floor myofascial release. These symptoms distinguish subjects with myofascial dysfunction from subjects with OAB, IC/BPS, and asymptomatic controls, confirming MUFS is a distinct LUTS symptom complex.

Affected patients typically seek care for nonspecific symptoms of urinary frequency, urgency, pelvic pressure, or a sensation of incomplete bladder emptying, embodied in the symptomatic concept we identified as “persistency”. While MUFS shares many features with myofascial pain described in the pain cohort characterized above, the presentation of these patients is distinct in that they do not *report* pain. Although pain can sometimes be elicited or trigger points identified on pelvic exam, patients’ reasons for seeking care are primarily urinary, which can lead to difficulties suspecting the pelvic floor as an etiology of their symptoms if a detailed pelvic floor exam is not performed. While the co-existence of urinary complaints in patients with MFP is well-documented,(27) few reports have detailed the urinary manifestations associated with myofascial dysfunction in the absence of baseline bladder/pelvic pain.(28-30) We hypothesize that this MUFS phenotype is a milder form of MFP that should fall under the spectrum of IC/BPS disorders.

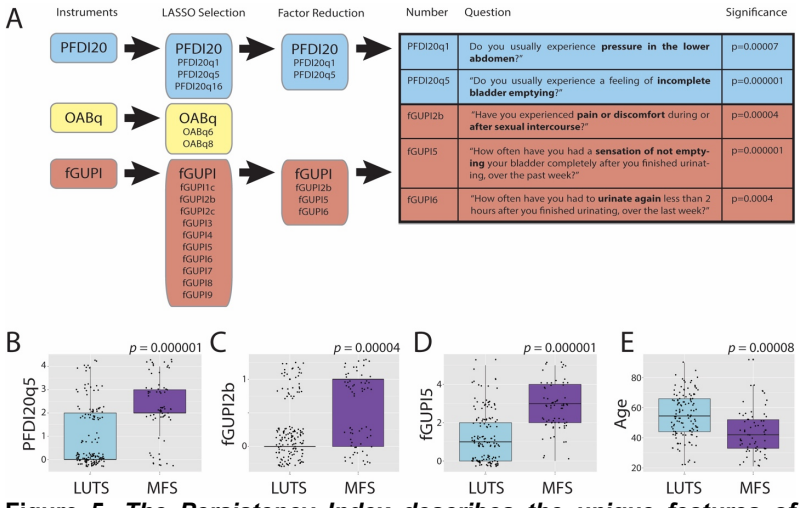


Figure 5. ***The Persistency Index describes the unique features of subjects with LUTS of a myofascial origin.*** A) Least Angle Shrinkage and Selection Operator (LASSO) with 10-fold cross-validation (λ=0.01307) identified 20 of the 41 variables from the OABq, fGUPI and PFDI as potential predictors. Five of these variables with a positive standardized shrunken coefficient > 0.4 as well as face validity for capturing the underlying clinical phenotype were used in a multivariable logistic regression model. Variables with statistically significant model coefficients (PFDI5, GUPI5, GUPI2B) were retained resulting in a reduced model consisting of these three predictors weighted based on these coefficients, which together comprise the Persistency Composite Index (PCI). Box and whisker plots compare the distribution of scores on the PFDI20 question 5 (B), fGUPI question 2b (C), fGUPI question 5 (D) and age (E) for the population of patients with myofascial frequency syndrome (MUFS) in comparison to subjects with any other bothersome LUTS.

Despite being exceedingly common,(31) due to the vague mix of uncomfortable bladder sensations and urinary complaints, MUFS is often mistaken for other symptom complexes, such as IC/BPS, OAB, pelvic organ prolapse (POP), or even urinary tract infection (UTI).(31-33) No specific ICD-10 code specifies this diagnosis, making epidemiologic assessment and surveillance difficult. Given the non-specific constellation of symptoms, MUFS can be challenging for providers to recognize, as our diagnostic approach thus far required discriminant pelvic exam, sufficient understanding of the global symptom complex, and ruling out confounding conditions.(33) Given these challenges, which can be compounded by increasing

reliance on telemedicine and limited visit times, improved tools are required to assist providers in recognizing MUFS. We therefore also developed a questionnaire-based, symptoms measure associated with the MUFS phenotype to assist providers in suspecting MUFS. As initial characterization of MUFS revealed a consistent pattern of associated symptoms across multiple independent cohorts, (34) we hypothesized it would be feasible to construct a symptoms measure to identify MUFS subjects. With a patient-derived indicator that is able to identify these patients and differentiate them from OAB, earlier interventions with appropriate treatment (e.g., pelvic floor physical therapy) can be achieved, even when providers are less facile at making the diagnosis.

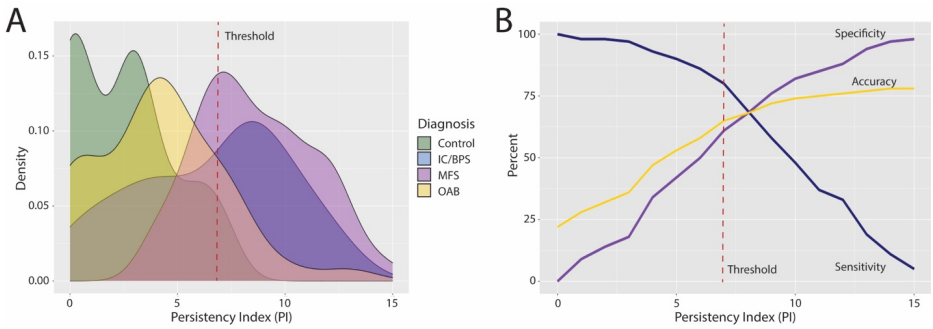


Figure 6. ***Performance of the Persistency Composite Index.*** A) Distribution of Persistency across a pooled population of 215 subjects by diagnosis. Positivity on the PCI was defined as >7, which best defined the population with myofascial frequency syndrome. B) Sensitivity, Specificity, and Overall Accuracy of the PCI for identifying MUFS in the Validation Dataset. A summated score of 7 denotes the cut point threshold that maximizes both sensitivity and specificity. IC/BPS: interstitial cystitis/bladder pain syndrome; MUFS: myofascial frequency syndrome; OAB: Overactive Bladder.

We therefore sought to develop a new screening index to identify patients with possible MUFS for use in telemedicine and by providers unskilled with a discriminate pelvic exam. By comparing a population of MUFS subjects with patients unequivocally categorized as OAB or the BPS phenotype of IC/BPS (above), we developed a novel measure, which we term the Persistency Index (PI), to screen for this underrecognized type of LUTS (**Fig. 5**). This screening measure performs well in a real-world, unselected population of patients seeking care for LUTS to identify MUFS with an overall accuracy of 65%. This accuracy reflects the fact that the chosen threshold for diagnosis tends to overpredict the likelihood of MUFS, but misses few with true MUFS, as evidenced by the 80% sensitivity (**Fig. 6**). As the likely outcome of obtaining a diagnosis of MUFS would be a referral to pelvic floor physical therapy, a treatment that carries very few side effects and the potential for symptomatic improvements even in patients with other diagnoses, the risks of overdiagnosing MUFS are minimal. This risk-benefit ratio reflects the optimal features of a screening measure, especially for an

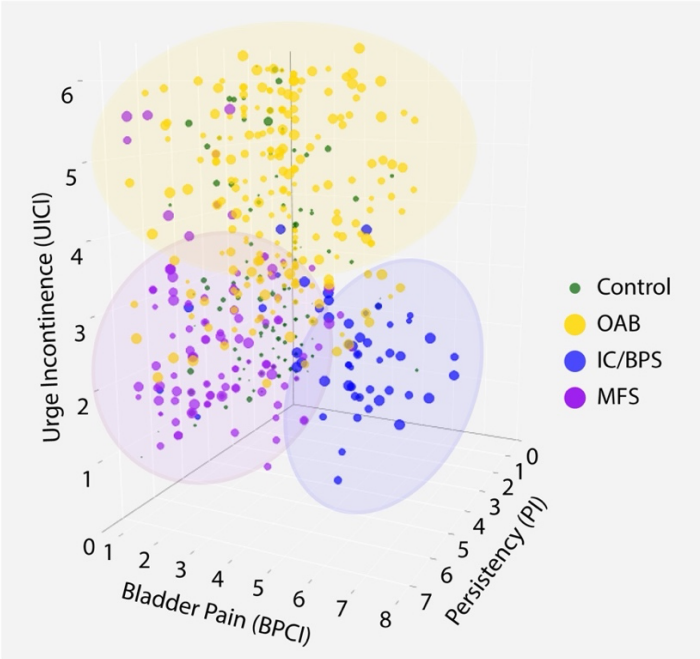


Figure 7. ***Bladder Pain (BPCI), Urgency Incontinence (UICI) and Persistency (PI) Indices define distinct symptomatic populations with LUTS.*** Subjects in an independent Validation Dataset were plotted in a 3D plot with each index on a different axis. Bother is indicated by the size of the sphere indicating each subject. The colors represent the diagnosis given by the consulting subspecialty physician. Diagnosis correlated well with the position in the 3D plot designated by the ellipses for each LUTS phenotype designated by the same color.

underrecognized condition which could assist providers in identifying patients that would benefit from consideration of myofascial-directed therapies and perhaps avoid unnecessary pharmacologic or even surgical interventions. We further proposed a modified diagnostic nomogram incorporating this measure that is capable of differentiating this cohort of patients from classical OAB and IC/BPS (**Fig. 7**). These findings were just accepted for publication:

Ackerman AL, Torosis M, Jackson NJ, Caron AT, Kaufman MR, Lowder JL, Routh JC. The Persistency Index: a novel screening tool for identifying myofascial pelvic floor dysfunction in patients seeking care for lower urinary tract symptoms. Am J Obstet Gynecol. 2023 Aug 24:S0002-9378(23)00587-2. doi: 10.1016/j.ajog.2023.08.017. Online ahead of print. PMID: 37633575

Future work will include the development of similar indices to identify the two remaining IC/BPS phenotypes, followed by their inclusion into a single risk assessment to help guide treatment assignments for patients.

3. Bacterial And Fungal Community Profiling

a. Microbial Profiling by Next-Generation Sequencing (Task 3.1)

To identify relevant microbial biomarkers that correlate with IC/BPS, catheterized urine samples obtained from a population of 49 age-matched, pre-menopausal women with IC/BPS were examined. 16S V2-V3 NGS revealed three distinct urinary bacterial community states (**Fig. 8**), known as "urotypes". K-means clustering of NGS data objectively confirmed this classification; each urotype was dominated by a different bacterial taxon: non-iners *Lactobacilli* (NIL), *Lactobacillus iners* (LI), or *Escherichia/Shigella*, which includes *Escherichia coli* (EC). The NIL and LI groups were nearly identical in composition, differing only in the absence or presence of LI, while the EC group was more diverse.

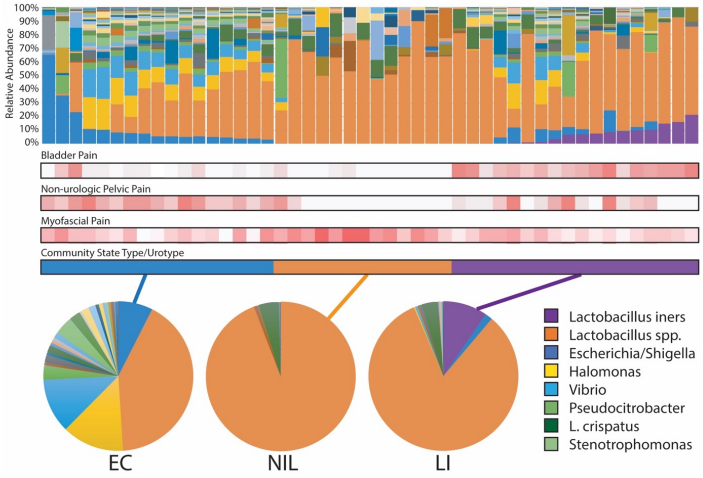


Figure 8. *Correlation of microbial patterns with pain phenotypes.* (A) The individual urinary microbial compositions of an independent verification population of 49 additional subjects, all with bladder pain, are exhibited in stacked box plots, ordered by urotype. This independent population reiterated the correlation of LI with bladder pain, EC with non-urologic pelvic pain, and NIL with myofascial pain, for which the severity of each is quantitated in the heat bars below the plot. The pie charts below indicate the median microbial composition for each urotype designated in the color bar. The NIL group and LI groups differed minimally, except for the presence of *Lactobacillus iners*. The EC group was significantly more diverse, frequently featuring *Vibrio* and *Halomonas* spp.

To correlate these urotypes with the distinct clinical phenotypes above, we examined subjects' symptomatic complaints on multiple questionnaires examining GU symptomatology. The LI urotype demonstrated increased bladder pain symptoms, as seen in the BPS phenotype, in which bladder-specific pain (ICSI4) was worse with bladder filling (GUPI2c) and relieved by bladder emptying (GUPI2d). The EC urotype exhibited symptoms consistent with the NUPP phenotype, characterized by global pelvic pain (GUPI1d) unrelieved by bladder emptying (GUPI2d) and increased co-incident urethral (GUPI1c) and vaginal (GUPI1a,b) pain and dyspareunia (GUPI2b). The NIL urotype correlated with increased frequency, a

sensation of incomplete emptying, bladder urge unrelieved by voiding, similar to the features of the MFP phenotype. The NIL urotype seen in pain patients was indistinguishable in bacterial composition from controls, suggesting this third IC/BPS phenotype (MFP) is likely unrelated to microbial alterations. Interestingly, the associations of LI and EC relative abundance with BPS and NUPP, respectively, were dose-dependent and highly significant ($p<0.00001$), even in this small population.

b. Validation of Community Profiling by qPCR (Task 3.2)

While highly sensitive, NGS overestimates microbial diversity, is unreliable for species identification, and provides only relative abundance within a community. To validate the findings described above as well as begin to develop a quantitative test for IC/BPS-associated microbial biomarkers, we evaluated species-specific qPCR with validated primers for *Lactobacillus crispatus*, *L. gasseri*, *L. jensenii*, *L. iners* and *E. coli* (**Fig. 9A**). Rescreening of our pilot population verified the NGS results, confirming the NIL abundance in controls and the MFP phenotype. Elevated levels of LI in BPS and EC in NUPP demonstrated clear, clinically relevant thresholds that could be used to distinguish these two phenotypes from controls and MFP subjects as well as from each other (**Fig. 9B**). These data both confirm the microbial patterns observed by NGS and suggest that targeted, rapid microbial profiling has clinical potential in IC/BPS phenotyping.

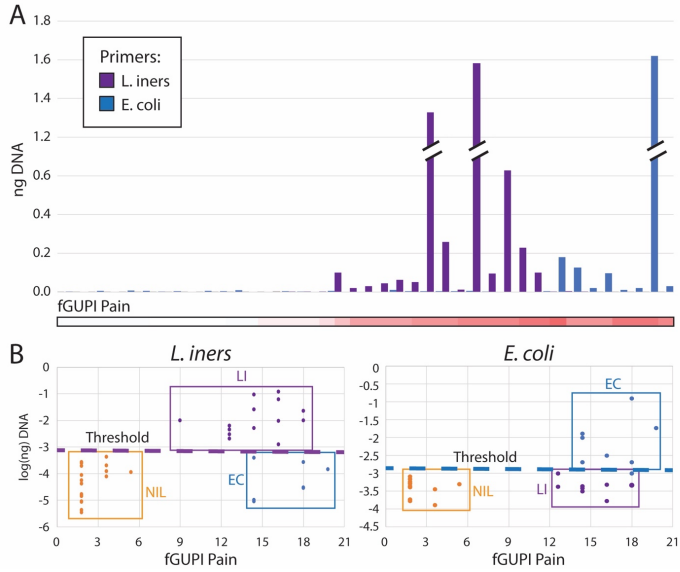


Figure 9. ***Quantitative PCR provides rapid, scalable testing with objective thresholds to facilitate patient diagnosis and sub-classification.*** (A) Using the female Genitourinary Pain Index (fGUPI) as an indicator of patients presenting with and without pain, expressed in the heat bar below the graph, quantitative PCR detecting *Lactobacillus iners* and *Escherichia coli* accurately separated patients with bladder-related pain from asymptomatic controls. (B) These two microbial markers alone subclassified unselected patients into distinct groups with diagnostically useful thresholds, as indicated by the dotted lines on scatter plots of the absolute DNA quantities for each species.

We are currently in the process of drafting these results for publication. We plan to evaluate further the prognostic potential of rapid qPCR testing as a prognostic indicator after the entirety of the population has been recruited.

4. Validation Of Microbial Markers as Prognostic Indicators

a. Correlation of qPCR Microbial Biomarker Assay with Symptomatically-Defined Phenotypes (Task 4.1)

We also have performed an intial evaluation of Microbial Urotypes as potential diagnostic biomarkers. As additional taxa, such as Vibrio and Halomonas, also segregated with urotype, we used linear discriminant analysis (LDA) to determine the optimal taxa for IC/BPS diagnosis (**Fig. 10**). This analysis confirmed *L. iners* and *E. coli* as the only bacterial taxa exceeding an LDA effect size of 4, confirming their clinical utility in IC/BPS diagnosis. Conversely, *L. gasseri*, a commensal non-iners Lactobacillus, was associated with controls. To assess the utility of these bacteria as

markers of individual IC/BPS phenotypes, we utilized Multivariate Association with Linear Models (MaAsLin) to examine associations between symptomatic profiles and microbial abundance. Controlling for confounding variables of age, BMI, and hormonal medications, MaAsLin confirmed the association of LI with BPS and EC with NUPP (**Fig. 10**). No bacterial taxa were significantly associated with the MFP phenotype when asymptomatic controls were included in the analysis. These findings suggest that out qPCR-based microbial community assessment has potential as a biomarker of IC/BPS diagnostic phenotyping. Future studies will need to examine whether these markers can serve as prognostic biomarkers with utility in treatment assignment.

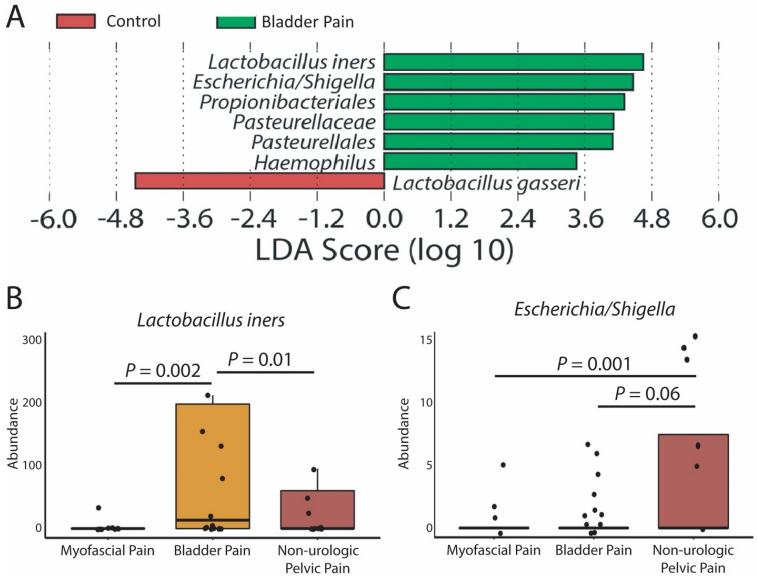


Figure 10. ***Microbial associations persist even after correction for confounders and multiple comparisons***. (A) Linear discriminant analysis (LDA) assesses the statistical and biological relevance of specific taxa as biomarkers for pelvic pain. Differential bacterial features are ranked by linear discriminant analysis effect size (LEfSe), with green and red indicating associations with pain or the asymptomatic state, respectively. A logarithmic LDA score >4.0 was used to identify taxa that significantly differed in abundance between IC/BPS and control subjects. (B,C) Box and whisker plots demonstrate the differences in *L. iners* and *E. coli* abundance in the BPS, NUPP, and MFP subgroups after controlling for age, BMI, and hormonal supplementation using Multivariate Association with Linear Models (MaAsLin).

5. Exploration Of Host-Microbe Interactions Related to IC/BPS

a. Generation of Primary Clinical Microbial Isolate Library (Task 5.2.1)

We have expanded our initial library of urinary fungal strains to more than 51 total, including multiple *Candida, Aspergillus, Rhodotorula, Nakaseomyces,* and *Cladosporium isolates*. Of the Candida isolates, we have more than 35 *Candida albicans* strains, as well as a variety of other *Candida* species, including *C. sake*, *C. tropicalis*, *C. glabrata, and C. parapsilosis*. We have also obtained 100s of bacterial isolates, of a wide range of genera, including Enterocpoccus, Staphylococcus, Proteus, Aerococcus, Escherichia, Klebsiella, Corynebacterium, Streptococcus, and Actinomyces. We have been focusing on the characterization of *Lactobacillus* spp., of which we have accumulated a wide range of strains from healthy controls and bladder pain patients. We now have more than 45 *L. crispatus* isolates in our library, in addition to isolates of *L. acidophilus, L. iners, L. gasseri, L. jensenii, L. helveticus*, and *L. vaginalis*.

b. Examination of Virulence of Primary Candida Strains (Task 5.2.1)

We continue to focus on the characterization of the *in vitro* behavior of clinical fungal isolates in co-culture with human urothelial cells. We have focused our attention on the characterization of *Candida* isolates in independent culture and co-culture conditions. The release of lactate dehydrogenase (LDH) by urothelial cells was used to quantify the urothelial cell killing following *Candida* challenge using a CytoTox 96 nonradioactive cytotoxicity assay. *Candida* strains from patients with pain demonstrate differential killing of benign urothelial cell lines, with significantly higher levels of cell damage noted for those pain-associated strains.

In this reporting period, however, with better elucidation of the phenotypes of IC/BPS, we began to breakdown the individual virulence of Candida strains accoding the the IC/BPS phenotype of the patient of origin. We discovered that strains from the BPS phenotype of patients, who have the most bladder-centric pain (pain related to the voiding cycle), were significantly more virulent than strains from either control subjects, or patients in either the NUPP or MFP phenotypes (**Fig. 11**). This effect required live *Candida* cells; no urothelial killing was observed after heat killing of the pathogenic strains. In addition, the effect appeared to require close proximity of the fungi to the urothelium; neither cultured media from pure fungal cultures nor separation of the fungi from the urothelium by a membrane (in a transwelll assay system) resulted in significant urothelial killing.

c. Examination of Virulence of Primary Candida Strains (Task 5.3.3)

We continue to study genes encoding known virulence factors and regions associated with antifungal resistance. We are isolating fungal strains from patients in longitudinal fashion to allow examination of the *in vivo* evolution of fungal strains throughout the course of disease, examining for the correlation of symptomatic changes with genetic changes seen over time.

In our examination of the *Candida* strains isolated from subjects before any intervention, we have performed analysis of RNA differential expression between the pain-associated strains and the strains from controls. This analysis revealed 14 genes that were differentially expressed between the healthy controls and IC/BPS subjects. While the function of most of these genes are unknown, two of these are known. Both have clear associations with cell wall regulation. SCW11, a cell wall-associated glucanase, remodels the cell wall during cell division and morphogenesis. The gene was expressed at 2.89-fold higher levels in the pain-associated strains than in controls. We have been able to confirm these changes in expression by quantitative reverse-transcriptase PCR (qRT-PCR). We next examined the upregulation of this gene in Candida strains isolated from different IC/BPS phenotypes. By qRT-PCR, SCW11 tended to be upregulated in strains from the BPS phenotype (p = 0.07), but not the MFP or NUPP phebnotypes. We are currently examining the role of a second gene, PGA39, a glycosylphosphatidylinositol (GPI) anchor protein that is also involved in regulatoion of the cell wall. Previously described mutations in this gene affect both virulence and survival. The gene exhibited 2.9-fold reductions in expression in the pain-associated strains, which we have confirmed by qRT-PCR, but we are currently examining the associations of these changes in expression with different phenotypic patterns of the subjects of origin. While the power of this analysis is limited by the number of strains examined thus far, the findings correlate well with the differences

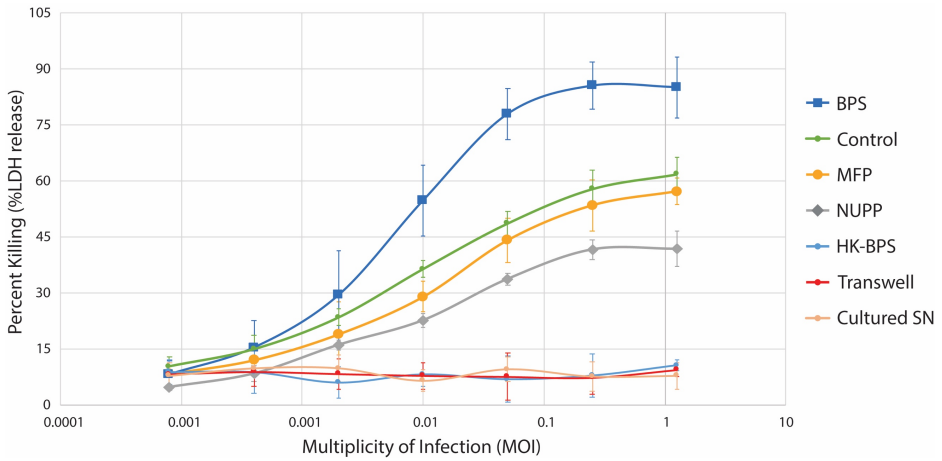


Figure 11. *Urinary fungal isolatesexhibit different levels of virulence according to IC/BPS phenotype.* Urothelial cells were co-cultured *C. albicans* strains purchased from subjects with or without bladder pain, categorized according to phenotype determined as described above. The *C. albicans* strains from BPS phenotype patients induced significantly more urothelial cell death than vaginal strains (VAG8) or isolates from asymptomatic patients with microhematuria (MH9), stress incontinence (SUI3). Heat-killed HP6 (HK-HP6) did not induce appreciable killing. This data is representative of thirteen pain-associated and nine asymptomatic unique *C. albicans* strains. Each subgroup is representative of >4 strains each performed in triplicate.

observed in filamentation between the strains, suggesting that alterations in cell wall regulation may contribute to the increased virulence seen in the BPS phenotype-associated strains.

6. Probe Fungal Antagonism of Lactobacilli in Urothelial Co-Culture

Now that we have an extensive library of primary strains of Lactobacillus and Candida from both healthy, asymptomatic subjects and IC/BPS subjects, we have begun to establish the experimental assays needed to test exclusion, displacement, and competition experiments. We plan to focus on these studies in the upcoming reporting period.

- **What opportunities for training and professional development has the project provided?**
    - *Dr. Ackerman has* been able to engage in a wide range of research and didactic activities to advance her scientific career. She participated in the Annual Meetings for the subspecialty societies most pertinent to this award, the Society for Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU), the American Urological Association (AUA), as well as the American Urogynecologic Society (AUGS). She also completed the "Statistical Learning" course sponsored by Stanford University through the online EdX platform and have completed the AUGS-sponsored UrogynCREST program, which is aimed at helping young investigators increase their knowledge of clinical study design, data science and analytics, and data visualization and communication through a variety of interactive didactic and hands-on experiences.
    - She has also continued online coursework in data visualization and analytics through the DataCamp online learning platform, increasingly gaining proficiency in statistical analysis in R and python. She is gaining increasing experience with microbial community analysis and now is able to take microbial analysis experiments from DNA preparation from biological samples through NGS library generation to sequence analysis, quality control, and multi-omic association analysis. She is currently completing the *Data Scientist with R* track, having finished 14 of the 22 courses, and is continuing to expand her skills with data analysis and visualization through this platform.

    - Dr. Ackerman has also had the opportunity to develop leadership skills in the urologic/urogynecologic community through service to our professional organizations. She continues to serve on the SUFU Basic Science Program Committee, in which she advocates heavily for the promotion of other early career scientist and clinician-scientists. She also served as the chair of the SUFU Research Grant committee as well. She also has begun her tenure as the Sub-Committee lead on Infection and Inflammation for the Société Internationale d'Urologie (SIU) Academy. In addition to continued service as a member of the AUA *Recurrent Urinary Tract Infections Guidelines* committee, she serves as a member of the AUA committee developing novel *Guidelines on the Management of Genitourinary Syndrome of Menopause* and as a committee member of the AUGS committee developing a clinical guidance document on *Differentiating Asymptomatic Bacteriuria/Chronic Bladder Colonization from Recurrent UTI*. She also has participated as an AUGS representative to the International Urogynecology Association working group focused on defining the *Terminology on Female Bladder Pain,* which should be available later this year. She has recently begun to assist in grant review for the NIDDK, serving on study sections for the P20 FORWARD proposals and ISAC Pilot Awards. She served as a guest editor for Frontiers in Cellular and Infection Microbiology in the publishing of a special

edition on the Urobiome and now serve as an associate editor for Neurourology and Urodynamics.

- **How were the results disseminated to communities of interest?**

  - The research team was able to discuss many of the findings from this research period at national and international conferences, including the ESSIC 2023: International Society for the Study of IC/BPS Annual Meeting, the American Urological Association Annual Meeting, the European Association of Urology Annual (AUA) Meeting, Clinical Society of Genitourinary Surgeons 99th Annual Meeting, Urology Siriraj Annual Meeting in Bangkok, Japanese Urological Association Annual Meeting, the 19th Urological Association of Asia Annual Meeting, and the 45th Annual Scientific Meeting of the Indonesian Urological Association.
  - Dr. Ackerman also served as faculty for the course on the detailing the Diagnosis and Management of Interstitial Cystitis/Bladder Pain Syndrome at the AUA Annual Meeting, in which she led the discussion of microbial changes in IC/BPS. In addition, she taught the pelvic medicine section of the Asian Urology Residents Course, which featured a section on Interstitial Cystitis and the Evaluation of Pelvic Pain for Urologists, in she was able to discuss some of these preliminary findings.
  - Dr. Ackerman was also able to share some of these findings in two public webinars, one of “Female Pelvic Triangle Microbiomes” and a second on “Phenotyping Bladder Pain”, sponsored by the Interstitial Cystitis Association. She also gave Grand Rounds presentations on phenotyping in IC/BPS at Yale-New Haven Hospital, Weill-Cornell Medical College, and Shinshu Univeristy in Matsumoto, Japan.

- **What do you plan to do during the next reporting period to accomplish the goals?**

  - Subject recruitment continues to be slow, but we continue to gradually ramp up recruitment and complete the study protocol for enrolled patients. We will be emphasizing this research opportunity with patients, residents, and fellows to stimulate the identification of potential subjects and have focused on community partnerships to increase enrollment moving forward.

  - We continue to expand the library of clinical microbial isolates and characterize new strains as they are obtained.

  - We are incorporating novel microbial profiling techniques such as adaptive metagenomics, which can provide more comprehensive characterization of microbial communities in biological samples, into building community profiles. Such approaches can also provide deeper genomic characterization of individual strains, which may facilitate a breakdown of the microbial genomic characteristics associated with bladder pain without the need to isolate and grow each individual strain.

  - We plan to complete the proposed *in vitro* exploration of host-microbe interactions related to IC/BPS. We have characterized markers of virulence, such as filamentation, in yeast strains isolated from patients with bladder pain, as well as the induction of host cell killing and inflammatory mediators (described above). We are currently trying to dissect the mechanism by which these fungi mediate these effects. As live fungi are needed to mediate the pathogenic impact of pain-associated clinical isolates on urothelial cells and it appears that direct or paracrine interaction of the fungi with the host cells is required, we will next seek to determine the molecular pathways involved in urothelial damage. We are also continuing our genomic analysis of these strains with the hopes of identifying common bladder pain-associated genomic alterations.

- We will continue the bioinformatic analysis of the microbial data, with a focus on the potential of the microbial community detection as diagnostic markers for subjects with IC/BPS.
- We will put a great deal of effort into dissemination of these initial results, especially those relating to the microbial community profiling. We currently have several manuscripts addressing both the fungal and bacterial communities that we are preparing for publication.

4. **IMPACT:**

a. **What was the impact on the development of the principal discipline(s) of the project?**

- As noted previously, we believe the most impactful finding from this report is the recognition that isolated myofascial pain and dysfunction can be experienced by patients as bladder pain co-existing with urinary symptoms, such as urgency and frequency. This condition, while manifesting with symptoms that are extremely similar to subjects with bladder-derived pain, has a unique etiology and responds to a different set of therapies. The recognition that musculoskeletal dysfunction can cause these symptoms may help to provide these patients with better therapies aimed at recognizing and correcting the underlying causes (joint dysfunction, gait issues, back injuries, etc.) and addressing the dysfunction (e.g., with physical therapy), avoiding prolonged and unnecessary therapies with pharmacologic agents (e.g., centrally-acting medications such as gabapentin and amitriptyline) or invasive bladder-directed therapies (e.g., cystoscopy or bladder instillations) that are unlikely to impact their disease course. The dissemination of this perspective through professional meetings and publications should reduce the time to effective treatment for many patients and potentially lead to significantly reduced costs. In addition, with the publication of a novel objective index capable of providing a risk assessment of whether myofascial dysfunction is a contributing etiology of the patient's symptoms (Ackerman et al., Am J Obstet Gynecol. 2023 PMID: 37633575) will help both specialists, urologic and gynecologic provider, and even non-specialty providers recognize patients who may benefit from myofascially-directed therapies. Pelvic floor physical therapy is one of the most effective treatments for IC/BPS in clinical trials; we hope that the simplicity of use of this index in clinical practice will provide a new tool for providers of any skill and specialty to improve the care of patients.
- The phenotyping schema that we have developed and now validated in an independent population redefines the structure in which to examine the microbial, inflammatory, and genetic data we have accumulated for IC/BPS patients thus far. As IC/BPS as a diagnosis includes patients with several different etiologies, the heterogeneity of study populations has previously prevented advances in understanding the disease, as findings unique to one specific subgroup or are obscured by the subjects with different phenotypes. Thus, for decades, little progress has been made to understand the nature of this condition. A theme throughout our exploration of patients with IC/BPS is that a multitude of difference are much more clearly evident when each of these phenotypes is considered independently. Employment of our phenotyping schema has allowed us to elucidate microbial, genetic, and inflammatory alterations in IC/BPS subjects that have previously remained occult. Using this refined clinical phenotyping to identify participant IC/BPS sub-populations, we have been able to identify distinct patterns

in uncultivated commensal microbial communities and host inflammatory responses that are associated with specific lower urinary tract symptom phenotypes, particularly for genitourinary pain. Moving forward, we hope that clinical studies and trial of new therapeutic agents can incorporate the need for phenotyping into their study design so that promising agents for the treatment of bladder pain can be developed and provided to the subpopulation of patients likely to improve with that therapy.

b. **What was the impact on other disciplines?**

- While it has only been published recently, our description of a objective index to identify myofascial dysfunction in patients without a clinical examination using questionnaire scores alone provides a wide range of providers, including advanced-practice providers and primary care physicians, a tool to identify this patient population that would benefit from early referral to pelvic floor physical therapy.

c. **What was the impact on technology transfer?**

- Nothing to Report

d. **What was the impact on society beyond science and technology?**

- Nothing to Report

5. **CHANGES/PROBLEMS:**

a. **Changes in approach and reasons for change**

- Nothing to Report

b. **Actual or anticipated problems or delays and actions or plans to resolve them**

- We continue to have a backlog in care that has limited clinical access for many patients with chronic conditions. Our specialized clinic solely for patients with bladder pain has facilitated easier access for these patients. We have also established partnerships with a wide range of community providers to facilitate the rapid referral of patients with bladder pain into our clinic. This has also begun to increase patient recruitment in the past few months.

c. **Changes that had a significant impact on expenditures**

- *As we were unable to recruit a qualified Post-doctoral fellow, we have added a skilled laboratory technician.*

d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

- Nothing to Report

e. **Significant changes in use or care of human subjects**

- Nothing to Report

f. **Significant changes in use or care of vertebrate animals.**

- Nothing to Report

g. **Significant changes in use of biohazards and/or select agents**

- Nothing to Report

6. **PRODUCTS:**

a. **Publications, conference papers, and presentations**

- **Journal publications.**

Ackerman AL, Torosis M, Jackson NJ, Caron AT, Kaufman MR, Lowder JL, Routh JC. The Persistency Index: a novel screening tool for identifying myofascial pelvic floor dysfunction in patients seeking care for lower urinary tract symptoms. Am J Obstet Gynecol. 2023 Aug 24:S0002-9378(23)00587-2. doi: 10.1016/j.ajog.2023.08.017. Online ahead of print. PMID: 37633575

Dallas KB, Chiang JN, Caron AT, Anger JT, Kaufman MR, **Ackerman AL**. Development and Validation of a Machine Learning Algorithm to Classify Lower Urinary Tract Symptoms. medRxiv 2022.12.25.22283168; Preprint. doi: 10.1101/2022.12.25.22283168. *In submission.*

Nettey OS, Gu C, Jackson NJ, **Ackerman AL**. Validation of Distinct Bladder Pain Phenotypes Utilizing the MAPP Research Network Cohort. *In submission.*

- **Books or other non-periodical, one-time publications.**

Interstitial Cystitis/Bladder Pain Syndrome
by: **A. Lenore Ackerman,** H.Henry Lai
in: American Urological Association Core Curriculum
Ed: Larissa Bresler, Matthew Rutman, et al.
Published: January, 2023

- **Other publications, conference papers, and presentations.**

1. *Other Publications*:

McGinn-Szlachta AW, **Ackerman AL.** Asymptomatic Bacteriuria, Atypical UTI, and the Urinary Microbiome. AUA Update Series. Volume 40. Lesson 30. *Published: September 1, 2022.*

2. *Conference Papers:*

Ackerman AL, Szlachta-McGinn A, Lagree K, Khalique MU, Caron AT, Ackerman JE, Cheng Z, Jackson NJ, Eilber KS, Anger JT, Underhill DM, Genitourinary Fungi Associate with Distinct Patterns of Microbial Species in Symptomatic Female Urogynecology Patients: A Retrospective Cohort Analysis. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.

Szlachta-McGinn A, Ackerman JE, Jackson NJ, **Ackerman AL**. Urinary Quantitative Polymerase Chain Reaction of Common Genitourinary Microbes Cannot Distinguish Between Urinary Tract Infection and Chronic Lower Urinary Tract Symptoms in Urogynecology Patients. Society of

Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.

Nettey O, Gu C, Jackson NJ, **Ackerman AL**. Distinct Phenotypes of Bladder Pain Identified in the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Reserch Network Dataset. American Urological Association Annual Meeting; April 2023; Chicago, IL.

3. *Presentations:*

UTI Diagnostics: A Clinical Perspective	Urinary Tract Infection Global Alliance	Virtual	2023
The patient with the positive urine NGS report: What's a clinician to do?	ESSIC 2023: International Society for the Study of IC/BPS Annual Meeting	New York, NY	2023
Dysuria: Evaluation and Clinical Significance	ESSIC 2023: International Society for the Study of IC/BPS Annual Meeting	New York, NY	2023
Diagnosis and Management of Interstitial Cystitis/Bladder Pain Syndrome	Instructional Course: American Urological Association Annual Meeting	Chicago, IL	2023
State-of-the-Art Lecture: Treatment of Fungal Urinary Tract Infections	American Urological Association Annual Meeting	Chicago, IL	2023
Molecular Diagnostics in UTI	SUFU at the American Urological Association Annual Meeting	Chicago, IL	2023
Urosepsis for Urologists	European Association of Urology Annual Meeting	Milan, Italy	2023
The urobiome: The urinary microbiome and its influence on lower urinary tract function	Clinical Society of Genitourinary Surgeons 99th meeting	Los Angeles, CA	2022
The urinary microbiome and implications for management of lower urinary tract symptoms	Urology Siriraj Annual Meeting (USAM)	Bangkok, Thailand	2022
Interstitial Cystitis/Bladder Pain Syndrome and the role of the microbiome in pelvic pain	Japanese Urological Association, AUA Scholarship Forum	Karuizawa, Japan	2022
New Perspectives in UTI: Novel Approaches to Diagnosis and Management	Shinshu University School of Medicine	Matsumoto, Japan	2022
Urogenital Pain Syndromes: New Diagnostic Schema and Microbial Biomarkers	Shinshu University Urology Grand Rounds	Matsumoto, Japan	2022
Is there anything new in the	19th Urological Association of Asia	Sydney, Australia	2022

management of recurrent UTIs?	Congress		
The Urinary Microbiome	19th Urological Association of Asia Congress	Sydney, Australia	2022
Instructor, Female Pelvic Medicine and Reconstructive Surgery	Asian Urology Residents Course Urological Association of Asia/ American Urological Association	Sydney, Australia	2022
	Guidelines for Recurrent UTI Interstitial Cystitis and the Evaluation of Pelvic Pain for Urologists Evaluation and Management of Overactive Bladder Fistulae and Grafts/Flaps for Urogenital Reconstruction		
Current Perspectives in UTI Diagnostic and Management: Beyond the Guidelines	45th Annual Scientific Meeting of the Indonesian Urological Association	South Sulawesi, Indonesia	2022

b. **Website(s) or other Internet site(s)**

Infection and Inflammation in Urology	European Association of Urology TV	March, 2023
Asymptomatic Bacteriuria, Atypical Urinary Tract Infection and the Urinary Microbiome	AUAUniversity Podcast	December, 2022
To Pee or Not to Pee	Webinar, sponsored by UCLA Health	November, 2022
Female Pelvic Triangle Microbiomes	Webinar, sponsored by Solv Wellness	September, 2022
Phenotyping Bladder Pain	Webinar, sponsored by the Interstitial Cystitis Association and Desert Harvest	July, 2022

c. **Technologies or techniques**

- We previously developed a diagnostic model for the classification of pelvic pain that correlates in preliminary studies with treatment outcomes, which was described in Mwesigwa *et al.* 2021. The model was validated using the Multidisciplinary Approach to Pelvic Pain cohort, which is now described in a subsequent paper that is currently in submission (Nettey et al., see above).

d. **Inventions, patent applications, and/or licenses**

- Nothing to Report

e. **Other Products**

- We continue to develop a library of clinical fungal isolates from women with and without bladder pain. This currently has 51 strains of 5 different genera and we continue to add to this collection to facilitate further study.
- We also now have 45 clinical Lactobacillus isolates from women with and without bladder pain as well as 15 Escherichia isolates from women with bladder pain.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

a. **What individuals have worked on the project?**

- Dr. A. Lenore Ackerman, Dr. David Underhill

Name:	*L. Marcella Henao*
Project Role:	*Research Technician*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Henao has been examining the effects of isolated clinical strains of fungi and bacteria on urothelial cells. She is primarily responsible for the management and processing of patients samples, including DNA isolation, immunologic assays, creation of DNA libraries for next-generation sequencing. She is also primarily responsible for regulatory management of the scientific protocols and biochemical safety.*
Funding Support:	*DOD Award*

Name:	*Crystal Cisneros*
Project Role:	*Clinical Research Coordinator*
Researcher Identifier (e.g. ORCID ID):	*N/A*
Nearest person month worked:	*4*
Contribution to Project:	*Ms. Cisneros is coordinating our dedicated pelvic pain clinic, which oversees the recruitment and continuous care of bladder pain subjects enrolled in this study. She also oversees data management and the regulatory aspects of the project.*
Funding Support:	*DOD Award*

Name:	*Aryana Zarandi*
Project Role:	*Research Technician*
Researcher Identifier (e.g. ORCID ID):	*N/A*

Nearest person month worked:	3
Contribution to Project:	*Ms. Zarandi is primarily responsible for isolation of clinical bacterial and fungal strains and their characterization. She also assist with the processing of patient specimens, data management, and preparations of DNA for sequencing,*
Funding Support:	*DOD Award*

b. **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

- *Nothing to Report*

c. **What other organizations were involved as partners?**

- Cedars-Sinai Medical Center, where Dr. David Underhill and his lab are located, served as a partner institution supported by this award.

1. **Organization Name:** Cedars-Sinai Medical Center
2. **Location of Organization:** Los Angeles, CA
3. **Partner's contribution to the projec**t *(identify one or more)*

a. **Collaboration:** The research team of Dr. Underhill has helped significantly with research looking at the fungal species isolated from patients with bladder pain, specifically looking at surrogate markers for virulence, including the quantitation of filamentation.

8. **SPECIAL REPORTING REQUIREMENTS**

a. Nothing to Report

9. **APPENDICES: (following)**

a. Updated Curriculum Vitae (Ackerman)

b. Ackerman AL, et al. Am J Obstet Gynecol. 2023 PMID: 37633575

c. Szlachta-McGinn A, *et al.* Eur Urol Open Sci. 2022 PMID: 36093322

d. Dallas KB, *et al*. Development and Validation of a Machine Learning Algorithm to Classify Lower Urinary Tract Symptoms. doi: 10.1101/2022.12.25.22283168

13. REFERENCES

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A. Lenore Ackerman

CURRICULUM VITAE

July 27, 2023

Professional Contact Information:
UCLA Medical Center
Women's Pelvic Health Center
200 Medical Plaza, Suite 140
Los Angeles, CA 90095
AAckerman@mednet.ucla.edu

Education:

Bachelor of Science	Yale University	1998
Doctor of Philosophy	Yale University	2004
Doctor of Medicine	Yale University	2008
Internship	UCLA-David Geffen	2008 – 2009
Residency	UCLA-David Geffen	2009 – 2014
Fellowship	UCLA-Reagan Medical Center	2014 – 2016
Clinical Scholars Program	Cedars-Sinai Medical Center	2016 – 2018
UrogynCREST	American Urogynecologic Society, Duke University	2020 – 2022

Licensure: Medical Board of California, #A112910
CA Fluoroscopy – Xray Supervisor and Operator, #RHC00202007

Board Certification:

American Board of Urology	2018 –
Female Pelvic Medicine and Reconstructive Surgery	2018 –

Professional Experience:

Associate Professor	UCLA-David Geffen Urology	2021 –
Assistant Professor	UCLA-David Geffen Urology	2020 – 2021
Director of Research	Women's Pelvic Health Center	2020 –
Adjunct Asst. Professor	UCLA-David Geffen Urology	2016 – 2020
Assistant Professor	Cedars-Sinai Medical Center Female Pelvic Medicine and Reconstructuve Surgery	2016 – 2020
Staff Physician	Cedars-Sinai Medical Center Dept. of Surgery, Division of Urology	2016 – 2020

Professional Activities:

Professional Society Membership

Société Internationale d'Urologie (SIU)	2022 –
Western Section – American Urologic Association	2018 –
Society for Basic Urologic Research	2016 –
International Urogynecological Association	2016 –
Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction	2015 –
American Urogynecological Society	2015 –

Federation of Clinical Immunology Societies	2015 –
Society for Women in Urology	2014 –
Los Angeles Urological Society	2008 –
American Urological Association	2008 –
American Medical Association	2004 –
American Association of Immunologists	2000 –

Committee/Professional Service

Genitourinary Syndrome of Menopause Guidelines Committee (American Urological Association)	2023 –
Program Chair, AUA Basic Science Symposium	2022 – 2023
Study Section, NIDDK P20 FORWARD	2022 –
Sub-Committee Lead on Infection and Inflammation, SIU Academy, Société Internationale d'Urologie (SIU)	2022 –
Differentiating Asymptomatic Bacteriuria/Chronic Bladder Colonization from Recurrent UTI Clinical Guidance Committee (AUGS)	2021 –
Core Curriculum for Interstitial Cystitis/Bladder Pain Syndrome AUA University	2021 –
Chair, Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction Grant Research Committee	2020 – 2022
Committee Member, Terminology on Female Bladder Pain (International Urogynecological Association/American Urogynecologic Society)	2020 –
AUA Clinical Problem-Solving (CPS) Module: Recurrent Uncomplicated Urinary Tract Infections in Women	2019
Basic Science Program Committee (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction)	2018 –
Recurrent Urinary Tract Infections Guidelines Committee (American Urological Association)	2018 –
Women's Health Technology (WHT) Coordinated Registry Network (CRN), POP Working Group	2018 – 2019

Community Service Activities

Volunteer – California State Parks Foundation	2021 –
Volunteer – Urology Community Outreach, Leo Baeck	2019
Volunteer – Medicine for Humanity	2015
Volunteer – Yale-HAVEN Free Clinic	2005 – 2008
Coordinator – Medical Reserve Corps	2004 – 2008
Program Coordinator – Graduate Student Research Symposium, Yale University,	2000
Volunteer – Genetics Education Outreach Program, Yale University	1999-2002
Volunteer – Pediatric Emergency Department, Yale-New Haven Hospital	1998-2000

Editorial Services

Section Editor, Infection and Inflammation and the Microbiome, Neurourology and Urodynamics	2023 –
PLOS Pathogens	2022 –
Guest Editor, Frontiers in Cellular and Infection Microbiology, Urobiome Section	2020 – 2022

Frontiers in Pain Research	2021 –
Section Editor, Microbiome and Urologic Infections, Grand Rounds in Urology	2020 –
Frontiers in Cellular and Infection Microbiology	2019 –
European Urology	2018 –
Neurourology and Urodynamics	2016 –
Journal of Urology	2015 –
International Urogynecological Journal	2015 –
Urology	2015 –
PLOS One	2015 –

Professional Activities:

UCLA Urology Equity, Diversity, and Inclusion Subcommittee on Education and Training	2021 –
UCLA MSTP Admissions Committee	2020 –
CSMG Clinical Care Optimization/Urology Member	2019 – 2020
CSMC Clinical Competency Committee, Member	2017 – 2020

Honors and Special Awards:

McGuire-Zimskind Award (SUFU)	2023
AUA/JUA Exchange Scholar	2022
SuperDoctors, Southern California Rising Star	2022
Visiting Professor, University of Texas Southwestern Departments of Urology and Geriatrics	2021
Urology Care Foundation Rising Star in Urology	2021
Diokno-Lapides Essay Contest, Second Place	2021
American Urologic Association: Best Poster Infections/Inflammation/Cystic Disease of the Genitourinary Tract: Kidney and Bladder II	2020
Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction- Basic Science Poster Award, Second Place	2019, 2022
American Urologic Association: Research Forum: First Place Early-Career Investigators Showcase	2018
American Urologic Association: Best Poster Basic Research and Pathophysiology II	2017
American Urologic Association: Best Poster Practice Patterns, Quality of Life and Shared Decision Making V	2017
Cedars-Sinai Patient Satisfaction Award	2016 – 2018
Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction-Best Basic Science Poster	2016
Pfizer/Urology Care Foundation Research Scholar	2015

Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction Resident Travel Award	2012
American Urogynecologic Society Resident Research Scholar	2011
Yale Minority Science, Technology, and Research Fellow	1996
Yale University Class of 1954 Fellow	1995 – 1997
Yale University Hiram B. Manville Scholar	1995
Yale Club of Atlanta Community Service Fellow	1995
Coca-Cola National Scholar	1994

Research Grants and Fellowships Received:

Society for Urodyn. and Urogenital Reconstruction	High Frequency Pelvic Floor Stimulation for the Management of Myofascial Pain SUFU Research Grant		2023 – 2025
	Principal Investigator	1% effort	
CureAccelerator/ Cures Within Reach	Repurposing Pelvic Floor Electrical Stimulation for the Treatment of Chronic Pain Repurposing Award	2022 – 2024	
	Repurposing Research Led by a US-Based Racial/Ethnic Minority PI Principal Investigator	10% effort	
Department of Defense Congressionally-Directed Medical Research Program	Phenotyping of IC/BPS Using Microbial Community States: Validation of a Novel Noninvasive Biomarker Peer Reviewed Medical Research Program (PRMRP) Expansion Award		2021 – 2024
	Principal Investigator	10% effort	
National Institute of Aging (NIH)	The Role of the Vaginal Microbiota in Urgency Urinary Incontinence in Older Women Grants for Early Medical/Surgical Specialists' Transition to Aging Research (R03)		2020 – 2022
	Principal Investigator	10% effort	
National Institute of Diabetes and Digestive And Kidney Diseases (NIH)	The Urinary Mycobiota and Host Inflammation in Lower Urinary Tract Symptoms Mentored Clinical Scientist Research Career Development Award (K08)	2019 – 2024 75%	
	Principal Investigator	effort	
Society for Urodyn. Female Pelvic Med. and Urogenital Reconstruction	The Role of the GU Microbiota in predicting Responses to Sacral Neuromodulation for Overactive Bladder in Older Women Neuromodulation Award	1%	2019 – 2021
	Principal Investigator	effort	
University of California Los Angeles, Clinical and Translational Science Institute	The Microbiome of Interstitial Cystitis Subjects with Hunner's Ulcers Technology Core Vouchers	1%	2019 – 2020
	Co-Investigator	effort	
University of CA Los Angeles, Clinical	The Role of the Vaginal Microbiota in Urgency Urinary Incontinence Iris Cantor-UCLA Executive Advisory		2019 – 2020

and Translational Science Institute	Board/CTSI Pilot Award Principal Investigator	1% effort	
University of CA Los Angeles, Clinical and Translational Science Institute	The Urinary Microbiota and Host Inflammation in Lower Urinary Tract Symptoms KL2 Mentored Clinical Scientist Training Award Principal Investigator	2019 – 2020 75% effort	
Shaffer Family Foundation	Vaginal Fractionated CO2 Laser Treatment – Effects on the Genitourinary Microbiome Co-Investigator	1% effort	2018 – 2020
Department of Defense Congressionally-Directed Medical Research Program	The Urinary Fungal Mycobiome and Host Responses in Patients with Interstitial Cystitis PRMRP Discovery Award Principal Investigator	5% effort	2017 – 2019
Society for Urodyn. Female Pelvic Med. and Urogenital Recon.	The Microbiome as a Predictor of Outcome of Intravesical Botox Chemodenervation Award Principal Investigator	1% effort	2017 – 2019
University of California Los Angeles, Clinical and Translational Science Institute	Temporal Dynamics of the Female Genitourinary Microbiota Technology Core Vouchers Principal Investigator	1% effort	2016 – 2017
Urology Care Foundation	Inflammatory Responses and the Microbiome in OAB Urologic Research Training Award Principal Investigator	50% effort	2015 – 2016
National Institute of Allergy and Infectious Diseases (NIH)	Cellular Mechanisms of Cross-presentation in Dendritic Cells Individual National Research Service Award Minority Fellowship Principal Investigator	100% effort	2000 – 2004
National Heart, Lung, and Blood Institute (NIH)	Generation of Soluble Antibody/T-cell Receptor Chimeras as Immunosuppressive Adjuncts in Xenotransplantation Under-represented Minority Summer Research Fellowship Principal Investigator	100% effort	1998

Research Projects and Research Focus or Interest:

Clinical Trials — I have been involved in multiple trials of novel therapeutics in the treatment of benign urologic diseases, serving as site coordinator for multiple industry-sponsored trials of oral and local therapies for interstitial cystitis and overactive bladder. Current interests include the manipulation of the genitourinary microbiome in the treatment and prevention of lower urinary tract symptoms and infections.

Clinical Research — My primary interest is the application of machine learning to the diagnosis and phenotyping of benign urologic diseases to provide more objective diagnostic schemata and effective screening in the primary care setting as well as better prognostication in treatment decision-making. We seek to develop these tools

in combination with digital resources and health coaching to provide better non-pharmacologic management of lower urinary tract symptoms.

Basic Research

I have a particular interest in the relationship between genitourinary microbial communities and host inflammatory responses and how the interactions between them influence lower urinary tract physiology and pathology. My laboratory is focused on identifying the associations of particular microbial communities with benign urologic disease phenotypes and modeling these phenotypes in in-vitro systems and animal models. Early studies have identified a role for fungal speies in bladder pain; we are currently focused on developing *in vitro* and animal models to further study pathologic urinary fungi, such as *Candida albicans*. Using these systems we are examining the mediators that result in bladder inflammation and pain and exploring potential approaches to inhibiting these responses that may serve as possible novel therapeutics in urogenital pain syndromes.

Invited Lectures and Presentations:

Mini State of the Art: Interstitial Cystitis/Painful Bladder Syndrome	PFD Week 2023 – American Urogynecologic Society Annual Meeting	Portland, OR	2023
UTI Diagnostics: A Clinical Perspective	Urinary Tract Infection Global Alliance	Virtual	2023
The patient with the positive urine NGS report: What's a clinician to do?	ESSIC 2023: International Society for the Study of IC/BPS Annual Meeting	New York, NY	2023
Dysuria: Evaluation and Clinical Significance	ESSIC 2023: International Society for the Study of IC/BPS Annual Meeting	New York, NY	2023
Diagnosis and Management of Interstitial Cystitis/Bladder Pain Syndrome	Instructional Course: American Urological Association Annual Meeting	Chicago, IL	2023
State-of-the-Art Lecture: Treatment of Fungal Urinary Tract Infections	American Urological Association Annual Meeting	Chicago, IL	2023
Molecular Diagnostics in UTI	SUFU at the American Urological Association Annual Meeting	Chicago, IL	2023
Urosepsis for Urologists	European Association of Urology Annual Meeting	Milan, Italy	2023
The urobiome: The urinary microbiome and its influence on lower urinary tract function	Clinical Society of Genitourinary Surgeons 99th meeting	Los Angeles, CA	2022
The urinary microbiome and implications for the management of lower urinary tract symptoms	Urology Siriraj Annual Meeting (USAM)	Bangkok, Thailand	2022

Interstitial Cystitis/Bladder Pain Syndrome and the role of the microbiome in pelvic pain	Japanese Urological Association, AUA Scholarship Forum	Karuizawa, Japan	2022
New Perspectives in UTI: Novel Approaches to Diagnosis and Management	Shinshu University School of Medicine	Matsumoto, Japan	2022
Urogenital Pain Syndromes: New Diagnostic Schema and Microbial Biomarkers	Shinshu University Urology	Matsumoto, Japan	2022
Is there anything new in the management of recurrent UTIs?	19th Urological Association of Asia Congress	Sydney, Australia	2022
The Urinary Microbiome	19th Urological Association of Asia Congress	Sydney, Australia	2022
Instructor, Female Pelvic Medicine and Reconstructive Surgery Guidelines for Recurrent UTI Interstitial Cystitis and the Evaluation of Pelvic Pain for Urologists Evaluation and Management of Overactive Bladder Fistulae and Grafts/Flaps for Urogenital Reconstruction	Asian Urology Residents Course Urological Association of Asia/ American Urological Association	Sydney, Australia	2022
Current Perspectives in UTI Diagnostic and Management: Beyond the Guidelines	45th Annual Scientific Meeting of the Indonesian Urological Association	South Sulawesi, Indonesia	2022
Molecular Urinary Tract Infection Testing	American Urological Association Annual Meeting	New Orleans, LA	2022
Where the Field of Pelvic Pain Needs to Go	Society for Infection and Inflammation in Urology at the AUA	New Orleans, LA	2022
Recurrent UTI in women: Is there a role for cranberry or other non-antibiotic solutions?	SUFU at the American Urological Association Annual Meeting	New Orleans, LA	2022
Early Investigator Spotlight	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction	San Diego, CA	2022
Point-Counterpoint: MUS vs. Bulking Agent in a 55-year-old Woman with SUI	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction	San Diego, CA	2022
The Genitourinary Microbiome and UTI: How a Better Understanding of the Urobiome Influences Understanding of UTI	30th Annual Perspectives in Urology: Point Counterpoint	San Diego, CA	2021

Host-Microbe Interactions in Lower Urinary Tract Disorders	Society for Basic Urologic Research 2021 Annual Meeting	Virtual	2021
Use of the Urinary Microbiome To Guide Clinical Care of Lower Urinary Tract Symptoms	2021 UTSW Visiting Professor in Urology and Geriatrics	Dallas-Ft Worth, TX	2021
The Genitourinary Microbiome In Women: Microbes, Menopause, and Micturition	2021 UTSW Visiting Professor in Urology and Geriatrics	Dallas-Ft Worth, TX	2021
Microbiome Abnormalities in the Lower Urinary Tract SUFU Invited Speaker	International Continence Society 2021 Annual Meeting	Virtual	2021
Fungal Infections in Urology, Past and Future	Society for Infection and Inflammation in Urology at the AUA	Virtual	2021
Panel Discussion: Challenging Cases in Complicated Recurrent UTI	American Urological Association Annual Meeting	Virtual	2021
Clarifying Recent Guidelines and Clinical Studies on Non-antibiotic Management of Recurrent UTIs	Online Webinar by Solv Wellness	Virtual	2021
Careers Panel	KUH R25 Summer Undergraduate Research Symposium	Virtual	2021
Pathways to Surgeon-Scientist Panelist	EMPIRE “Hidden Curriculum” AYA NY Section	Virtual	2021
Big Data in Benign Urological Disease	SUFU 2021 Winter Meeting Basic and Translational Science	Virtual	2021
Say Hello to My Little Friends: How We Use the Microbiome In Clinical Urology	SUFU 2021 Winter Meeting General Session	Virtual	2021
Microbiome: How is it used in Urogynecology?	PFD Week 2020 (American Urogynecologic Society Annual Meeting	Virtual	2020
Urinary Tract Infections	FPMRS Fellows Webinar American Urogynecologic Society	Virtual	2020
Take Home Messages: Infection/Inflammation	American Urological Assoc. Annual Meeting	Washington, DC	2020
Beyond Bacteria: Fungi In the Urinary Tract	UROBIOME 2020	San Diego, CA	2020

Recurrent Urinary Tract Infections: Imaging and Molecular Diagnostics	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction	Scottsdale, AZ	2020
Recurrent Urinary Tract Infection: Lessons from the Guidelines	American Urologic Association Annual Meeting	Chicago, IL	2019
Female Pelvic Pain: Why Does It Hurt Down There?	Advanced Practice Provider Program at the AUA	Chicago, IL	2019
Vaginal Laser Therapy in Today's Urology Practice: What the Evidence Tells Us	SUFU at the American Urological Association Annual Meeting	Chicago, IL	2019
The Urinary Mycobiome and Lower Urinary Tract Symptoms	Duke University, Annual Multidisciplinary Benign Urology Research Day	Durham, NC	2019
Expert Panel-Recurrent UTI A Case-based Approach	Western Section, American Urological Association	Maui, HI	2018
The Mycobiome of the Urinary Tract and Its Potential Role in Urologic Conditions	University of California, San Diego	San Diego, CA	2018
The Urinary Microbiota and Host Inflammation in Lower Urinary Tract Symptoms	American Urological Association Annual Meeting Research Forum	San Francisco, CA	2018
Recent Advances in Urinary Microbiota and the Diagnosis of UTI	Mediterranean Incontinence and Pelvic Floor Society Annual Meeting	Rome, Italy	2018
Pathways to Independence in Urologic Research: It Takes a Village	Individualizing Treatment of Urinary Incontinence NIDDK/NIH	Bethesda, MD	2018
Imaging in FPMRS: Ultrasound	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction	Austin, TX	2018
The Urinary Microbiota: A New Paradigm in the Study of Lower Urinary Tract Symptoms	Yale University, Department of Urology	New Haven, CT	2017
Female Sexual Dysfunction in the Older Patient	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction	Scottsdale, AZ	2017
Instructor, Female Pelvic Medicine and Reconstructive Surgery	Curso de Actualizacion en Urología Sociedad Argentina de Urología/ American Urological Association	San Miguel de Tucuman, Argentina	2016

AUA/SUFU Guidelines on Overactive Bladder
Genitourinary Fistulae: Approaches, Tips and Techniques

Overactive Bladder: A New Perspective on Bladder Hypersensitivity Syndromes	Congresso Argnetino de Urología, Sociedad Argentina de Urología/American Urological Association Joint Symposium	San Miguel de Tucuman,Argentina	2016
Basic Sciences Symposium. Inflammatory Responses and the Microbiome in OAB.	American Urological Association Annual Meeting	San Diego, CA	2016

Teaching Activities and/or Other off-campus:

UCLA Teaching Activities:

Urology Residents:
- On Call Teaching Rounds (2020 –)
- Yearly Journal Club (2020 –)
- Lectures bimonthly on the Urology Core Curriculum (2020 –)
- Individual teaching on consulting cases, operative cases, clinical supervision (2020 –)
- Participation/Teaching during weekly Grand Rounds, Case Conferences, Morbidity and Mortality Conferences (2020 –)

Female Pelvic Medicine and Reconstructive Surgery Fellows:
- Monthly Research Didactics (2021 –)
- Weekly Didactic, Pre-opperative Conferences (2020 –)
- Individual teaching on consulting cases, operative cases, clinical supervision (2020 –)
- Quarterly FPMRS Los Angeles Area Journal Club (2016 –)
- Academy for Pelvic Surgery Regional Cadaver Lab for FPMRS Fellows (2016 –)

Research Fellows:
- Weekly Laboratory Meetings (2020 –)
- Monthly Host-Microbe Journal Club (2020 –)
- Participation/Teaching during monthly Research In Progress Seminars (2020 –)

Research Mentees:
- Ariel Moradzadeh, M.D. (2017 – 2018)
- Victoria C.S. Scott, M.D. (2018 – 2019)
- Kai Dallas, M.D. (2019 – 2021)
- Colby P. Souders, M.D. (2019 – 2020)
- Ashley Caron, B.S. (2019 – 2021)
- Julia Guo, B.S. (2019 – 2020)
- Sarah B. Andebrhan, MPH (2020 – 2021)
- Patricia L. Mwesigwa, M.D. (2020 – 2021)
- Michele Torosis, M.D. (2020 –)
- Rotimi Nettey, M.D. (2020 – 2022)
- Natalia Garcia Peñaloza, B.S. (2021 –)
- Nuha Khalfay, B.S. (2021 –)
- Alec Szlachta-McGinn, M.D. (2021 –)
- Taylor Sadun, M.D. (2021-)
- Georgina Dominique, B.S. (2022 –)

Emma Dixon, B.S. (2022 –)

CME/Educational Events:

Infection and Inflammation in Urology	European Association of Urology TV	2023
Mental Health in Medicine Panel	UCLA MEDLIFE	2023
Asymptomatic Bacteriuria, Atypical Urinary Tract Infection and the Urinary Microbiome	AUAUniversity Podcast	2022
To Pee or Not to Pee	Webinar, sponsored by UCLA Health	2022
Female Pelvic Triangle Microbiomes	Webinar, sponsored by Solv Wellness	2022
Phenotyping Bladder Pain	Webinar, sponsored by the Interstitial Cystitis Association and Desert Harvest	2022
Classifying Patients with Pelvic Pain To Guide Treatment Decisions	47th Annual UCLA State-of-the-Art Urology Conference	2022
Defining Properly Collected Urine: Thresholds of Urinalysis for Microscopic Hematuria Evaluation in Women	Grand Rounds in Urology Webcast	2022
Optimizing the Treatment of Complicated UTIs	AUAUniversity Podcast	2021
Value of Genetic Testing and Next Generation Sequencing in Diagnosis of UTI	46th Annual UCLA State-of-the-Art Urology Conference Live Virtual Conference	2021
Mycoplasma and Ureaplasma Molecular Testing Does Not Correlate with Irritative or Painful Lower Urinary Tract Symptoms	Grand Rounds in Urology Webcast	2021
Prolapse and Sexual Dysfunction after Menopause: Diagnostic Approaches and Treatments	Annual Cedars-Sinai Update in Obstetrics and Gynecology Cedars-Sinai Medical Center	2020
Does My Vagina Need a Makeover? Prolapse, Female Sexual Dysfunction, And Vaginal Rejuvenation	What's New in Urology: A Primer for the Primary Care Physician Cedars-Sinai Medical Center	2019
Obstructive Sleep Apnea and Personal Urological Health	Otolaryngology Symposium Cedars-Sinai Medical Center	2019
Urinary Incontinence and Pelvic Organ Prolapse: Common Complaints	Community Urology CME Event Cedars-Sinai Medical Center	2017

Why Does It Hurt Down There? Primary Care and Pelvic Pain	What's New in Urology: A Primer for the Primary Care Physician Cedars-Sinai Medical Center	2018
Management of Urinary Incontinence	Community Urology CME Event Cedars-Sinai Medical Center	2017
Urinary Complications of Prostate Cancer Treatment	Urologic Cancer Update Cedars-Sinai Medical Center	2017
Urinary Incontinence: Diagnosis And Management	Annual Cedars-Sinai Update In Obstetrics and Gynecology Cedars-Sinai Medical Center	2016

Grand Rounds/Noon Conferences Lectures:

Microbial Interactions in Pelvic Pain	Urology Grand Rounds Yale-New Haven Hospital	2023
Using the Microbiome to Guide Clinical Care of Lower Urinary Tract Symptoms	FPMRS Didactic Conference Weill-Cornell Medical College	2023
Overactive Bladder and Storage LUTS: Machine Learning and the Microbiome	Internal Medicine Grand Rounds Harbor-UCLA Medical Center	2021
The Urinary Microbiota: A New Perspective On the Definitions and Management of GU Infections	USC FPMRS Rounds USC-Keck Medical Center	2021
Lower Urinary Tract Symptoms in Older Women:Using the Microbiome to Improve Care	UCLA Geriatrics Grand Rounds UCLA Medical Center	2021
Case-based Review of the New AUA Guidelines for the Management of Recurrent Urinary Tract Infections	UCLA FPMRS Grand Rounds UCLA Medical Center	2021
Urinary Microbiota in Benign Lower Urinary Tract Symptoms: New Approaches to Disease Phenotyping	UCLA Urology Grand Rounds UCLA Medical Center	2021
A New Perspective on the Definitions and Management of GU Infection	UPMC Magee Women's Hospital Urogynecology Grand Rounds	2021
The Urinary Microbiota in LUTS: Microbial Perspectives on Diagnosis and Classification	UCLA FPMRS Grand Rounds, UCLA Medical Center	2020
Female Sexual Dysfunction in Older Patients	Obstetrics and Gynecology Grand Rounds, Cedars-Sinai Medical Center	2020

The Urinary Microbiota in Older Women: Influences of Sex Hormones on LUTS	Center for Research in Women's Health and Sex Differences, CSMC	2020
The Urinary Microbiome in Inflammation of the Urogenital Tract	Microbe Club, Cedars-Sinai Medical Center	2020
Urinary Microbiota and Host Inflammation In Lower Urinary Tract Symptoms	Yale University Department of Urology Grand Rounds, Yale-New Haven Hospital	2020
The Urinary Microbiome in LUTS: A New Paradigm	BIDMC Urology Grand Rounds, Beth Israel-Deaconess Medical Center	2019
Urinary Microbial Profiling in Lower Urinary Tract Symptoms	Urology Grand Rounds, Virginia Commonwealth University	2019
The Urinary Microbiome and Urinary Tract Infection	UCLA FPMRS Grand Rounds, UCLA Medical Center	2019
The Vaginal Microbiome in Health and Disease	Obstetrics and Gynecology Grand Rounds, Cedars-Sinai Medical Center	2019
Recent Advances in our Understanding of the Diagnosis and Treatment of Urinary Tract Infection	Urgent Care Grand Rounds Cedars-Sinai Medical Center	2018
The Urinary Mycobiome in the Development of Lower Urinary Tract Symptoms	IBIRI Center Group Meeting Cedars-Sinai Medical Center	2017
Host Responses to the Urinary Microbiome in Lower Urinary Tract Symptoms	Immunology Research In Progress Cedars-Sinai Medical Center	2017
A New Perspective on Bladder Hypersensitivity Syndromes: The Urinary Microbiome	Urology Grand Rounds, Cedars-Sinai Medical Center	2017
The Urinary Microbiome and Bladder Hypersensitivity Syndromes	General Surgery Grand Rounds, Cedars-Sinai Medical Center	2017
Interstitial Cystitis: Etiology, Management and Mismanagement	Cedars-Sinai Medical Center Obstetrics and Gynecology Grand Rounds	2016

Undegraduate/Graduate Courses:

Medical Impact of Basic Science	Teaching Assistant, Yale University	2001 – 2003
Graduate Teaching Center at Yale	Science Teaching Consultant	2000 – 2002

Biological Mechanisms of Reaction to Injury	Teaching Assistant, Yale University	2000
Biology of AIDS	Adjunct Professor, Albertus Magnus College	2000
Cellular Basis of Behavior	Teaching Assistant, Yale University	1999

PUBLICATION/BIBLIOGRAPHY:
RESEARCH PAPERS

Research Papers (Peer Reviewed)

A. RESEARCH PAPERS – PEER REVIEWED

1. Fleming KG, **Ackerman AL**, Engelman DM. The effect of point mutations on the free energy of transmembrane alpha-helix dimerization. J Mol Biol. 1997 Sep 19;272(2):266-75. doi: 10.1006/jmbi.1997.1236. PMID: 9299353.
2. **Ackerman AL**, Cresswell P. Regulation of MHC class I transport in human dendritic cells and the dendritic-like cell line KG-1. J Immunol. 2003 Apr 15;170(8):4178-88. doi: 10.4049/jimmunol.170.8.4178. PMID: 12682250.
3. **Ackerman AL**, Kyritsis C, Tampé R, Cresswell P. Early phagosomes in dendritic cells form a cellular compartment sufficient for cross presentation of exogenous antigens. Proc Natl Acad Sci USA. 2003 Oct 28;100(22):12889-94. doi: 10.1073/pnas.1735556100. PMID: 14561893.
4. **Ackerman AL**, Cresswell P. Cellular mechanisms governing cross-presentation of exogenous antigens. Nat Immunol. 2004 Jul;5(7):678-84. doi: 10.1038/ni1082. PMID: 15224093.
5. **Ackerman AL**, Kyritsis C, Tampé R, Cresswell P. Access of soluble antigens to the endoplasmic reticulum can explain cross-presentation by dendritic cells. Immunol. 2005 Jan;6(1):107-13. doi: 10.1038/ni1147. PMID: 15592474.
6. Shen H, **Ackerman AL***, Cody V, Giodini A, Hinson ER, Cresswell P, Edelson RL, Saltzman WM, Hanlon DJ. (*co-first author) Enhanced and prolonged cross-presentation following endosomal escape of exogenous antigens encapsulated in biodegradable nanoparticles. Immunology. 2006 Jan;117(1):78-88. doi: 10.1111/j.1365-2567.2005.02268.x. PMID: 16423043.
7. **Ackerman AL**, Giodini A, Cresswell P. A role for the endoplasmic reticulum protein retrotranslocation machinery during cross presentation by dendritic cells. Immunity. 2006 Oct;25(4):607-17. doi: 10.1016/j.immuni.2006.08.017. PMID: 17027300.
8. Kiyosaki K, **Ackerman AL**, Histed S, Sevilla C, Eilber K, Maliski S, Rogers RG, Anger J. Patients' understanding of pelvic floor disorders: what women want to know. Female Pelvic Med Reconstr Surg. 2012 May-Jun;18(3):137-42. doi: 10.1097/SPV.0b013e318254f09c. PMID: 22543763.
9. Lee U, **Ackerman AL**, Wu A, Zhang R, Leung J, Bradesi S, Mayer E, Rodriguez LV. Chronic Psychological Stress in High Anxiety Rats Induces Sustained Bladder Hyperalgesia. *Physiol Behav*. 2015 Feb; 139:541-548. doi: 10.1016/j.physbeh.2014.11.045. PMID: 25449389.
10. **Ackerman AL**, Lee UJ, Jellison F, Tan N, Patel M, Raman SS, Rodriguez LV. MRI suggests increased tonicity of the levator ani in women with Interstitial Cystitis/Bladder Pain Syndrome. *Int Urogyn J.* 2016 Jan;27(1):77-83. doi: 10.1007/s00192-015-2794-6. PMID: 26231233.
11. **Ackerman AL**, Jellison FC, Lee UJ, Bradesi S, Rodriguez LV. Glt1 glutamate receptor mediates the establishment and perpetuation of chronic visceral pain in an animal model of stress-induced bladder hyperalgesia. Am J Physiol Renal Physiol. 2016 Apr 1;310(7):F628-F636. doi: 10.1152/ajprenal.00297.2015. PMID: 26697981.
12. Cohen SA, Chaudhry Z, Oliver JL, Kreydin EI, Nguyen MT, Mills SA, **Ackerman AL**, Kim JH, Tarnay CM, Raz S. Comparison of Times to Ureteral Efflux After

Administration of Sodium Fluorescein and Phenazopyridine. J Urol. 2017 Feb;197(2):519-523. doi: 10.1016/j.juro.2016.07.099. PMID: 27664579.
13. Ramart P, **Ackerman AL***, Cohen SA, Kim JH, Raz S. (*co-first author)The Frequency of Urinary Incontinence after Suburethral Mesh Removal Requiring Anti-Incontinence Procedure. Urology. 2017 Aug;106:203-209. doi: 10.1016/j.urology.2017.01.060. PMID: 2847668.
14. Clemens JQ, Mullins C, **Ackerman AL**, Bavendam T, van Bokhoven A, Ellingson BM, Harte SE, Kutch JJ, Lai HH, Martucci KT, Moldwin R, Naliboff BD, Pontari MA, Sutcliffe S, Landis JR; MAPP Research Network Study Group. Urologic chronic pelvic pain syndrome: insights from the MAPP Research Network. Nat Rev Urol. 2019 Mar;16(3):187-200. doi: 10.1038/s41585-018-0135-5. PMID: 30560936.
15. Weinberger JM, Houman J, Caron AT, Patel DN, Baskin AS, **Ackerman AL**, Eilber KS, Anger JT. Female Sexual Dysfunction and the Placebo Effect: A Meta-analysis. Obstet Gynecol. 2018 Aug;132(2):453-458. doi: 10.1097/AOG.0000000000002733. PMID: 29995725.
16. Moradzadeh A, Jamnagerwalla J, Eilber KS, Anger JT, **Ackerman AL**. High catastrophizing in subjects with painful mesh complications have worse outcomes. Urology. 2019 Feb;124:83-90. doi: 10.1016/j.urology.2018.05.050. PMID: 30076941.
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21. Anger J, Lee U, **Ackerman AL,** Chou R, Chughtai B, Clemens JQ, Hickling D, Kapoor A, Kenton KS, Kaufman MR, Rondanina MA, Stapleton A, Stothers L, Chai TC. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol. 2019 Aug;202(2):282-289. doi: 10.1097/JU.0000000000000296. PMID: 31042112.
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a Single Health Care System: Room for Improvement. Obstet Gynecol. 2019 Aug;134(2):318-322. doi: 10.1097/AOG.0000000000003355. PMID: 31306311.
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27. Souders CP, Lo EM, **Ackerman AL**. Underrepresentation of functional conditions of the lower urinary tract in adults in US federal research funding. Neurourol Urodyn. 2020 Jun 7;. doi: 10.1002/nau.24413. PMID: 32506674
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30. Guo JZ, Souders CP, McClelland L, Anger JT, Scott VCS, Eilber KS, **Ackerman AL**. Vaginal Laser Treatment of Genitourinary Syndrome of Menopause: Does the Evidence Support the FDA Safety Communication? Menopause. 2020 Aug 10. doi: 10.1097/GME.0000000000001577. PMID: 32796292
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33. Souders CP, Scott VCS, Ackerman JE, Khalique MU, Eilber KS, Anger JT, Underhill DM, **Ackerman AL**. Mycoplasma and Ureaplasma Molecular Testing Does Not Correlate with Irritative or Painful Lower Urinary Tract Symptoms. J Urol. 2021 Mar 29;101097JU0000000000001750. PMID: 33780281
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37. Chen A, Caron A, Jackson NJ, Kanji F, Kuhlmann P, Le CH, Eilber KS, Anger JT, **Ackerman AL**. Defining Properly Collected Urine: Thresholds to Improve the Accuracy of Urinalysis for Microscopic Hematuria Evaluation in Women. J Urol. 2021 Sep 21. doi: 10.1097/JU.0000000000002200. PMID: 34544262.
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44. Torosis M, Jackson NJ, Nitti V, **Ackerman AL**. Overactive Bladder Patients With and Without Urgency Incontinence: A Spectrum of One Condition or Different Phenotypes? Urogynecology. October 3, 2022 doi: 10.1097/SPV.0000000000001254. PMID: 36548103 PMCID: PMC9859670
45. Khalfay N, Lo E, Grisales T, **Ackerman AL**. An Analysis of Stated Insurance Coverage and Estimated Patient-Incurred Costs of Treatments for Lower Urinary Tract Symptoms. Urogynecology (Hagerstown). 2023 Feb 1;29(2):287-294. doi: 10.1097/SPV.0000000000001307. PubMed PMID: 36735446.
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B. RESEARCH PAPERS – PEER REVIEWED (IN PRESS)

1. **Ackerman AL**, Jackson NJ, Caron AT, Kaufman MR, Routh JC, Lowder JL. Myofascial Frequency Syndrome: A novel syndrome of bothersome lower urinary tract symptoms associated with myofascial pelvic floor dysfunction. medRxiv. 2023 Apr 17:2023.04.14.23288590. doi: 10.1101/2023.04.14.23288590. Preprint. *In Revision.* PMID: 37131628

C. RESEARCH PAPERS – PEER REVIEWED (SUBMITTED)

1. Nettey OS, Gu C, Jackson NJ, **Ackerman AL**. Validation of Distinct Bladder Pain Phenotypes Utilizing the MAPP Research Network Cohort. *In submission.*
2. Dallas KB, Chiang JN, Caron AT, Anger JT, Kaufman MR, **Ackerman AL**. Development and Validation of a Machine Learning Algorithm to Classify Lower Urinary Tract Symptoms. medRxiv 2022.12.25.22283168; Preprint. doi: 10.1101/2022.12.25.22283168. *In submission.*
3. Torosis M, Carey E, Christensen K, Kaufman MR, Kenton K, Kotarinos R, Lai HH, Lee UJ, Lowder JL, Meister M, Spitnagle T, Wright K, **Ackerman AL**. A Clinical Consensus Treatment Algorithm for Patients with High-tone Pelvic Floor Dysfunction: a Delphi Study of National Experts. *In Submission.*
4. Park J, Torosis M, Kim J-H, **Ackerman AL**. Primary Care Perceptions on the Barriers to Providing Guideline-Driven Care for Recurrent UTI. *In Submission*.
5. Dolendo I, Kuhlmann PK, Stewart CA, Kim J, Zhao H, Maniskas S, Shorter B, Moldwin R, **Ackerman AL**, Eilber KS, Freedland SJ, Anger JT. Evidence Linking Dietary Intake to Interstitial Cystitis/Bladder Pain Syndrome: A Systematic Review. *In Submission.*
6. Torosis M, Fullerton M, Kaefer D, Nitti V, **Ackerman AL,** Grisales T. Pudendal Block at Time of Transvaginal Prolapse Repair Does Not Improve Post-op Pain: A Randomized Controlled Trial. *In Submission.*
7. Bondok M, Stothers ML, Macnab A, **Ackerman AL,** Dixon E, Trochez M, Petersen K, Selvakumar R. Evaluation of YouTube content on recurrent UTI in women for compliance with current international clinical guidelines. *In Submission.*

D. RESEARCH PAPERS – NON-PEER REVIEWED

1. **Ackerman AL**, Anger JT. The Role of the Urinary Microbiome in Urological Disease. AUA News, September, 2017.
2. **Ackerman AL**, Raz S. Complete Mesh Removal is Appropriate for Chronic Mesh Related Pain. AUA News, October, 2017.
3. **Ackerman AL**. Emergent Themes in Infection and Inflammation of the Genitourinary Tract. AUA News, August, 2020.
4. Souders CP, **Ackerman AL**. Ureaplasma/Mycoplasma Colonization is Negatively Associated with Chronic Urinary Symptoms. AUA News, November, 2020.
5. **Ackerman AL.** The Challenging Patient with Recurrent UTI: A Preview of AUA2021. AUA News, August, 2021.
6. Volkin D, Nitti V, **Ackerman AL.** Patient Perceptions with Fixed-Life vs Rechargeable Sacral Neuromodulation. AUA News, May, 2022.

7. Ackerman AL. AUA News

Chapters

1. The role of power morcellation and controversies
by **A. Lenore Ackerman**
in: Use of Robotic Technology in Female Pelvic Floor Reconstruction
Ed: Jennifer T. Anger, Karyn S. Eilber
Published: October 18, 2017

2. Native Tissue Repair After Failed Synthetic Materials
by: **A. Lenore Ackerman**, Seth A. Cohen, Shlomo Raz
in: Native Tissue Repair For Incontinence and Prolapse
Ed: Phillipe Zimmern, Elise De
Published: March 28, 2017

3. Bulbocavernosus Muscle and Fat Pad Supplement
by: **A. Lenore Ackerman**, Shlomo Raz
in: Hinman's Atlas of Urologic Surgery, Fourth Edition
Ed: Joseph A. Smith, Jr., Stuart S. Howards, Glenn M. Preminger and Roger M. Dmochowski
Published: March 1, 2017

4. Interstitial Cystitis/Bladder Pain Syndrome
by: **A. Lenore Ackerman,** H.Henry Lai
in: American Urological Association Core Curriculum
Ed: Larissa Bresler, Matthew Rutman, et al.
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Reviews

1. Cresswell P, **Ackerman AL**, Giodini A, Peaper DR, Wearsch PA. Mechanisms of MHC class I-restricted antigen processing and cross-presentation. Immunol Rev. 2005 Oct;207:145-57. doi: 10.1111/j.0105-2896.2005.00316.x. PMID: 16181333.
2. **Ackerman AL**, Blavais J, Anger J. Female Urethral Reconstruction. *Curr Bladder Dysfunct Rep*. 2010 Oct; 5:225-232. doi: 10.1007/s11884-010-0071-6. PMID: 21475706.
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4. **Ackerman AL**, Underhill DM. The mycobiome of the human urinary tract: potential roles for fungi in urology. Ann Transl Med. 2017 Jan;5(2):31. doi: 10.21037/atm.2016.12.69. PMID: 28217696.
5. **Ackerman AL,** Parameshwar P, Anger JT. Diagnosis and Treatment of Patients with Prostatic Abscess in the Post-Antibiotic Era. Int J Urol. 2018 Feb;25(2):103-110. doi: 10.1111/iju.13451. PMID: 28944509.
6. Nik-Ahd F, **Ackerman AL**, Anger J. Recurrent Urinary Tract Infections in Females and the Overlap with Overactive Bladder. Curr Urol Rep. 2018 Sep 13;19(11):94. doi: 10.1007/s11934-018-0839-3. PMID: 30215140.
7. **Ackerman AL** and TC Chai. The Bladder is Not Sterile: an Update on the Urinary Microbiome. *Curr Bladder Dysfunct Rep*. 2019;14(4):331-341. doi: 10.1007/s11884-019-00543-6. PMID: 32612735.

8. Dallas KB, Stewart CS, **Ackerman AL,** Anger JT. OAB and IC/BPS: Two Conditions or a Continuum of One? *Curr Bladder Dysfunct Rep*. 2020; 15, 15–20. doi: 10.1007/s11884-019-00567-y.
9. **Ackerman AL**. Recurrent Uncomplicated UTIs in Women: A Case Based Approach. AUA Update Series Volume 40. Lesson 17. *Published: Jun 1 2021.*
10. McGinn-Szlachta AW, **Ackerman AL.** Asymptomatic Bacteriuria, Atypical UTI, and the Urinary Microbiome. AUA Update Series. Volume 41. Lesson 30. *Published: September 1 2022*
11. Ramart P, **Ackerman AL**. Recurrent urinary tract infection in women from a urologist's perspective. *Siriraj Medical Journal*. 2023; 75(1):55-61. doi: 10.33192/smj.v75i1.260531
12. Gu C, **Ackerman AL**. An Oldie but a Goodie: Methenamine as a Non-Antibiotic Solution to the Prevention of Recurrent Urinary Tract Infections. *PLoS Pathog.* 2023 Jun 15;19(6):e1011405. doi: 10.1371/journal.ppat.1011405. PMID: 37319137

Editorials

1. **Ackerman AL** and Raz S. Difference of Opinion – Are Synthetic Slings Safe? Opinion: No. Int Braz J Urol. 2016 Jul-Aug;42(4):640-4. doi: 10.1590/S1677-5538.IBJU.2016.04.03. PMID: 27564272.
2. **Ackerman AL**. Symptom and Quality of Life Improvements After Pelvic Floor Physical Therapy in a Clinical Population of Women With Pelvic Pain and Other Symptoms. PracticeUpdate. 2020 January. https://www.practiceupdate.com/ content/symptom-and-qol-improvements-after-pelvic-floor-physical therapy/93850/65/3/1.
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4. **Ackerman AL.** Penny-wise but Pound-foolish: The Hidden Costs of Step Therapy for Overactive Bladder. J Urol. 2023 Jun;209(6):1045-1047. doi: 10.1097/JU.0000000000003430. Epub 2023 Mar 23.PMID: 36950931

Papers in Preparation (Research Completed)

1. **Ackerman AL**, Khalique MU, Cheng Z, Ackerman JE, Anger JT, Eilber KS, Underhill DM. Microbiological phenotyping of bladder and pelvic pain reveals distinct clinical profiles with implications for prognosis and treatment.
2. Yang J, Scott VCS, Thum LW, Khalique MU, Ackerman JE, Underhill DM, Jacobs J, **Ackerman AL.** Temporal Dynamics of the Female Geintourinary Microbiome.
3. **Ackerman AL,** Liu G, Hu X, Scott VCS, Kreydin E, Shi W, Raz S**.** Bacterial persistence on Transvaginal Slings is Associated with Delayed-Onset Chronic Pain.
4. **Ackerman AL**, Lima BP, Mellano EM, Ramart P, Pizarro-Rojas M, Shi W, Lux R, Raz S. A Pro-Inflammatory Mesh-Associated Microbiota in Transvaginal Slings Explanted from Patients with Delayed-Onset Chronic Pain.

Abstracts

1. **Ackerman AL** and Cresswell P. Regulation of MHC Class I Transport in Human Dendritic Cells and the Dendritic-like Cell Line KG-1. International Congress of Immunology, Stockholm, Sweden, July 2001.

2. **Ackerman AL** and Cresswell P. Regulated MHC Class I Transport in Human Dendritic Cells Facilitates Proper Immune Activation and Limits Autoimmunity. Keystone Symposium on Dendritic Cells, Keystone, Colorado, March 2003.
3. Hanlon DJ, **Ackerman AL**, Shen H, Cresswell P, Saltzman M. Nanoparticle-Mediated Delivery of Antigens to Dendritic Cells: Increased Efficiency and Duration of Antigen Processing and Presentation. International Congress of Immunology, Montreal, Canada, July 2004.
4. **Ackerman AL**, Kyritsis C, Tampé R, Cresswell P. Early Phagosomes in Dendritic Cells Form a Cellular Compartment Sufficient for Cross Presentation of Exogenous Antigens. International Congress of Immunology, Montreal, Canada, July 2004.
5. **Ackerman AL**, Giodini A, Cresswell P. A Role for the Endoplasmic Reticulum Protein Retrotranslocation Machinery in Cross Presentation by Dendritic Cells. Annual MD/PhD Student Conference, Keystone, Colorado, July 2007. Recipient of Diversity Travel Award.
6. Le NB, Jellison F, **Ackerman AL**, Rogo-Gupta L, Chow D, Baxter ZC, Treat E, Hartshorn T, Kim JH, Rodriguez L, Raz S. Anterior Colporraphy Using Polypropylene Sutures: Our Two-year Experience. Society of Urodynamics and Female Urology Annual Meeting, New Orleans, LA, February 2012.
7. Chow D, Jellison F, Hartshorn T, Rogo-Gupta L, Le NB, **Ackerman AL**, Staack A, Rodriguez LV, Raz S. Translabial Ultrasound for Localization of Vaginal Mesh. Society of Urodynamics and Female Urology Annual Meeting, New Orleans, LA, February 2012.
8. **Ackerman AL**, Chestovich P, Dubina E, Tillou A, Anger JT. Patterns of Care for Urethral Trauma in Patients with Pelvic Fracture. Society of Urodynamics and Female Urology Annual Meeting, New Orleans, LA, February 2012.
9. **Ackerman, AL**, Lee U, Zhang R, Le N-B, Leung J, Bradesi S, Rodriguez LV. Alterations in Neurotransmitter Processing in Rodents Exposed to Chronic Water Avoidance Stress. Society of Urodynamics and Female Urology Annual Meeting, New Orleans, LA, February 2012.
10. **Ackerman AL**, Le N-B, Jellison F, Rogo-Gupta L, Chow D, Hartshorn TG, Rodriguez LV, Raz S. Anatomical, functional, and quality of life outcomes of transvaginal sacrouterine ligament suspension for vaginal vault prolapse. Society of Urodynamics and Female Urology Annual Meeting, New Orleans, LA, February 2012. Recipient of Resident Travel Award.
11. Jellison F, Le NB, **Ackerman AL**, Rogo-Gupta L, Chow D, Chamie K, Raman S, Rodriguez LV, et. al. Relationship Between Physical Examination, Dynamic MRI, and Intra-operative Findings in the Treatment of Pelvic Organ Prolapse. American Urological Association Annual Meeting, Atlanta, GA, May 2012.
12. Rogo-Gupta L, Hartshorn TG, Chow D, Le NB, Jellison F, **Ackerman AL**, Rodriguez LV, Raz S. Complications of Mesh-augmented Pelvic Organ Prolapse and Incontinence Repairs: Case Series of 319 Procedures. American Urological Association Annual Meeting, Atlanta, GA, May 2012.
13. **Ackerman AL**, Lee UJ, Tan N, Raz S, Raman SS, Rodriguez LV. Alterations in the Pelvic Floor Musculature on Pelvic MRI in Patients with Interstitial Cystits. American Urological Association Annual Meeting, Atlanta, GA, May 2012.
14. Le N-B, **Ackerman AL**, Zhang R, Lee UJ, Leung J, Rodriguez LV. Mast Cell Activation, Mediator Levels, Tactile Allodynia, and Urothelial Topography in Wistar-Kyoto Rodents Exposed to Chronic Water Avoidance Stress. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Las Vegas, NV, February 2013.
15. Mellano EM, Lima B, Ramart P, **Ackerman AL**, Lux R, Shi W, Raz S. The Role of Bacterial Biofilms and Chronic Inflammation in the Delayed Development of Pain following Transvaginal Placement of Mesh Slings for Incontinence. AUGS Annual Meeting, October 2015, Seattle, WA.

16. Kang D, Hartshorn T, Pollard M, Choi J, Rodriguez L, Kim JH, **Ackerman AL**, Cohen S, Ramapart P, Raz S. Patient Quality of Life after Removal of Vaginal Mesh. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, February 2015.
17. Choi JM, Ramart P, Kang D, **Ackerman AL**, Cohen S, Raz S. Abdominal Sacrocolpopexy Mesh Complications: Presentation and Surgical Removal Techniques. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, February 2015.
18. **Ackerman AL**, Lima BP, Ramart P, Mellano E, Lux R, Shi W, Raz S. The Role of Bacterial Biofilms and Chronic Inflammation in the Delayed Development of Systemic Side Effects Following Transvaginal Placement of Mesh Slings for Incontinence. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, February 2015.
19. **Ackerman AL**, Lee UJ, Jellison FC, Margolis DC, Tan N, Patel M, Raz S, Raman SS, Rodriguez LV. MRI Imaging Suggests Increased Tonicity of the Levator Ani Muscle Complex in Women with Interstitial Cystitis/Bladder Pain Syndrome. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, February 2015.
20. Cohen SA, Mellano EM, Chaudhry Z, **Ackerman AL**, Ramart P, Scott VC, Kim J, Raz S. Cystocele Repair Using Autologous Iliotibial Band. Presentation: Video 15. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, February 2015.
21. **Ackerman AL**, Jellison FC, Lee UJ, Bradesi S, Rodríguez LV. Glt1 Glutamate Receptor Mediates The Establishment And Perpetuation Of Chronic Visceral Pain In An Animal Model Of Bladder Pain Syndrome/Interstitial Cystitis. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, February 2015.
22. Choi JM, Ramart P, Kang DC, Cohen SA, **Ackerman AL**, Raz S. Pubovaginal Sling with Tensor Fascia Lata. American Urological Association Annual Meeting, New Orleans, LA, May 2015.
23. Cohen SA, Viragh KA, Nakamura LY, **Ackerman AL**, Ramart P, Kang DC, Choi JM, Kim J-H, Raman SS, Raz S. Using Translabial Ultrasound as an Effective Tool to Visualize Mesh Erosion into the Urethra and Bladder. American Urological Association Annual Meeting, New Orleans, LA, May 2015.
24. Ramart P**, Ackerman AL**, Cohen SA, Kang DC, Choi JM, Kim J-H, Raz S. Urinary incontinence after suburethral mesh removal requiring anti-incontinence procedure. International Continence Society Annual Meeting, Montreal, Canada, October 2015.
25. **Ackerman AL**, Eilber KS, Caron AT, Pollard ME, Anger JT. Outcomes of Pregnancy Following Surgery for Pelvic Organ Prolapse: A Systematic Review. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016.
26. Scott VCS, Cohen SA, Greenberg SA, Kreydin EI, Oliver JL, **Ackerman AL**, Chaudhry Z, Nguyen MT, Kim J-H, Raz S. Use of Iliotibial Band (Fascia Lata) as a Salvage Continence Repair After Mesh Removal – At Least 6 Months Follow Up. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016.
27. Kreydin EI, Kim MM, Oliver JL, Cohen SA, **Ackerman AL**, Kim J-H, Raz S. Higher Urine Levels of Environmental Toxins Are Associated with Increased Incontinence and Nocturia in Men. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016.

28. Kreydin EI, Oliver JL, Kim MM, **Ackerman AL**, Cohen SA, Kim J-H, Raz S. 'Til Death Do Us Part: The Relationship Between Urinary Incontinence and Marital Status Among US Women and Men. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016.
29. Cohen SA, Oliver JL, Kreydin EI, Chaudhry Z, Nguyen MT, Mills SA, **Ackerman AL**, Kim J-H, Tarnay CM, Raz S. Comparison of Times to Ureteral Efflux After Administeration of Sodium Fluorescein and Phenazopyridine. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016.
30. Ramart P, **Ackerman AL**, Cohen SA, Kim J-H, Raz S. Urinary Incontinence After Suburethral Mesh Removal Requiring Anti-Incontinence Procedures. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016.
31. **Ackerman AL**, Anger JT, Eilber KS, Funari V, Tang J, Kim J, Freeman MR. Identification of a Diverse Fungal Community ("Mycobiome") in the Normal Female Human Lower Urinary Tract. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, New Orleans, LA, February 2016. Recipient of Best Basic Science Poster Award.
32. Kreydin E, Oliver J, Kim M, Cohen S, **Ackerman AL**, Raz S, Lerner L. Prostate Ablation and Enucleation: Comparison of Patient Characteristics and 30-day Surgical Outcomes Using a National Database. American Urological Association Annual Meeting, San Diego, CA, May 2016.
33. Kreydin E, Kim M, Oliver J, Cohen S, **Ackerman AL**, Chaudhry Z, Nguyen MT, Kim JH, Raz S. Til Death Do Us Part: The Relationship between Urinary Incontinence and Marital Status among US Women and Men. American Urological Association Annual Meeting, San Diego, CA, May 2016.
34. **Ackerman AL**, Anger JT, Eilber K, Funari V, Tang J, Kim J, Freeman M. Identification of a Diverse Fungal Community ("Mycobiome") in the Normal Female Human Lower Urinary Tract. American Urological Association Annual Meeting, San Diego, CA, May 2016.
35. **Ackerman AL**, Eilber KS, Tang J, J. Kim3 , Freeman MR, Anger JT. A Diverse, Viable Fungal Community ("Mycobiome") Exists in the Urine of Healthy Asymptomatic Females. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, September/October 2016, V22:5 p. S35. Oral Poster 1.
36. Samimi P, Handler SJ, **Ackerman AL**, Eilber KS, Anger JT. Recurrent UTI in Women: Patient Characteristics, Natural History, and Referral Practice Patterns. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale,AZ, September/October 2016, V22:5 p. S103. Poster 76.
37. Handler SJ, Samimi P, **Ackerman AL**, Anger JT, K. S. Eilber KS. Practice Patterns for the Evaluation of Asymptomatic Micoscopic Hematuria in Women in a Single Healthcare System: Room for Improvement? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, September/October 2016, V22:5 p. S103. Poster 77.
38. Nguyen MT, Cohen SA, Mei JY, **Ackerman AL**, Oliver J, Kreydin KI. Preliminary Report on the Use of the Vastur Lateralis-Fascia Lata Graft for Repair of Anterior Vaginal Wall Prolapse. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, Scottsdale, AZ, September/October 2016, V22:5 p. S149. Poster 180.
39. **AL Ackerman**, KS Eilber, J Tang, J Kim, MR Freeman, JT Anger. A Diverse, Viable Fungal Community ("Mycobiome") Exists in the Urine of Healthy Asymptomatic Females. American Urogynecologic Society Annual Meeting/Pelvic Floor Disorders Week, September 2016, Denver, CO.

40. Van den Broek I, Fu Q, Ackerman AL, Anger JT, Kushon S, Chansky K, Millis K, Percy A, Agreste T, Van Eyk JE. Accuracy of Volumetric Absorptive Microsampling for Quantification of Protein Biomarkers. The Association for Mass Spectrometry: Applications to the Clinical Lab, January 2017, Palm Springs, CA.
41. Van den Broek I, Fu Q, Kushon S, Chansky K, Kowalski MP, Millis K, Percy A, Agreste T, **Ackerman AL**, Anger JT, Holewinski R, Venkatraman V, Van Eyk JE. A Precision Proteomics Pipeline for Remote Blood Monitoring: Integrating Volumetric Absorptive Microsampling with High-Throughput Mass Spectrometric Proteotyping. US HUPO 13th Annual Meeting: Precision Proteomics for Discovery and Health, March 2017, San Diego, CA.
42. Weinberger J, Houman J, Caron A, Baskin A, **Ackerman AL**, Eilber KS, Anger JT. Female Sexual Dysfunction Treatment: A Meta-Analysis of the Placebo Effect Across Randomized Controlled Trials. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
43. **Ackerman AL**, Lai HH, Eilber KS, Anger JT. Symptomatic Overlap in Overactive Bladder and Interstitial Cystitis/Painful Bladder Syndrome. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
44. **Ackerman AL**, Handler S, Samimi P, Anger JT, Eilber KS. Practice Patterns for the Evaluation of Asymptomatic Microscopic Hematuria in Women in a Single Healthcare System: Room for Improvement? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
45. Parameshwar PS, Kayondo M, **Ackerman AL**, Anger JT, Tarnay C. Effects of Group Rehabilitation upon Women Undergoing Surgery for Obstetric Fistula. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
46. Thum DJ, Wood LM, Moradzadeh A, Hannemann A, Li A, **Ackerman AL**, Anger JT, Eilber KS. Concomitant Treatment of Stress Urinary Incontinence and Gynecologic Oncology Surgery: Are We Undertreating? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
47. **Ackerman AL**, Eilber KS, Tang J, Kim J, Underhill DM, Anger JT, Freeman MR. Optimization of DNA Extraction from Human Urinary Samples for Microbial Community Profiling. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
48. **Ackerman AL**, Tang J, Eilber KS, Kim J, Anger JT, Underhill DM, Freeman MR. Decreased Urinary Fungal Burden and Diversity in Overactive Bladder. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
49. **Ackerman AL**, Anger JT, Tang J, Eilber KS, Kim J, Freeman MR, Underhill DM. Alterations in the Urinary Fungal Mycobiome in Patients with Bladder Pain and Urinary Urgency. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
50. **Ackerman AL**, Jie Tang J, Eilber KS, Kim J, Nickel JC, Ehrlich G, Underhill DM, Jennifer Anger JT. Shared Alterations in Urinary Bacterial Communities in Patients with Interstitial Cystitis and Overactive Bladder. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2017, Scottsdale, AZ.
51. Parameshwar PS, Borok JF, Wood LN, **Ackerman AL**, Eilber KS, Anger JT. Writing in the Margins of Sexual Function Questionnaires: A Qualitative Analysis From Women With Pelvic Floor Disorders. American Urological Association Annual Meeting, May 2017, Boston, MA.

52. **Ackerman AL**, Anger JT, Tang J, Eilber KS, Kim J, Freeman MR, Underhill DM. Alterations in the Urinary Fungal Mycobiome in Patients with Bladder Pain and Urinary Urgency. American Urological Association Annual Meeting, May 2017, Boston, MA.
53. **Ackerman AL**, Lai HH, Eilber KS, Anger JT. Symptomatic Overlap in Overactive Bladder and Interstitial Cystitis/Painful Bladder Syndrome. American Urological Association Annual Meeting, May 2017, Boston, MA.
54. Weinberger J, Houman J, Caron A, Baskin A, **Ackerman AL**, Eilber KS, Anger JT. Female Sexual Dysfunction Treatment: A Meta-Analysis of the Placebo Effect Across Randomized Controlled Trials. American Urological Association Annual Meeting, May 2017, Boston, MA.
55. Juzar Jamnagerwalla J, Anger JT, Eilber KS, **Ackerman AL**. High Catastrophizing in Patients with Self-reported Painful Mesh Complications Have Poorer Outcomes. American Urological Association Annual Meeting, May 2017, Boston, MA.
56. **Ackerman AL**, Tang J, Eilber KS, Kim J, Anger JT, Underhill DM, Freeman MR. Decreased Urinary Fungal Burden and Diversity in Overactive Bladder. American Urological Association Annual Meeting, May 2017, Boston, MA.
57. **Ackerman AL**, Jie Tang J, Eilber KS, Kim J, Nickel JC, Ehrlich G, Underhill DM, Jennifer Anger JT. Shared Alterations in Urinary Bacterial Communities in Patients with Interstitial Cystitis and Overactive Bladder. American Urological Association Annual Meeting, May 2017, Boston, MA.
58. Parameshwar PS, Kayondo M, **Ackerman AL**, Eilber KS, Anger JT, Tarnay CM. Post-Operative Pain Management In Patients Undergoing Perineal And Vaginal Reconstructive Surgery: An Alternative To Narcotics. American Urogynecologic Society Annual Meeting/Pelvic Floor Disorders Week, October 2017, Providence, RI.
59. Kuhlmann P, Chen A, Johnson J, Hubbard L, **Ackerman AL**, Eilber KS, Anger JT. Concomitant Procedures Performed at the Time of Midurethral Sling Affect Post-operative Urinary Retention Rate. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2018, Austin, TX.
60. Moradzadeh A, Jamnagerwalla J, Eilber KS, Anger JT, **Ackerman AL**. High Catastrophizing in Subjects with Self-Reported Painful Mesh Complications Have Poorer Outcomes. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2018, Austin, TX.
61. Scott V, Tang J, Drell T, Simm J, Salumets A, Metsis M, Underhill D, **Ackerman AL**. Evaluation of the Vaginal Mycobiome in Asymptomatic Pre-menopausal Women. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2018, Austin, TX.
62. Scott V, **Ackerman AL**, Liu G, Shi W, Raz S. Immunofluorescence Localization of Bacterial Biofilms on Explanted Transvaginal Mesh Slings Removed for Chronic Pain. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2018, Austin, TX.
63. Anger JT, **Ackerman AL**, Spivia W, van den Broek I, Crear D, Eilber KS, Freeman M, Kim J, Fu Q, Van Eyk J. Differential Protein Expression in Patients with UCPPS: A MAPP Study. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2018, Austin, TX.
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65. Scott V, **Ackerman AL**, Liu G, Shi W, Raz S. Immunofluorescence Localization of Bacterial Biofilms on Explanted Transvaginal Mesh Slings Removed for Chronic Pain. Annual Meeting. American Urological Association; May 2018; San Francisco, CA, USA.

66. **Ackerman AL**, Scott V, Liu G, Shi W, Raz S. Characterization of Bacteria Identified on Explanted Mesh Slings Using Next-generation Sequencing Techniques. Annual Meeting. American Urological Association; May 2018; San Francisco, CA, USA
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68. Kuhlmann PK, Chen A, Johnson J, Hubbard L, **Ackerman AL**, et al. Concomitant Procedures Performed at the Time of Midurethral Sling Affect Post-operative Urinary Retention Rate. Annual Meeting. American Urological Association; May 2018; San Francisco, CA, USA.
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70. van den Broek I, Mouapi KN, Mastali M, Holewinski R, Venkataraman V, Fu Q, **Ackerman AL**, Kim J, Freeman M, Anger JT, Millis K, Percy A, Van Eyk J. A stable-isotope labeled protein and peptide mixture for global normalization in targeted and data-independent quantitative bottom-up proteomics. ASMS Conference on Mass Spectrometry and Allied Topics, June 2018, San Diego, CA.
71. Kuhlmann PK, Chen A, **Ackerman AL**, Anger JT, Eilber KS. Higher BMI and Concomitant Pelvic Organ Prolapse Repair are Protective Against Intraoperative Bladder Perforation During Midurethral Sling Placement. American Urogynecologic Society Annual Meeting/Pelvic Floor Disorders Week, October 2018, Chicago, IL.
72. Patel DN, Gonzales-Alabastro C, Houman J, **Ackerman AL**, Eilber KS, Anger JT. Comparative Effectiveness of One- Versus Two-Stage Sacral Neuromodulation Device Placement. American Urogynecologic Society Annual Meeting/Pelvic Floor Disorders Week, October 2018, Chicago, IL
73. **Ackerman AL**, Khalique MU, Ackerman JE, Tang J, Eilber KS, Anger JT, Underhill DM. The Urinary Microbiota and Host Inflammation in Lower Urinary Tract Symptoms. Western Section American Urological Association Annual Meeting, Maui, HI, October 2018.
74. Scott VCS, Thum LW, Ackerman JE, Khalique MU, Eilber KS, Anger JT, Underhill DM, **Ackerman AL**. Temporal Dynamics of the Genitourinary Microbiome. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
75. Burton C, O'Brien R, Eilber KS, **Ackerman AL**, Anger JT. Identifying barriers to urinary incontinence care among primary care providers. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
76. Scott VCS, Lerner LB, Anger JT, Van Kuiken M, **Ackerman AL**. Satisfaction of women urologists with maternity leave, childbirth timining and work-family balanace ten years later. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
77. Souders C, Caron AT, Obi N, Clark K, McClelland L, **Ackerman AL,** Anger JT, Eilber KS. 60 minutes and vaginal mesh: did the media tell the whole story? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
78. Cohen T, Burton C, Francis S, Patel D, Othman N, Lam P, **Ackerman AL,** Eilber KS, Anger JT. Improving patient experience with sacral neuromodulation: a human factors approach. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
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Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.

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81. Scott VCS, Lerner LB, Anger JT, Van Kuiken M, **Ackerman AL**. Re-evaluation of birth trends and pregnancy complications among female urologists: have we made any progress? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
82. Burton C, Gonzalez-Alabastro C, Choi E, Parameshwar P, Gonzalez G, Bresee C, Eilber KS, **Ackerman AL,** Anger JT. Overuse of specialty care for women with urinary incontinence. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
83. Souders C, McClelland L, Caron AT, Alazzeh M, Zukotynski B, Ackerman AL, Eilber KS, Anger JT. Transvaginal mesh litigation has significant geographic variation. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
84. Caron AT, **Ackerman AL,** Parameshwar P, Eilber KS, Anger JT. Outcomes of pregnancy following surgery for pelvic organ prolapse: a systematic review. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
85. Stewart CA, Zhao H, Gonzales G, Gonzales-Alabastro C, Zaghiyan K, Moore B, Magner D, **Ackerman AL,** Anger JT, Eilber KS. Outcomes of sacrocolpopexy with concurrent colorectal surgery for multicompartment prolapse repair. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
86. Zhao H, Stewart CA, Gonzalez G, Gonzales-Alabastro C, **Ackerman AL,** Eilber KS, Anger JT. De novo defecatory symptoms and posterior compartment prolapse as a complication of sacrocolpopexy. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting, March 2019, Miami, FL.
87. Stewart CA, Zhao H, Gonzales G, Gonzales-Alabastro C, **Ackerman AL,** Eilber KS, Anger JT. Outcomes of prophylactic sling at the time of robotic assisted sacrocolpopexy. American Urological Association Annual Meeting, May 2019, Chicago, IL.
88. Kuhlmann P, Stewart CA, Souders C, Moradzadeh A, Houman J, **Ackerman AL,** Anger JT, Eilber KS. What is "vaginal rejuvenation"? A survey of medical professionals and lay persons. American Urological Association Annual Meeting, May 2019, Chicago, IL.
89. Cohen T, Burton CS, Francis S, **Ackerman AL**, Eilber KS, Anger JT. Improving patient experience with sacral neuromodulation: a human factors approach. American Urological Association Annual Meeting, May 2019, Chicago, IL.
90. Anger JT, Spivia W, **Ackerman AL,** Eilber KS, Kim J, Fu Q, Michael Freeman MR, Van Eyk J. The Serum Proteome Correlates with Clinical Phenotypes of UCPPS: a MAPP Study. American Urological Association Annual Meeting, May 2019, Chicago, IL.
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92. Dallas K, **Ackerman AL**, Eilber K, Rogo-Gupta L, Scott V, Troung M, Cohen T, Anger J. Validated Surgical Steps of the Robotic Assisted Sacrocolpopexy Operation. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA. c.

93. Burton C, Markowitz M, Kanji F, Stewart C, Scott V, Eilber K, **Ackerman AL**, Anger J. Validation of the Pelvic Floor Awareness and Knowledge Survey (PFAKS). Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA. c.
94. Burton C, Gonzalez G, Bresee C, Scott V, Eilber K, **Ackerman AL**, Wieslander C, Anger J. Urinary Incontinence Referral Patterns in Academic and County Hospitals: The Impact of Econsult. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
95. Kuhlmann P, Ackerman J, Khalique M, Caron A, Kanji F, Anger J, Eilber K, Underhill D, **Ackerman AL**. Urinary Aerococcus Defines a Severe, Treatment-refractory Phenotype of Urgency Urinary Incontinence in Older Women. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
96. Scott V, Souders C, Khalique M, Ackerman J, **Ackerman AL**. Is Ureaplasma Truly a Urinary Tract Pathogen? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
97. Guo J, Souders C, McClelland L, Anger J, Eilber K, **Ackerman AL**. Safety and Legal Environment for Vaginal Lasers: Uncovering the Evidence Behind the FDA Safety Communication. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
98. Kuhlmann P, Dallas K, Masterson J, Patel D, Casteneda P, Reddy A, Tsai K, **Ackerman AL**. Risk Factors for Intraoperative Bladder Perforation at the Time of Midurethral Sling Placement. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
99. Masterson J, Kuhlmann P, Dallas K, Reddy A, Tsai K, Castaneda P, Eilber K, Anger J, **Ackerman AL**. Overactive Bladder Following Midurethral Sling Placement: De Novo or Persistent? Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
100. Burton C, Lo E, Kanji F, Caron A, Cohen T, Miller D, Wenger N, Scott V, **Ackerman AL**, Eilber K, Anger J. Implementation of a Primary Care Intervention to Improve Care for Women with Urinary Incontinence. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
101. **Ackerman AL**, Caron A, Ackerman J, Anger J, Eilber K, Kaufman M. 'Persistency': A Novel Urinary Symptom Measure Encompassing the Myofascial Component of LUTS. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA
102. Dallas K, Kuhlmann P, Masterson J, Reddy A, Tsai K, Casteneda P, **Ackerman AL**, Eilber K, Anger J. Urinary Tract Infection after Mid-urethral Sling: Rates and Risk Factors. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
103. Kuhlmann P, Masterson J, Dallas K, Tsai K, Reddy A, Casteneda P, **Ackerman AL**, Eilber K, Anger J. Development of Post-operative Urinary Retention after Midurethral Sling Placement: Can We Counsel Patients on Duration?. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
104. Dallas K, Caron A, Anger J, Eilber K, **Ackerman AL**. Application of Machine Learning Algorithms to Classify Storage Lower Urinary Tract Symptoms. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
105. Burton C, Gonzalez G, Kanji F, Caron A, Bresee C, Eilber K, **Ackerman AL**, Anger J. Rates of Tertiary Procedures among Women Referred for Urinary Incontinence. Society of

Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA. c.

106. Souders C, **Ackerman AL** Underrepresentation of FPMRS in Federal Funding for Benign Urologic Conditions. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
107. **Ackerman AL**, Khalique M, Ackerman J, Cheng Z, Eilber K, Anger J, Underhill D. Microbial Composition Defines Pelvic Pain Phenotypes in Reproductive-Age Women. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
108. Dallas K, Anger J, Caron A, Eilber K, **Ackerman AL**. Validation of the Diagnostic Accuracy of Diagnostic Groupings of Patients with Storage Lower Urinary Tract Symptoms Generated by Machine Learning Algorithms. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
109. Cohen T, Burton C, Cohen K, **Ackerman AL**, Eilber K, Anger J. Using a Human Factors Approach to Develop Interventions Aimed at Improving Patient Experience with Sacral Neuromodulation. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
110. Burton C, Tran J, Gonzalez G, Bresee C, Choi E, Scott V, **Ackerman AL**, Eilber K, Anger J. Urinary Incontinence Care for Older Adults: Difference or Disparity. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2020 February; Scottsdale, AZ, USA.
111. **Ackerman AL**, Caron AS, Ackerman JE, Anger JT, Eilber KS, Kaufman M. 'Persistency': A Novel Urinary Symptom Measure Encompassing the Myofascial Component of LUTS. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
112. **Ackerman AL**, Khalique MU, Ackerman JE, Cheng Z, Eilber KS, Anger JT, Underhill DM. Microbial Composition Defines Pelvic Pain Phenotypes in Reproductive-age Women. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
113. Scott VCS, Souders CP, Khalique MU, Ackerman JE, **Ackerman AL**. Is Ureaplasma a Urinary Tract Pathogen? American Urological Association Annual Meeting, May 2020, Virtual Meeting.
114. Dallas K, Caron AS, Anger JT, Eilber KS, **Ackerman AL**. Application of Machine Learning Algorithms to Classify Storage Lower Urinary Tract Symptoms. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
115. Dallas K, **Ackerman AL**, Eilber KS, Rogo-Gupta L, Scott VCS, Troung M, Cohen T, Anger JT. Validated Surgical Steps of the Robotic Assisted Sacrocolpopexy Operation. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
116. Burton CS, Markowitz MA, Kanji F, Scott VCS, **Ackerman AL**, Eilber KS, Anger JT. Validation of the Pelvic Floor Awareness and Knowledge Survey. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
117. Kanji F, Burton CS, Cohen T, Bresee C, Scott VCS, **Ackerman AL**, Eilber KS, Anger JT. Developing a Urinary Incontinence Screening Tool for Use in Primary Care: Trials and Tribulations. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
118. Burton CS, Tran J, Gonzalez G, Bresee C, Choi E, Scott VCS, **Ackerman AL**, Eilber KS, Anger JT. Urinary Incontinence Care for Older Adults: Difference or Disparity? American Urological Association Annual Meeting, May 2020, Virtual Meeting.
119. Kuhlmann PK, Ackerman JE, Khalique MU, Caron AS, Kanji F, Anger JT, Eilber KS, Underhill DM, **Ackerman AL**. Urinary Aerococcus Defines a Severe, Treatment-refractory Phenotype of Urge Incontinence in Older Women. American Urological Association Annual Meeting, May 2020, Virtual Meeting.

120. Lai HH, Clemens JQ, Newcomb C, Appleby D, **Ackerman AL**, Anger JT, Nickel JC, Gupta P, Rodriguez L, Landis JR. Comparison of Deep Phenotyping Features of UCPPS Patients with and without Hunner Lesion – A MAPP Research Network Study. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
121. Burton CS, Lo EM, Kanji F, Caron A, Cohen T, Miller D, Wenger N, Scott VCS, **Ackerman AL**, Eilber KS, Anger JT. Implementation of a Primary Care Intervention to Improve Care for Women with Urinary Incontinence. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
122. Gupta P, Lai HH, Anger JT, **Ackerman AL**, Gallop R, Landis JR, Clemens JQ. Impact of History of Urinary Tract Infections on Patients with Urologic Chronic Pelvic Pain Syndromes: Findings from Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Study. American Urological Association Annual Meeting, May 2020, Virtual Meeting.
123. Hopp M, **Ackerman AL**, et al. Sexual and Urinary Health in OSA Patients. American Academy of Otolaryngology-Head and Neck Surgery Annual Meeting, September 2020, Virtual Meeting.
124. Dallas K, Anger JT, Elliott CS, **Ackerman AL**. Racial Disparities Exist in Outcomes in a Population Based Cohort of 35,000 Women Undergoing Myomectomy for Fibroid Disease. PFD Week 2020 – American Urogynecologic Society Annual Meeting, October, 2020, Virtual Meeting.
125. Tholemeier LN, Choi E, Bresee CT, Kanji FF, **Ackerman AL**, Anger JT, Eilber KS. IMACTIV: A Pilot Study of the Impact of Unrestricted Activity Following Mid-Urethral Sling Surgery. PFD Week 2020 – American Urogynecologic Society Annual Meeting, October, 2020, Virtual Meeting.
126. Nettey O, Caron AT, Khalique UM, Ackerman JE, Eilber KS, Anger JT, **Ackerman AL**. Natural History of the Urinary Microbiome in Women Across the Menopausal Transition. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; 2021 February; Virtual Meeting.
127. Chen A, Caron AT, Kanji FF, Kuhlmann P, Eilber KS, Anger JT, **Ackerman AL**. The Utility of Catheterization to Improve the Accuracy of Microscopic Hematuria Evaluation in Women. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; 2021 February; Virtual Meeting.
128. Choi E, Anger JT, Ackerman JE, Ramsay JW, Eilber KS, Stothers L, **Ackerman AL**. "Chronic UTI": An Exploration of Patient Perceptions of Refractory Painful Genitourinary Symptoms. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction. Annual Meeting; 2021 February; Virtual Meeting.
129. Kanji FF, Burton C, Cohen T, Bresee C, Scott VCS, **Ackerman AL**, Eilber KS, Anger JT. Developing a Urinary Incontinence Screening Tool for Use in Primary Care: Trials and Tribulations. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; 2021 February; Virtual Meeting.
130. Mwesigwa PL, Caron AT, Kanji FF, Ramsey JW, Scott VCS, Eilber KS, Anger JT, **Ackerman AL**. Unsupervised Machine Learning Approaches Reveal Distinct Pelvic Pain Phenotypes. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; 2021 February; Virtual Meeting.
131. Torosis M, Caron AT, Ramsey JW, Eilber KS, Anger JT, **Ackerman AL**. Urologic Manifestations of High-Tone Pelvic Floor Myofascial Dysfunction. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; 2021 February; Virtual Meeting.
132. Nettey O, Caron AT, Khalique UM, Ackerman JE, Eilber KS, Anger JT, **Ackerman AL**. Natural History of the Urinary Microbiome in Women Across the Menopausal

Transition. American Urological Association Annual Meeting; 2021 September; Virtual Meeting.

133. Nickel JC, Stephens A, **Ackerman AL**, Anger JT, Lai HH, Ehrlich GD. The Normal Healthy Urinary Microbiome in the MAPP Network Study: Relation to Gender, Age and Menopausal Status. American Urological Association Annual Meeting; 2021 September; Virtual Meeting.
134. Torosis M, Jackson NJ. **Ackerman AL**. Are Overactive Bladder Patients With and Without Urgency Incontinence the Same Phenotype? PFD Week 2020 – American Urogynecologic Society Annual Meeting, October, 2021, Phoenix, AZ .
135. **Ackerman AL**, Szlachta-McGinn A, Lagree K, Khalique MU, Caron AT, Ackerman JE, Cheng Z, Eilber KS, Anger JT, Underhill DM. Virulent Urinary Fungal Strains in Interstitial Cystitis/Bladder Pain Syndrome Increase Host Inflammatory Response and Induce Urothelial Cell Killing. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
136. Szlachta-McGinn A, Douglass KM, **Ackerman AL**. Next Generation Sequencing Versus Conventional Urine Culture For Diagnosis and Treatment of Urinary Tract Infection: A Systematic Review and Meta-Analysis. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
137. Shoureshi P, Caskey R, Anger JT, **Ackerman AL,** Dubinskaya A, Eilber KS. Biologic Grafts as a Safe Alternative to Mesh for Sacrocolpopexy. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
138. Volkin D, Kim J-H, Tarnay C, **Ackerman AL**, Nitti V. Fixed-Life Versus Rechargeable Sacral Neuromodulation (SNM): Patient Choice and Device Specific Satisfaction. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
139. Kaefer D, Chiang J, **Ackerman AL.** Rate of Progression to Sepsis in Patients Presenting in the Outpatient Setting for Evaluation of Acute Cystitis. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
140. Sadun TY, Cisneros C, **Ackerman AL.** Duration of Non-Obstructive Lower Urinary Tract Symptoms in End-Stage Renal Disease Patients Undergoing Renal Transplantation: A Systematic Review. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
141. Sadun TY, Jackson NJ, **Ackerman AL.** AUA-Symptom Scale is Not Reliable for Use in Measuring Storage Phase Dysfunction. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
142. Nettey O, Dallas K, **Ackerman AL.** To Hyst or Not: Concomitant Vaginal Hysterectomy at Time of Colpocleisis. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; February 2022; San Diego, CA.
143. Kaefer D, Chiang J, **Ackerman AL**. Rate of progression to sepsis following presentation for acute cystitis. American Urological Association Annual Meeting; May 2022; New Orleans, LA.
144. Sadun TY, Jackson NJ, **Ackerman AL**. AUA-Symptom Scale Is Not Reliable For Use in Measuring Storage Phase Dysfunction. American Urological Association Annual Meeting; May 2022; New Orleans, LA.
145. Weinberger JM, Henao LM, Cisneros C, Ackerman JE, **Ackerman AL**. Urotypes in Young Women with Pelvic Pain: A Pilot Analysis of Clinical Urinary Microbiome

Classification. American Urological Association Annual Meeting; May 2022; New Orleans, LA.

146. Nettey O, Dallas K, **Ackerman AL**. To Hyst or Not: Concurrent Vaginal Hysterectomy at Time of Colpocleisis. American Urological Association Annual Meeting; May 2022; New Orleans, LA.
147. Cisneros C, Grisales T, Kim JK, Nitti VW, Rosenman AE, Tarnay CM, **Ackerman AL.** Low Medication Compliance in New Urogynecology Patients. American Urological Association Annual Meeting; May 2022; New Orleans, LA.
148. Szlachta-McGinn A, Ackerman JE, **Ackerman AL**. Quantitative Polymerase Chain Reaction to Identify Common Uropathogens in Urine in a Cohort of Female Urogynecology Patients With and Without Lower Urinary Tract Symptoms. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
149. Torosis M, Carey E, Christensen K, Kaufman M, Kenton K, Kotarinos R, Lai HH, Lee UJ, Lowder JL, Meister M, Spitznagle T, Wright K, **Ackerman AL**. A clinical consensus treatment algorithm for patients with high tone pelvic floor dysfunction: A Delphi study of national experts. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
150. Cisneros C, Tabak K, **Ackerman AL**. Shortage of Specialized Pelvic Floor Therapists across the Country. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
151. **Ackerman AL**, Torosis M, Jackson NJ, Routh JC, Lowder JL. A Novel Screening Tool for Identifying Myofascial Pelvic Floor Dysfunction in Patients Seeking Care for Lower Urinary Tract Symptoms: Development of the Persistency Index. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
152. Park J, Torosis M, Kim JH, **Ackerman AL**. Primary Care Perceptions on the Diagnosis and Management of Recurrent UTI: Barriers to Guideline-Driven Care. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
153. Khalfay N, Lo EM, Grisales T, **Ackerman AL**. An Analysis of Stated Insurance Coverage and Estimated Actual Cost of Treatments for Female Pelvic Conditions. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
154. Szlachta-McGinn A, Tipton C, Diaz N, Martin R, Nickel JC, **Ackerman AL**. Characterizing Urogenital Fungi in Women with Bothersome Urogenital Symptoms Compatible with Inflammation and/or Infection: A Retrospective Cohort Analysis. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
155. Sadun T, Jackson NJ, **Ackerman AL**, Nitti VW. Sensation of Incomplete Bladder Emptying: A Marker of Pelvic Organ Prolapse versus Pelvic Floor Dysfunction Pending Post Void Residual. American Urogynecologic Society/International Urogynecological Association Scientific Meeting, June 2022, Austin, TX.
156. **Ackerman AL**, Szlachta-McGinn A, Lagree K, Khalique MU, Caron AT, Ackerman JE, Cheng Z, Jackson NJ, Eilber KS, Anger JT, Underhill DM, Genitourinary Fungi Associate with Distinct Patterns of Microbial Species in Symptomatic Female Urogynecology Patients: A Retrospective Cohort Analysis. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.
157. Szlachta-McGinn A, Ackerman JE, Jackson NJ, **Ackerman AL**. Urinary Quantitative Polymerase Chain Reaction of Common Genitourinary Microbes Cannot Distinguish

Between Urinary Tract Infection and Chronic Lower Urinary Tract Symptoms in Urogynecology Patients. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.

158. Sadun T, Anger JT, **Ackerman AL,** Kim JH. Changes in Education and Consistency Needed in Recurrent Urinary Tract Infection Care: Patient and Expert Physician Perspectives. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.
159. Garcia Penaloza N, Dominique G, Elashoff E, Chiang JN, **Ackerman AL**. Microhematuria and Asymptomatic Bacteriuria in Women in the Outpatient Setting with Referral To Urology. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.
160. Torosis M, Fullerton M, Kaefer D, Nitti V, **Ackerman AL,** Grisales T. Pudendal Block at Time of Transvaginal Prolapse Repair Does Not Improve Postop Pain: A Randomized Controlled Trial. Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction Annual Meeting; March 2023; Nashville, TN.
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The Persistency Index: a novel screening tool for identifying myofascial pelvic floor dysfunction in patients seeking care for lower urinary tract symptoms

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The Persistency Index: a novel screening tool for identifying myofascial pelvic floor dysfunction in patients seeking care for lower urinary tract symptoms

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Word count: 3000
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Abbreviations: Area Under Curve (AUC), Bladder Pain (BP), Bladder Pain Composite Index (BPCI), Colorectal-Anal Distress Inventory (CRADI-8), Double Negative (DN), Double Positive (DP), female Genitourinary Pain Index (fGUPI), Female Pelvic Medicine and Reconstructive Surgery (FPMRS), Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS), Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Least Angle Shrinkage and Selection Operator (LASSO), Lower Urinary Tract Symptoms (LUTS), Myofascial Urinary

Frequency Syndrome (MUFS), Myofascial Pelvic Pain/Pelvic Floor Myalgia (MPP/PFM), Overactive Bladder (OAB), Overactive Bladder questionnaire (OABq), Persistency Index (PI), Pelvic Floor Distress Index – 20 (PFDI), Pelvic Floor Physical Therapy (PFPT), Pelvic Organ Prolapse Distress Inventory 6 (POPDI-6), Persistency Composite Index (PCI), Phenotyping of Comprehensive Lower Urinary Symptoms (p-CLUS), Predictive Accuracy (PA), Urgency Incontinence (UI), Urge Incontinence Composite Index (UICI), Urinary Distress Inventory 6 (UDI-6), Urinary Tract Infection (UTI).

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Tweetable Statement: The Persistency Index is a new screening measure to identify patients with urinary symptoms related to myofascial pelvic floor dysfunction based on validated survey data.

Short Title: The Persistency Index: a novel screening tool for myofascial pelvic floor dysfunction

AJOG at a Glance:

- We developed an algorithmic screening measure based on patient reported symptoms to identify patients with urinary symptoms related to myofascial pelvic floor dysfunction.

- This algorithm separated populations of women, a total of 1,084, in both derivation and validation cohorts who were seeking care for lower urinary tract symptoms into groups consistent with Overactive Bladder, Interstitial Cystitis/Bladder Pain Syndrome, and Myofascial Urinary Frequency Syndrome phenotypes with an overall diagnostic accuracy of 82%.

- This screening approach will help identify patients with myofascial pelvic floor dysfunction who would likely benefit from myofascial-directed therapies. Early identification of such patients would facilitate targeted therapy, expedite recovery, and minimize unnecessary pharmacologic and procedural interventions

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Abstract

Background:

Patients with myofascial pelvic floor dysfunction often present with lower urinary tract symptoms (LUTS) such as urinary frequency, urgency, and bladder pressure. Often confused with other lower urinary tract disorders, this constellation of symptoms, recently termed myofascial urinary frequency syndrome (MUFS), is distinct from other LUTS and optimally responds to pelvic floor physical therapy . A detailed pelvic floor myofascial exam performed by a skilled provider is currently the only method to identify MUFS. Despite a high impact on quality of life, low awareness of this condition combined with no objective diagnostic testing leads to the frequent mis- or under-diagnosis of MUFS.

Objective:

To develop a screening measure to identify patients with MUFS (bothersome LUTS secondary to myofascial pelvic floor dysfunction) from patient-reported symptoms.

Study Design:

A population of patients with isolated MUFS was identified by provider diagnosis from a tertiary urology practice and verified by standardized pelvic floor myofascial exam and perineal surface pelvic floor electromyography. Least Angle Shrinkage and Selection Operator was employed to identify candidate features from the OAB-q, fGUPI, and PFDI questionnaires predictive of MUFS in a pooled population also containing subjects with overactive bladder (OAB, n=42), interstitial cystitis/bladder pain syndrome (IC/BPS, n=51), and asymptomatic controls (n = 54) (*Derivation cohort*). A simple, summated score of the most discriminatory questions using the original scaling of the PFDI5 (0 to 4) and GUPI5 (0 to 5) and modified scaling of fGUPI2B (0 or 3) had an Area Under the Curve of 0.75. As MUFS was more prevalent in younger subjects,

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inclusion of an age penalty (3 points added if under age 50) improved the Area Under the Curve to 0.8. This score was defined as the Persistency Index (PI) (possible score 0-15). Youden's Index was used to identify the optimal cut point PI score for maximizing sensitivity and specificity.

Results:

Using a *Development cohort* of 215 subjects, the severity (PFDI5) and persistent nature (fGUPI5) of the sensation of incomplete bladder emptying as well as dyspareunia (fGUPI2b) were the most discriminatory characteristics of the MUFS group, which were combined with age to create the PI. The PI performed well in a *Validation cohort* of 719 patients with various LUTS, including OAB (n=285), IC/BPS (n=53), MUFS (n=111), controls (n=209) and unknown diagnoses (n=61), exhibiting an Area Under the Curve of 0.74. A PI score greater than or equal to 7 accurately identified patients with MUFS from an unselected population of individuals with LUTS with 80% sensitivity and 61% specificity. Combination of the PI with the previously defined bladder pain composite index and urge incontinence composite index separated a population of women seeking care for LUTS into groups consistent with OAB, IC/BPS, and MUFS phenotypes with an overall diagnostic accuracy of 82%.

Conclusions:

We propose a novel screening method for patients presenting with LUTS to identify patients with myofascial urinary frequency syndrome. As telemedicine becomes more common, this index provides a way of screening for MUFS and initiating pelvic floor physical therapy even prior to a confirmatory pelvic exam.

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Keywords: Storage lower urinary tract symptoms (LUTS), persistency, overactive bladder, interstitial cystitis, benign urological conditions, nomogram,

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Introduction

Lower urinary tract symptoms (LUTS), such as urinary frequency, urgency, and bladder discomfort, are common and affect most individuals during their life.[1] Despite this high prevalence, diagnostic tools are sparse and rely heavily on clinician judgement. This lack of objective criteria leads to inadequately defined diagnostic schema, which classify patients into symptom clusters such as overactive bladder (OAB) and interstitial cystitis/bladder pain syndrome (IC/BPS) that do not specify underlying pathophysiology. Such contemporary allocation strategies for LUTS do not effectively differentiate subsets of patients that require different treatment approaches. As a result, most patients with LUTS fail to respond to initial treatment approaches and are frequently lost to care.[2] Better tools to recognize more homogeneous LUTS phenotypes would dramatically improve both the recognition and management of patients with LUTS by primary care and specialist providers.

We recently described a novel LUTS diagnosis termed *Myofascial Urinary Frequency Syndrome* (MUFS).[3] This prevalent condition,[4] frequently seen in individuals with urinary frequency without true urgency, occurs when dysfunctional pelvic muscles result in a range of bothersome urinary complaints. Prominent features of MUFS include a sensation of incomplete bladder emptying (without true urinary retention), urinary frequency, and a persistent desire to urinate prompted more by pressure, fullness, or discomfort than fear of incontinence; a symptom complex we dubbed *persistency*.[3] Affected subjects display myofascial pelvic floor dysfunction (increased tone with or without pelvic floor trigger points) on examination and perineal surface electromyography and improve with as myofascial release-based physical therapy or biofeedback.

Despite being exceedingly common,[4] due to the vague mix of uncomfortable bladder sensations and urinary complaints, MUFS is often mistaken for other symptom complexes, such as IC/BPS, OAB, pelvic organ prolapse (POP), or even urinary tract infection (UTI).[4-6] No specific ICD-10 code specifies this diagnosis, making epidemiologic assessment and surveillance difficult. Given the non-specific constellation of symptoms, MUFS can be challenging for providers to recognize, as this diagnosis requires a detailed pelvic exam, sufficient understanding of the

157 global symptom complex, and ruling out confounding conditions.[6] Given these challenges, which
158 are compounded by increasing reliance on telemedicine and limited visit times, improved tools
159 are required to assist providers in recognizing MUFS. A symptoms-based measure associated
160 with the MUFS phenotype could greatly assist providers in suspecting a myofascial origin to a
161 patient's urinary symptoms, thus focusing the physical assessment and possible treatments.
162
163 As initial characterization of MUFS revealed a consistent pattern of associated symptoms across
164 multiple independent cohorts,[3] we hypothesized it would be feasible to construct a symptoms-
165 based measure to identify MUFS subjects. With a patient-derived indicator identifying these
166 patients, earlier interventions with appropriate treatment (i.e., pelvic floor physical therapy) can
167 be achieved, even when providers are less facile at making the diagnosis.
168
169 We therefore sought to develop a screening index to identify patients with possible MUFS for
170 use in telemedicine and by providers unskilled with a discriminate pelvic exam. By comparing a
171 population of MUFS subjects with patients unequivocally categorized as OAB or IC/BPS, we
172 developed a novel measure, termed the *Persistency Index (PI),* to screen for this underrecognized
173 type of LUTS. We further propose a modified diagnostic nomogram incorporating this measure
174 that is capable of differentiating this cohort of patients from classical OAB and IC/BPS.
175

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Materials and Methods

Study Inclusion

After local Institutional Review Board (IRB#00040261) approval, female subjects presenting for care in a specialized urogynecology clinic were included (**Fig. 1**). At initial consultation, all subjects were administered three validated questionnaires: the 1) female Genitourinary Pain Index (fGUPI)[7], 2) Overactive Bladder Questionnaire (OABq)[8], and 3) Pelvic Floor Distress Inventory (PFDI-20).[9] The fGUPI measures the nature and severity of genitourinary pain.[7] The OABq symptom questions (1-8) assess continent and incontinent OAB symptoms.[8] The PFDI-20 measures pelvic floor symptoms in three domains assessing: 1) urinary [Urinary Distress Inventory (UDI-6)], 2) defecatory [Colorectal-Anal Distress Inventory (CRADI-8)], and 3) prolapse [Pelvic Organ Prolapse Distress Inventory (POPDI-6)] symptoms.[9]

Study Cohorts

A *Derivation cohort* of 215 subjects from a single-center urogynecology practice between January and December 2018 was employed to develop the PI. This population contained 68 subjects with urinary symptoms determined to be derived from myofascial dysfunction by the assessing physician. Myofascial dysfunction was confirmed on standardized pelvic floor exam[10] with the observation of overactivity[11] on perineal surface pelvic floor electromyography. Myofascial dysfunction was secondarily verified as the source of their symptomatology by demonstrable improvements in urinary symptoms after myofascial release-based, pelvic floor physical therapy (PFPT). This group was compiled with two other LUTS groups: 1) 42 subjects diagnosed with OAB who endorsed significant urgency incontinence, displayed detrusor overactivity on urodynamic evaluation, and lacked bladder pain on exam or questionnaire assessment, and 2) 51 subjects with a clinical diagnosis of IC/BPS with significant bladder pain on physical examination, who endorsed pain with bladder filling on validated questionnaires, and who lacked any incontinence. An additional 54 subjects with asymptomatic questionnaire responses seeking care for asymptomatic conditions (commonly microhematuria) served as controls.

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A *Validation cohort* of 719 subjects evaluated consecutively between January and December of 2019 served to assess the performance of candidate symptomatic measures in an unselected population. This cohort contained 111 subjects with diagnosed MUFS (subjects with pelvic floor increased tone or trigger points on exam, presenting with urinary frequency, persistent bladder pressure, and a sensation of incomplete bladder emptying who bore a primary diagnosis of high-tone pelvic floor dysfunction), 285 subjects with OAB, 53 with IC/BPS, 209 subjects with minimal bother, and 61 subjects with more than one of these diagnoses. This cohort was additionally administered the O'Leary−Sant Indices, which include the Interstitial Cystitis Symptom and Problem Indices (ICSI/ICPI), that measures the severity and bother of urinary frequency, urgency, nocturia, and bladder pain.[12]

Derivation of the Persistency Index

We used the *Derivation cohort* to create a measure of urinary symptoms associated with a myofascial origin, termed the Persistency Index (PI). Least Angle Shrinkage and Selection Operator (LASSO) identified candidate predictors from individual questionnaire features. Ten-fold cross-validation selected the appropriate shrinkage parameter (λ=0.01307) which identified 20 of the 41 variables as potential predictors (i.e., non-zero coefficients). From these, variables with positive standardized shrunken coefficients > 0.4 that had acceptable face validity for capturing the underlying clinical phenotype (e.g., that were in agreement with previously defined phenotypic characteristics[3]) were used in a multivariable logistic regression model. Statistically significant, positive model coefficients were retained, resulting in a reduced model consisting of three predictors (PFDI5, fGUPI5, GUPI2B). As reduced age was significantly associated with myofascial dysfunction, age was added into the model. To increase usability of this model, we generated a simple summated score of these questions weighted approximately by their coefficients from the multivariable model. The smallest coefficient was normalized to 1 and other coefficients scaled to the nearest integer to preserve their relative relationships. That adjustment resulted in a score using the original scaling of the PFDI5 (0 to 4) and GUPI5 (0 to 5) with a modified scaling of GUPI2B (0 or 3 if positive) and an age penalty for subjects <50 (3 points added if under age 50), with a maximal possible score of 15.

Modification of Diagnostic Nomogram

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The Persistency Index was added to the previous diagnostic nomogram[13] to classify OAB vs. IC/BPS to generate the phenotyping Comprehensive Lower Urinary Symptoms (p-CLUS) nomogram. In this nomogram, the PI, bladder pain composite index (BPCI), urgency/urgency incontinence composite index (UICI), and Bother Index in combination classify patients as non-bothered subjects, IC/BPS, OAB, and MUFS. Inaccuracy was calculated as the percentage of subjects incorrectly classified by the nomogram to a diagnosis different from physician-assigned diagnosis.

Statistical analysis

Bivariate differences between groups were examined using Welch's t and chi-square tests in the *Derivation* and *Validation cohorts*. *P* values were adjusted using the Holm-Bonferroni correction for multiple comparisons.[14] All analyses were conducted in Stata version 16.1, Stata Corp (College Station, Texas, USA).

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Results

MUFS subjects are a distinct subset of subjects with LUTS.

The *Derivation cohort* (**Table 1, Supplemental Table 1**) consisted of patients presenting for care in a tertiary urogynecology practice in 2018. Subjects with confirmed MUFS (n=68), in whom myofascial dysfunction was confirmed on physical exam and pelvic floor electromyography, were compared to a population of controls (n=54) and cases with OAB (n=42) or IC/BPS (n=51). MUFS subjects exhibited similar levels of urinary frequency and urge as both OAB and IC/BPS subjects, but lacked urgency incontinence (OABq8, UDI-6 2) or pain with bladder filling (fGUPI 2c). This group specifically exhibited scores elevated over the other groups relating to a sensation of incomplete emptying (fGUPI5, POPDI-6 5), dyspareunia (fGUPI 2b), and defecatory dysfunction (CRADI-8 1,2).

Derivation of the Persistency Index.

We sought to generate a measure derived from individual, symptomatic questions that was associated with the MUFS group using the *Derivation cohort* (**Fig. 2**). To develop the PI, Least Angle Shrinkage and Selection Operator (LASSO) was used to identify candidate predictors from the administered validated questionnaires (**Supplemental Table 2**). Of the 20 (of 41) potential predictor variables with non-zero coefficients, five had positive standardized shrunken coefficients > 0.4, each of which reflected the common symptoms previously described for this condition (thus conveying good face validity).[3] These were then used in a multivariable logistic regression model to predict MUFS. Use of the three statistically significant model coefficients (PFDI5, fGUPI5, GUPI2B) resulted in a reduced model with an in-sample area under the curve (AUC) of 0.75 (CI: 0.68-0.83; **Supplemental Table 3**).

Age is a valuable predictor of MUFS

As MUFS subjects were noted to be significantly younger than OAB subjects with a similar severity of urinary symptoms, we evaluated the utility of including age as a predictor of MUFS. Inclusion of age in the multivariable regression model significantly increased the AUC to 0.8 (CI: 0.73-0.87; **Supplemental Table 4**). To simplify this model for ease of clinical use, regression coefficients were scaled to generate a simple, summated score of these questions. A

total possible score of 15 included the original scaling of the PFDI5 (0 to 4) and fGUPI5 (0 to 5), a modified scaling of GUPI2B (0 or 3 if positive), and an age factor for subjects <50 (3 points added if under age 50). This simplified, summated score also showed an in-sample AUC of 0.79 (95% CI: 0.72-0.87; **Supplemental Table 4**). Given greater ease of use to the simple, summated score with minimal loss of performance, this simple score was defined as the Persistency Index (PI).

The Persistency Index can identify the MUFS phenotype from unselected LUTS patients.

The PI was then applied to a *Validation cohort* consisting of 719 patients who consecutively sought care in the 2019 calendar year. This cohort included subjects with MUFS (n=111), OAB (n=285), IC/BPS (n=53), controls (n=209), and those with LUTS of unclear etiology (n=61). The out-of-sample AUC for the simple, summated PI in the *Validation cohort* was 0.74 (95% CI 0.67, 0.83) (**Supplemental Table 5**). Sensitivity and specificity were calculated for each PI score in the *Validation cohort* (**Supplemental Table 6**). Youden's Index was used to identify the optimal cut point for maximizing sensitivity and specificity, which was found to be a simple, summated score ≥ 7 which had 80% sensitivity and 61% specificity. Overall accuracy of diagnosis at this score was 65% (**Supplemental Table 6**, **Fig. 3**).

p-CLUS nomogram can distinguish different etiologies of LUTS

Application of these four indices (Bother, BPCI, UICI, and PI]) to this unselected population was able to separate the population into phenotypic groups, which correlated well with specialist-assigned diagnoses of OAB, IC/BPS, and MUFS (**Fig. 4**). Subjects identified as MUFS patients using PI>7 (n=125) were highly bothered subjects [median Bother Index: 9.0 (8.0-10.0)] with low scores on the UICI [2.0 (1.3-2.7)] and BPCI [0.6 (0.6-1.2)] and elevated PCI scores [8.4 (6.8-10.3)]. This independent population of MUFS subjects exhibited the same pattern of symptomatology on their patient-reported questionnaires as observed in the initial description of MUFS;[3] questions describing pelvic pressure and heaviness (POPDI-6 1 and 2), straining to defecate (CRADI-8 1), urinary frequency (UDI-6 1, ICSI2, ICPI1, fGUPI 6), incomplete emptying (UDI-6 5), and bladder/pelvic discomfort (UDI-6 6, fGUPI 1, fGUPI 4, ICPI4) were significantly increased over controls in this population (**Supplemental Table 7**). The algorithm categorized subjects with a known MUFS diagnosis with good overall accuracy; only 18% of

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314 subjects overall had a discordant nomogram classification to the physician-assigned diagnosis
315 (15% inaccuracy for IC/BPS, 13% inaccuracy for MUFS, and 23% inaccuracy for OAB).
316

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Comment

Principal Findings

MUFS, a symptom complex of urinary frequency, bladder pressure, sensation of incomplete emptying, and persistent desire to urinate associated with myofascial dysfunction, is common in patients presenting for urogynecologic care but remains underrecognized. Currently, most diagnostic approaches to LUTS only marginally address pelvic floor myofascial dysfunction as an independent contributor to urinary symptomatology. However, the pelvic floor plays a central role in pelvic, visceral function and dysregulation can provoke pelvic pain syndromes and urinary complaints,[15] improving with myofascial physical therapy.[16] While muscle laxity is widely acknowledged as a contributor to POP or SUI, increased muscle tone or discoordination is rarely recognized in non-painful LUTS. While understood to contribute to dysfunctional voiding, dyssynergia of the pelvic floor can demonstrate a vast spectrum of clinical presentations. Widely fluctuating estimates of its prevalence are indicative of a high rate of misdiagnosis and poor understanding of the contribution of the pelvic floor to urinary complaints.[17] A growing body of evidence, however, suggests that increased pelvic floor tone underlies many urinary, gastrointestinal, and sexual complaints, even in the absence of pain.[18]

Results in the Context of What is Known

In the colorectal literature, a high-tone or hypertonic pelvic floor is well understood to result in symptoms of fecal urgency, stool frequency, and obstructive defecation, which can often present as chronic, idiopathic constipation.[19] As in defecation, normal urinary function similarly requires appropriate relaxation and coordination of the pelvic floor muscles, including urinary sphincters. Thus, a growing body of evidence suggests that a high-tone pelvic floor ("non-relaxing" or fixed) can result in analogous symptoms in the urinary tract, embodied in the clinical phenotype of MUFS.[3, 4, 6, 20-22]

MUFS is prevalent in individuals highly bothered by their LUTS. In our unselected population of subjects seeking care in a pelvic medicine specialty clinic, MUFS comprised more than 20% of subjects presenting with LUTS, a similar prevalence to that seen in the initial cohort used to describe this condition.[3] This is similar to the prevalence of pelvic floor dysfunction (dyssynergic

defecation) in approximately 22-27% of patients presenting with chronic, idiopathic constipation.[23, 24] Increasing awareness of this prevalent cause of pelvic symptomatology, however, may not be sufficient to improve care; additional tools and standards for diagnosis are needed.

Clinical Implications

The screening measure developed in this study, the PI, performs well in a real-world, unselected population of patients seeking care for LUTS to identify MUFS with an overall accuracy of 65%. This accuracy reflects the fact that the chosen threshold for diagnosis tends to overpredict the likelihood of MUFS (**Supplemental Fig. 1**), but misses few with true MUFS, as evidenced by 80% sensitivity. As the likely outcome of obtaining a diagnosis of MUFS would be a referral to pelvic floor physical therapy, a treatment that carries very few side effects and the potential for symptomatic improvements even in patients with other diagnoses, the risks of over diagnosing MUFS are minimal. This risk-benefit ratio reflects the optimal features of a screening measure, especially for an underrecognized condition which could assist providers in identifying patients that would benefit from consideration of myofascial-directed therapies and perhaps avoid unnecessary pharmacologic or even surgical interventions.

The addition of the PI to our previously described LUTS diagnostic nomogram provided a new diagnostic algorithm, the *phenotyping Comprehensive Lower Urinary Symptoms* (p-CLUS) nomogram. Application of this classification method provided an overall accuracy of LUTS classification in an unselected population of care-seeking women of 82% (**Supplemental Fig. 2**), using only 11 symptomatic questions and patient age. As this information can be obtained without in-person assessment, this clinical tool could be used by providers across a range of disciplines, even when assessing patients by telemedicine, to help with initial diagnostic evaluation and treatment assignment.

Research Implications

As this dataset included only women, utilizing validated questionnaires that are specific to pelvic symptomatology in women, it is not clear how these symptoms manifest in men, nor the prevalence of myofascial dysfunction as a cause for LUTS. A comprehensive myofascial pelvic

exam is more challenging in men, as an internal assessment can only be performed during a digital rectal exam, which is frequently perceived as uncomfortable and may provoke reflexive pelvic floor contraction confounding the utility of examination.

Strengths and Limitations

Such discomfort on exam confounding assessment may also manifest in women. The accuracy of the PI at diagnosing MUFS was determined without an objective gold standard for diagnosis; the comparative measure determining whether a subject's urinary symptoms derived from a myofascial origin was based on symptom assessment and subjective pelvic floor exam by a board-certified urogynecologist. This method, while the current diagnostic standard, is itself an inconsistent measure.[25-27] It is possible that the real accuracy of the PI in identifying MUFS is greater than anticipated, as patients with MUFS may be misclassified by this subjective approach. In a 3-dimensional graphic representation of patient symptoms (**Fig. 4**), a significant number of patients diagnosed with OAB are noted within the region of the graph with a high PI, low BPCI (bladder pain) and low UICI (urgency/urgency incontinence). While it is possible the PI is not accurate in such subjects, it remains equally plausible that these patients represent misdiagnosed cases of MUFS which could have been recognized by using a screening method such as the PI. This lack of objective tests to identify MUFS may in-part explain the discrepancy between physician-assigned diagnosis and PI classification.

Conclusions

In summary, we provide a screening measure helpful in identifying patients with MUFS, which would likely benefit from myofascial-directed therapies. While the diagnostic utility of the PI will require further evaluation in prospective studies examining improvements in MUFS identification and treatment assignment, we anticipate early identification of such patients will facilitate targeted therapy, expedite recovery, and minimize unnecessary pharmacologic and procedural interventions.

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481 **Table 1:** ***Symptomatic Features of the Derivation Cohort by Diagnosis*****.**
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	Question	Scale	MUFS (n=68)	Cont (n=54	OAB (n=42)	IC/I
*Age**		0-95	43.62 (14.89)	54.22 (15.26)	64.03 (11.40)	49.05
OABq2	An uncomfortable urge to urinate	1-6	3.72 (1.34)	1.69 (1.16)	4.08 (1.56)	3.65
OABq3	A sudden urge to urinate	1-6	2.29 (1.50)	1.39 (0.81)	4.43 (1.19)	2.08
OABq4	Accidental loss of small amounts of urine	1-6	1.91 (1.47)	1.63 (0.78)	4.29 (1.38)	1.47
OABq5	Nighttime urination	1-6	2.87 (1.64)	2.09 (1.33)	4.00 (1.86)	2.98
OABq6	Waking at night because you had to urinate	1-6	3.29 (1.65)	2.38 (1.44)	4.44 (1.55)	3.29
OABq8	Urine loss associated with a strong desire to urinate	1-6	1.53 (1.13)	1.30 (0.57)	4.36 (1.39)	1.31
fGUPI1a†	Pain/discomfort at the entrance to the vagina	0-1	0.51	0.07	0.05	
fGUPI1b†	Pain/discomfort in the vagina	0-1	0.49	0.07	0.07	
fGUPI1c†	Pain/discomfort in the urethra	0-1	0.44	0.04	0.05	
fGUPI1d†	Pain/discomfort below the waist, in pubic or bladder area	0-1	0.42	0.08	0.10	
fGUPI2a†	Pain or burning during urination	0-1	0.44	0.02	0.10	
fGUPI2b†*	*Pain or discomfort during or after sexual intercourse*	0-1	0.52	0.09	0.12	
fGUPI2c†	Pain or discomfort as your bladder fills	0-1	0.09	0.00	0.00	
fGUPI2d†	Pain or discomfort relieved by voiding	0-1	0.23	0.06	0.05	
fGUPI3	Frequency of pain or discomfort over the last week	0-5	3.00 (1.43)	0.37 (0.66)	0.68 (0.91)	3.00
fGUPI4	Number that best describes average pain/discomfort	0-10	3.85 (2.23)	0.39 (1.08)	1.43 (1.74)	5.91
*fGUPI5**	*Frequency of sensation of incomplete emptying*	0-5	2.76 (1.25)	0.39 (0.60)	1.39 (1.18)	2.12
fGUPI6	Need to urinate <2 hours after last urinating	0-5	3.19 (1.21)	1.04 (1.06)	3.19 (1.40)	3.00
fGUPI7	Have your symptoms kept you from doing the kinds of things you would usually do	0-3	1.49 (1.03)	0.04 (0.19)	1.45 (1.15)	1.51
fGUPI8	How much did you think about your symptoms	0-3	2.50 (0.70)	0.37 (0.52)	2.43 (0.70)	2.51
fGUPI9	Satisfaction with current symptoms	0-6	4.59 (1.22)	1.59 (1.11)	4.62 (1.10)	5.04
POPDI-1	Pressure in the lower abdomen	0-4	1.83 (1.42)	0.34 (0.83)	0.85 (1.21)	1.80
POPDI-2	Heaviness or dullness in the lower abdomen	0-4	1.46 (1.45)	0.23 (0.64)	0.62 (1.11)	1.84
POPDI-3	A bulge or something falling out that can see or feel in the vaginal area	0-4	0.36 (0.99)	0.20 (0.74)	0.29 (0.72)	0.10

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POPDI-4	A need to push on the vagina or around the rectum to have a complete bowel movement	0-4	0.42 (0.89)	0.31 (0.89)	0.68 (1.25)	0.45
*POPDI-5**	*A feeling of incomplete bladder emptying*	0-4	2.31 (1.27)	0.33 (0.75)	1.38 (1.41)	1.29
POPDI-6	A need to push up in the vagina area to start or complete urination	0-4	0.16 (0.61)	0.02 (0.14)	0.07 (0.35)	0.12
CRADI-8-1	A need to strain too hard to have a bowel movement	0-4	1.31 (1.43)	0.20 (0.63)	1.10 (1.34)	0.80
CRADI-8-2	A feeling that you have not completely emptied your bowels after a bowel movement	0-4	1.33 (1.37)	0.36 (0.83)	0.83 (1.10)	0.80
CRADI-8-3	Losing stool without control when stools are well formed	0-4	0.12 (0.56)	0.11 (0.60)	0.32 (0.85)	0.10
CRADI-8-4	Losing stool without control when stool is loose or liquid	0-4	0.27 (0.77)	0.15 (0.76)	0.83 (1.25)	0.24
CRADI-8-5	Losing gas from the rectum without control	0-4	0.71 (1.22)	0.31 (0.73)	0.98 (1.33)	0.31
CRADI-8-6	Pain with passing stools	0-4	0.34 (0.91)	0.00 (0.00)	0.27 (0.71)	0.10
CRADI-8-7	A strong sense of urgency and have to rush to the bathroom to have a bowel movement	0-4	0.70 (1.18)	0.30 (0.85)	0.81 (1.15)	0.41
CRADI-8-8	Stool passes through the rectum and bulges outside during or after a bowel movement	0-4	0.24 (0.87)	0.13 (0.58)	0.22 (0.61)	0.04
UDI-6-1	Bothered by frequent urination	0-4	2.16 (1.40)	0.74 (1.12)	2.95 (1.27)	2.40
UDI-6-2	Bothered by leakage related to feeling of urgency	0-4	0.41 (0.78)	0.31 (0.72)	3.12 (0.92)	0.69
UDI-6-3	Bothered by leakage related to physical activity, coughing, or sneezing	0-4	0.79 (1.13)	0.83 (1.16)	2.00 (1.47)	0.63
UDI-6-4	Bothered by small amounts of leakage (drops)	0-4	0.76 (1.27)	0.42 (0.84)	2.26 (1.48)	0.31
UDI-6-5	Bothered by difficulty emptying bladder	0-4	1.61 (1.37)	0.15 (0.53)	0.74 (1.27)	1.45
UDI-6-6	Bothered by pain or discomfort in the lower abdominal or genital area	0-4	1.65 (1.52)	0.19 (0.62)	0.51 (1.05)	2.10

Means (standard deviation) are shown for all interval variables, except for the binary variables which document the population proportions scoring positive for each individual feature. Pairwise comparison of interval variables were compared using Welch's t test, while binary variables (designated with †) were examined using the Chi-square test. MUFS: Myofascial Urinary Frequency Syndrome; Cont: Asymptomatic Controls; OAB: Overactive Bladder; IC/BPS: Interstitial Cystitis/Bladder Pain Syndrome; OABq: Overactive Bladder Questionnaire; ICSI: Interstitial Cystitis Symptoms Index; ICPI: interstitial Cystitis Problem Index; fGUPI: female Genitourinary pain index; UDI-6: Urinary Distress Inventory Short Form; CRADI-8: Colorectal-Anal Distress Inventory; POPDI-6: Pelvic Organ Prolapse Distress Inventory**;** ns: Not significant.

* Variables used to create the Persistency Index

† Binary Variables: the values noted are proportions of each population answering "yes" to the symptomatic feature.

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Figure Legends:

Figure 1. ***Study Design.*** We derived a screening measure associated with myofascial urinary frequency syndrome (MUFS), dubbed the **Persistency Index**. This measure was comprised of the most salient features of MUFS identified by comparison of a group of subjects with LUTS, abnormal pelvic floor findings on exam and EMG findings of a tonically contracted pelvic floor to asymptomatic subjects and patients with OAB and IC/BPS (**Derivation Cohort**). We then determined the real-world performance of this measure in classifying subjects with MUFS from a large population of individuals presenting to a urogynecology clinic (**Validation Cohort**).

Figure 2. ***The Persistency Index describes the unique features of subjects with LUTS of a myofascial origin.*** A) Least Angle Shrinkage and Selection Operator (LASSO) with 10-fold cross-validation (λ=0.01307) identified 20 of the 41 variables from the OABq, fGUPI and PFDI as potential predictors. Five of these variables with a positive standardized shrunken coefficient > 0.4 as well as face validity for capturing the underlying clinical phenotype were used in a multivariable logistic regression model. Variables with statistically significant model coefficients (PFDI5, GUPI5, GUPI2B) were retained resulting in a reduced model consisting of these three predictors weighted based on these coefficients, which together comprise the Persistency Composite Index (PCI). Box and whisker plots compare the distribution of scores on the PFDI20 question 5 (B), fGUPI question 2b (C), fGUPI question 5 (D) and age (E) for the population of patients with myofascial urinary frequency syndrome (MUFS) in comparison to subjects with any other bothersome LUTS.

Figure 3. ***Performance of the Persistency Composite Index.*** A) Distribution of Persistency across the pooled population of 215 subjects by diagnosis (Derivation Dataset). Positivity on the PCI was defined as >7, which best defined the population with myofascial urinary frequency syndrome. B) Sensitivity, Specificity, and Overall Accuracy of the PCI for identifying MUFS in the Validation Dataset. A summated score of 7 denotes the cut point threshold that maximizes both sensitivity and specificity. IC/BPS: interstitial cystitis/bladder pain syndrome; MUFS: myofascial urinary frequency syndrome; OAB: Overactive Bladder.

Figure 4. ***BPCI, UICI and PI define distinct symptomatic populations with LUTS.*** A) Subjects from the *Validation Dataset* were plotted in a 3D plot with each index on a different axis. Bother is indicated by the size of the sphere indicating each subject. The colors represent the diagnosis given by the consulting subspecialty physician. Diagnosis correlated well with the position in the 3D plot designated by the ellipses for each LUTS phenotype designated by the same color.

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Table 1: ***Symptomatic Features of the Derivation Cohort by Diagnosis*.**

	Question	Scale	MUFS (n=68)	Cont (n=54)	OAB (n=42)	IC/BPS (n=51)	Adjusted *P* value (MUFS vs. Cont	OAB	IC/BPS
*Age**		0-95	43.62 (14.89)	54.22 (15.26)	64.03 (11.40)	49.05 (13.70)	<0.001	<0.001	0.054
OABq2	An uncomfortable urge to urinate	1-6	3.72 (1.34)	1.69 (1.16)	4.08 (1.56)	3.65 (1.57)	<0.001	0.214	0.784
OABq3	A sudden urge to urinate	1-6	2.29 (1.50)	1.39 (0.81)	4.43 (1.19)	2.08 (1.38)	<0.001	<0.001	0.423
OABq4	Accidental loss of small amounts of urine	1-6	1.91 (1.47)	1.63 (0.78)	4.29 (1.38)	1.47 (0.67)	0.206	<0.001	0.049
OABq5	Nighttime urination	1-6	2.87 (1.64)	2.09 (1.33)	4.00 (1.86)	2.98 (1.63)	0.006	0.001	0.712
OABq6	Waking at night because you had to urinate	1-6	3.29 (1.65)	2.38 (1.44)	4.44 (1.55)	3.29 (1.59)	0.002	<0.001	>0.999
OABq8	Urine loss associated with a strong desire to urinate	1-6	1.53 (1.13)	1.30 (0.57)	4.36 (1.39)	1.31 (0.65)	0.168	<0.001	0.224
fGUPI1a†	Pain/discomfort at the entrance to the vagina	0-1	0.51	0.07	0.05	0.43	<0.001	<0.001	0.372
fGUPI1b†	Pain/discomfort in the vagina	0-1	0.49	0.07	0.07	0.43	<0.001	<0.001	0.563
fGUPI1c†	Pain/discomfort in the urethra	0-1	0.44	0.04	0.05	0.59	<0.001	<0.001	0.114
fGUPI1d†	Pain/discomfort below the waist, in pubic or bladder area	0-1	0.42	0.08	0.10	0.90	<0.001	<0.001	<0.001
fGUPI2a†	Pain or burning during urination	0-1	0.44	0.02	0.10	0.62	<0.001	<0.001	0.055
fGUPI2b†*	*Pain or discomfort during or after sexual intercourse*	0-1	0.52	0.09	0.12	0.47	<0.001	<0.001	0.581
fGUPI2c†	Pain or discomfort as your bladder fills	0-1	0.09	0.00	0.00	0.92	0.025	0.048	<0.001
fGUPI2d†	Pain or discomfort relieved by voiding	0-1	0.23	0.06	0.05	0.73	0.009	0.011	<0.001
fGUPI3	Frequency of pain or discomfort over the last week	0-5	3.00 (1.43)	0.37 (0.66)	0.68 (0.91)	3.00 (1.31)	<0.001	<0.001	>0.999
fGUPI4	Number that best describes average pain/discomfort	0-10	3.85 (2.23)	0.39 (1.08)	1.43 (1.74)	5.91 (2.31)	<0.001	<0.001	<0.001
*fGUPI5**	*Frequency of sensation of incomplete emptying*	0-5	2.76 (1.25)	0.39 (0.60)	1.39 (1.18)	2.12 (1.48)	<0.001	<0.001	0.011
fGUPI6	Need to urinate <2 hours after last urinating	0-5	3.19 (1.21)	1.04 (1.06)	3.19 (1.40)	3.06 (1.52)	<0.001	0.998	0.598
fGUPI7	Have your symptoms kept you from doing the kinds of things you would usually do	0-3	1.49 (1.03)	0.04 (0.19)	1.45 (1.15)	1.51 (1.12)	<0.001	0.877	0.902
fGUPI8	How much did you think about your symptoms	0-3	2.50 (0.70)	0.37 (0.52)	2.43 (0.70)	2.51 (0.76)	<0.001	0.605	0.942
fGUPI9	Satisfaction with current symptoms	0-6	4.59 (1.22)	1.59 (1.11)	4.62 (1.10)	5.04 (1.02)	<0.001	0.894	0.035
POPDI-1	Pressure in the lower abdomen	0-4	1.83 (1.42)	0.34 (0.83)	0.85 (1.21)	1.80 (1.37)	<0.001	<0.001	0.887
POPDI-2	Heaviness or dullness in the lower abdomen	0-4	1.46 (1.45)	0.23 (0.64)	0.62 (1.11)	1.84 (1.43)	<0.001	0.002	0.156
POPDI-3	A bulge or something falling out that can see or feel in the vaginal area	0-4	0.36 (0.99)	0.20 (0.74)	0.29 (0.72)	0.16 (0.50)	0.326	0.690	0.175
POPDI-4	A need to push on the vagina or around the rectum to have a complete bowel movement	0-4	0.42 (0.89)	0.31 (0.89)	0.68 (1.25)	0.45 (1.10)	0.527	0.218	0.857
*POPDI-5**	*A feeling of incomplete bladder emptying*	0-4	2.31 (1.27)	0.33 (0.75)	1.38 (1.41)	1.29 (1.40)	<0.001	0.001	<0.001
POPDI-6	A need to push up in the vagina area to start or complete urination	0-4	0.16 (0.61)	0.02 (0.14)	0.07 (0.35)	0.12 (0.52)	0.095	0.399	0.679
CRADI-8-1	A need to strain too hard to have a bowel movement	0-4	1.31 (1.43)	0.20 (0.63)	1.10 (1.34)	0.80 (1.28)	<0.001	0.437	0.048
CRADI-8-2	A feeling that you have not completely emptied your bowels after a bowel movement	0-4	1.33 (1.37)	0.36 (0.83)	0.83 (1.10)	0.80 (1.20)	<0.001	0.050	0.031
CRADI-8-3	Losing stool without control when stools are well formed	0-4	0.12 (0.56)	0.11 (0.60)	0.32 (0.85)	0.10 (0.50)	0.938	0.149	0.831
CRADI-8-4	Losing stool without control when stool is loose or liquid	0-4	0.27 (0.77)	0.15 (0.76)	0.83 (1.25)	0.24 (0.74)	0.392	0.004	0.813
CRADI-8-5	Losing gas from the rectum without control	0-4	0.71 (1.22)	0.31 (0.73)	0.98 (1.33)	0.31 (0.73)	0.045	0.279	0.045
CRADI-8-6	Pain with passing stools	0-4	0.34 (0.91)	0.00 (0.00)	0.27 (0.71)	0.16 (0.64)	0.007	0.654	0.217
CRADI-8-7	A strong sense of urgency and have to rush to the bathroom to have a bowel movement	0-4	0.70 (1.18)	0.30 (0.85)	0.81 (1.15)	0.41 (0.85)	0.040	0.640	0.141
CRADI-8-8	Stool passes through the rectum and bulges outside during or after a bowel movement	0-4	0.24 (0.87)	0.13 (0.58)	0.22 (0.61)	0.04 (0.20)	0.444	0.919	0.116
UDI-6-1	Bothered by frequent urination	0-4	2.16 (1.40)	0.74 (1.12)	2.95 (1.27)	2.46 (1.18)	<0.001	0.004	0.225

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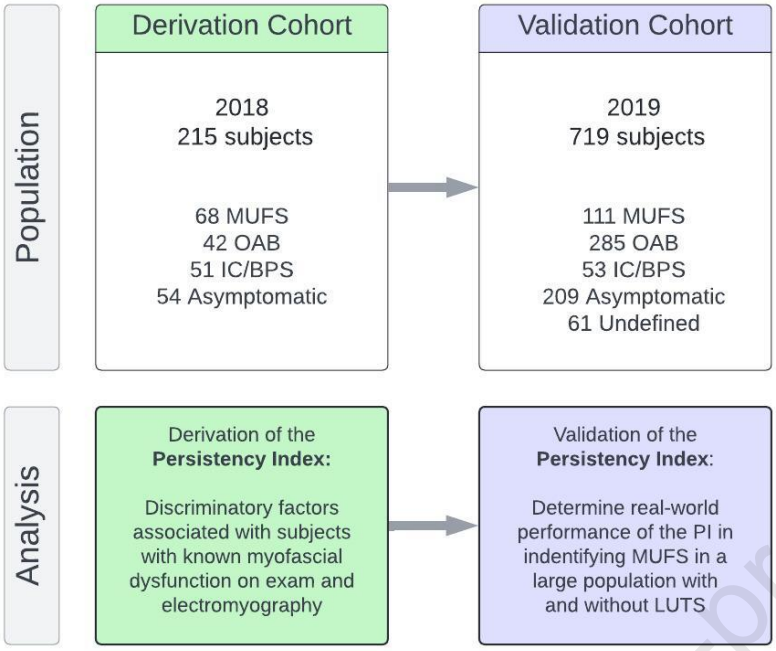
UDI-6-2	Bothered by leakage related to feeling of urgency	0-4	0.41 (0.78)	0.31 (0.72)	3.12 (0.92)	0.69 (0.79)	0.482	<0.001	0.060
UDI-6-3	Bothered by leakage related to physical activity, coughing, or sneezing	0-4	0.79 (1.13)	0.83 (1.16)	2.00 (1.47)	0.63 (1.00)	0.863	<0.001	0.404
UDI-6-4	Bothered by small amounts of leakage (drops)	0-4	0.76 (1.27)	0.42 (0.84)	2.26 (1.48)	0.31 (0.73)	0.090	<0.001	0.027
UDI-6-5	Bothered by difficulty emptying bladder	0-4	1.61 (1.37)	0.15 (0.53)	0.74 (1.27)	1.45 (1.39)	<0.001	0.001	0.546
UDI-6-6	Bothered by pain or discomfort in the lower abdominal or genital area	0-4	1.65 (1.52)	0.19 (0.62)	0.51 (1.05)	2.10 (1.43)	<0.001	<0.001	0.110

Means (standard deviation) are shown for all interval variables, except for the binary variables which document the population proportions scoring positive for each individual feature. Pairwise comparison of interval variables were compared using Welch's t test, while binary variables (designated with †) were examined using the Chi-square test. MUFS: Myofascial Urinary Frequency Syndrome; Cont: Asymptomatic Controls; OAB: Overactive Bladder; IC/BPS: Interstitial Cystitis/Bladder Pain Syndrome; OABq: Overactive Bladder Questionnaire; ICSI: Interstitial Cystitis Symptoms Index; ICPI: interstitial Cystitis Problem Index; fGUPI: female Genitourinary pain index; UDI-6: Urinary Distress Inventory Short Form; CRADI-8: Colorectal-Anal Distress Inventory; POPDI-6: Pelvic Organ Prolapse Distress Inventory.

* Variables used to create the Persistency Index

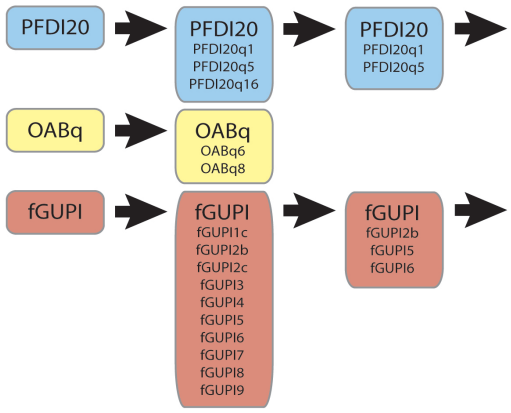
† Binary Variables: the values noted are proportions of each population answering "yes" to the symptomatic feature.

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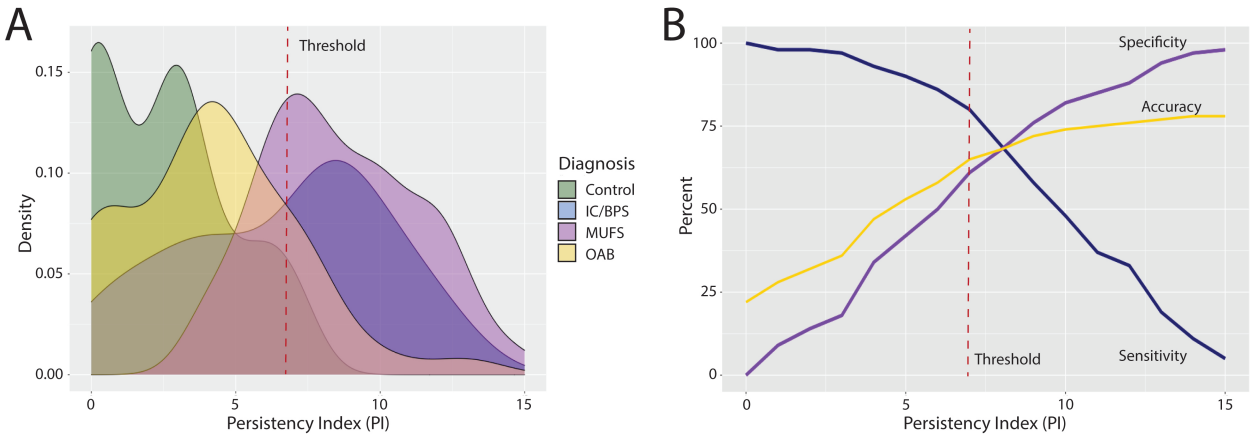
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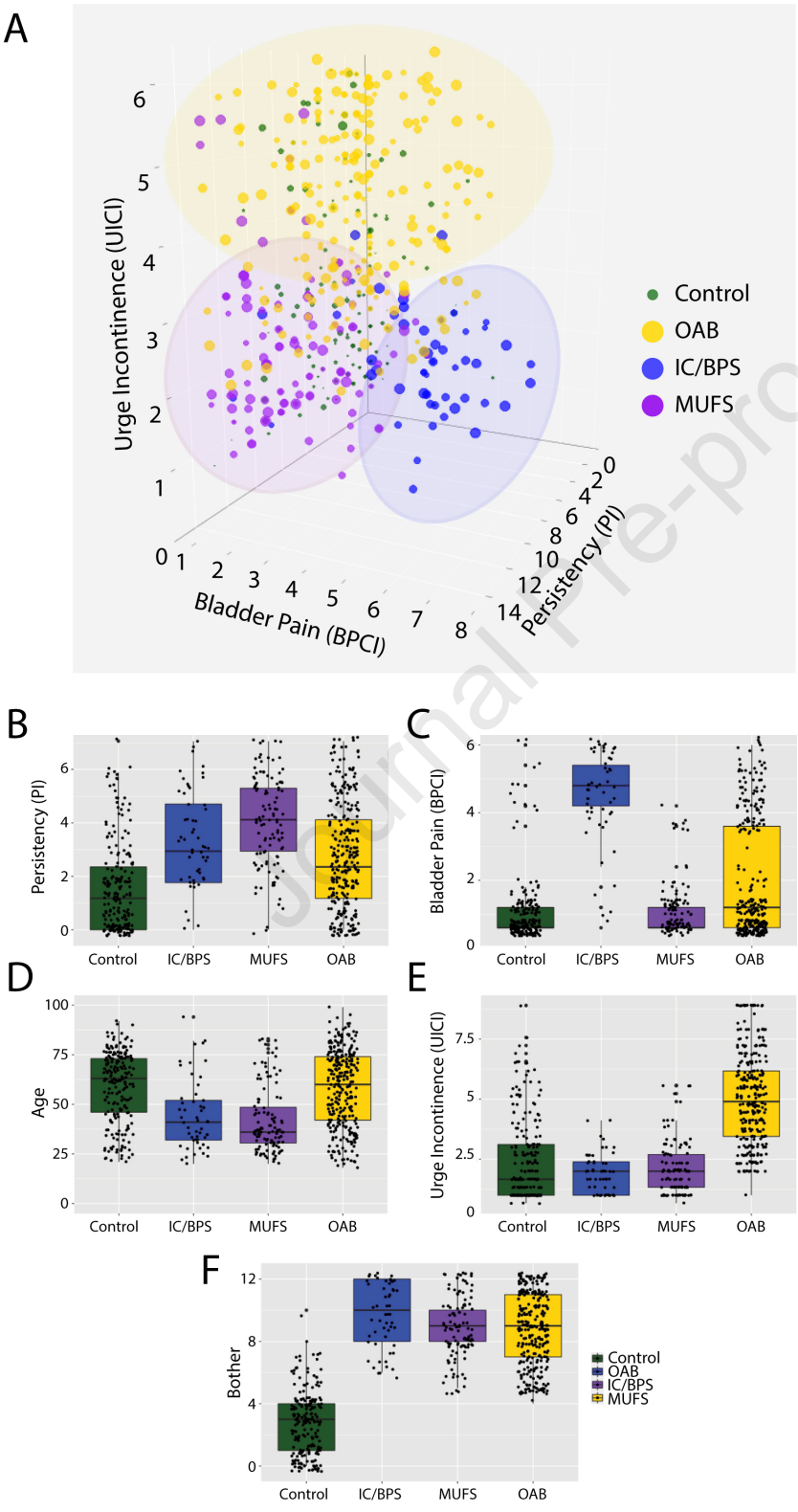


Number	Question	Significance
PFDI20q1	Do you usually experience **pressure in the lower abdomen**?"	p=0.00007
PFDI20q5	"Do you usually experience a feeling of **incomplete bladder emptying**?"	p=0.000001
fGUPI2b	"Have you experienced **pain or discomfort** during or **after sexual intercourse**?"	p=0.00004
fGUPI5	"How often have you had a **sensation of not emptying** your bladder completely after you finished urinating, over the past week?"	p=0.000001
fGUPI6	"How often have you had to **urinate again** less than 2 hours after you finished urinating, over the last week?"	p=0.0004
Age	Patient Age in Years	p=0.00008

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Supplemental Table 1. ***Demographic Characteristics of Each Cohort.***

	Derivation n = 215	*range*	**Validation** n=719	*range*	*p*
Age (median (IQR))	53 (38.3, 67.0)	18-92	56 (37.0, 68.3)	18-101	0.566
Parity (median (IQR))	1 (1, 2)	0-7	2 (1, 2)	0-6	0.716
Co-morbidities (n (%))					
Hypertension	37 (17.2)		137 (19.0)		0.656
Hyperlipidemia	26 (12.1)		81 (11.2)		0.942
Diabetes	19 (8.8)		85 (11.8)		0.317
Obesity	20 (9.3)		84 (11.6)		0.440
Anxiety or Depression	30 (13.9)		99 (13.7)		0.997
Non-urologic Chronic Pain	32 (14.8)		106 (14.7)		<0.999
Asymptomatic Prolapse	33 (15.3)		130 (18.1)		0.442

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Supplemental Table 2. ***Odds Ratios for each of the candidate predictors in models predicting identiy in MFS subgroup***.

		vs. All (With Controls)			**vs. other LUTS (No Controls)**		
Questionnaire	**Question**	***OR +/- SE***	***p***	***AUC***	***OR +/- SE***	***p***	***AUC***
GUPI	3	1.85 ± 0.19	<0.001	0.77	1.50 ± 0.17	<0.001	0.68
GUPI	**5**	**2.16 ± 0.27**	**<0.001**	**0.79**	**1.71 ± 0.22**	**<0.001**	**0.69**
GUPI	1a	4.51 ± 1.45	<0.001	0.66	3.05 ± 1.03	0.001	0.63
GUPI	8	2.12 ± 0.35	<0.001	0.68	1.05 ± 0.24	0.814	0.5
GUPI	1b	3.84 ± 1.22	<0.001	0.64	2.56 ± 0.86	0.005	0.61
GUPI	**2b**	**3.64 ± 1.14**	**<0.001**	**0.65**	**2.41 ± 0.80**	**0.008**	**0.61**
GUPI	6	1.43 ± 0.14	<0.001	0.65	1.04 ± 0.12	0.736	0.5
GUPI	9	1.40 ± 0.14	<0.001	0.63	0.82 ± 0.12	0.153	0.55
GUPI	2c	0.21 ± 0.10	0.001	0.62	0.09 ± 0.05	<0.001	0.71
GUPI	7	1.52 ± 0.20	0.002	0.64	1.00 ± 0.15	0.993	0.5
GUPI	1c	2.62 ± 0.82	0.002	0.6	1.50 ± 0.49	0.212	0.55
GUPI	4	1.16 ± 0.06	0.005	0.65	0.99 ± 0.06	0.884	0.49
GUPI	2a	2.37 ± 0.74	0.006	0.6	1.28 ± 0.42	0.457	0.53
GUPI	1d	1.30 ± 0.40	0.391	0.53	0.65 ± 0.22	0.196	0.55
GUPI	2d	0.77 ± 0.27	0.461	0.52	0.43 ± 0.16	0.021	0.59
OABq	8	0.71 ± 0.09	0.006	0.61	0.59 ± 0.08	<0.001	0.68
OABq	2	1.28 ± 0.12	0.008	0.61	0.95 ± 0.10	0.627	0.53
OABq	4	0.82 ± 0.09	0.066	0.6	0.72 ± 0.08	0.003	0.65
OABq	3	0.93 ± 0.09	0.398	0.52	0.73 ± 0.07	0.002	0.64
OABq	5	0.97 ± 0.08	0.758	0.51	0.82 ± 0.08	0.042	0.59
OABq	6	1.00 ± 0.09	0.964	0.5	0.83 ± 0.08	0.058	0.59
PFDI	**5**	**2.05 ± 0.25**	**<0.001**	**0.76**	**1.68 ± 0.21**	**<0.001**	**0.69**
PFDI	19	1.60 ± 0.18	<0.001	0.67	1.29 ± 0.15	0.032	0.6
PFDI	16	0.53 ± 0.08	<0.001	0.66	0.37 ± 0.07	<0.001	0.77
PFDI	1	1.55 ± 0.17	<0.001	0.66	1.27 ± 0.15	0.044	0.59
PFDI	8	1.58 ± 0.19	<0.001	0.64	1.39 ± 0.18	0.013	0.6
PFDI	7	1.46 ± 0.16	0.001	0.62	1.22 ± 0.14	0.088	0.57
PFDI	20	1.39 ± 0.14	0.001	0.63	1.13 ± 0.12	0.264	0.55
PFDI	2	1.33 ± 0.14	0.007	0.61	1.08 ± 0.12	0.509	0.53
PFDI	12	1.52 ± 0.32	0.046	0.54	1.25 ± 0.26	0.283	0.52
PFDI	17	0.82 ± 0.10	0.115	0.56	0.76 ± 0.10	0.035	0.59
PFDI	13	1.21 ± 0.17	0.163	0.54	1.10 ± 0.16	0.526	0.51
PFDI	6	1.50 ± 0.46	0.189	0.52	1.26 ± 0.39	0.451	0.52
PFDI	3	1.26 ± 0.23	0.195	0.51	1.26 ± 0.26	0.256	0.51
PFDI	11	1.18 ± 0.16	0.209	0.53	1.07 ± 0.15	0.611	0.51
PFDI	14	1.29 ± 0.28	0.243	0.51	1.31 ± 0.33	0.283	0.51
PFDI	15	1.09 ± 0.11	0.367	0.53	0.74 ± 0.09	0.015	0.61

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PFDI	10	0.87 ± 0.15	0.430	0.51	0.74 ± 0.14	0.123	0.55
PFDI	18	0.91 ± 0.11	0.442	0.53	0.80 ± 0.10	0.058	0.57
PFDI	9	0.88 ± 0.23	0.628	0.51	0.82 ± 0.23	0.460	0.51
PFDI	4	0.96 ± 0.14	0.768	0.5	0.89 ± 0.14	0.440	0.51

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Supplemental Table 3. ***Logit Coefficients Predicting Myofascial Urinary Frequency Syndrome***

	Derivation Dataset	**Validation Dataset**
Reduced Model		
Logit Coefficients		
PFDI5	0.38867	
GUPI5	0.39378	
GUPI2B	1.08865	
AUC (95% CI)	0.75 (0.68, 0.83)	0.72 (0.64, 0.81)
Summated Score Model		
Logit Coefficients		
Sum Score	0.38388	
AUC (95% CI)	0.78 (0.70, 0.85)	0.74 (0.67, 0.83)

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Supplemental Table 4. ***In-sample area under the curve (AUC) for models predicting MFS.***

	Based on Coefficients AUC	**Based on Sum Score AUC**
Derivation Dataset Competing Models		
Model A with *PFDI5, GUPI5, [2]GUPI2B*	0.75 (0.68, 0.83)	0.78 (0.70, 0.85)
Model B with [1]*AgeLte50, PFDI5, GUPI5*	0.77 (0.70, 0.85)	0.77 (0.69, 0.84)
Model C with [1]*AgeLte50, PFDI5, GUPI5, [2]GUPI2B*	*0.80 (0.73, 0.87)	0.79 (0.72, 0.87)

[1]Value of 3 assigned in sum score when Age ≤ 50
[2]Value of 3 assigned in sum score when GUPI2B endorsed

*p < 0.05 compared to Model A based on percentile bootstrap from 1,000 resamplings

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Supplemental Table 5. ***Out of sample AUC and Logit Coefficients for the simple summated PI in both cohorts.*** Minimal decrease in AUC was seen for the either the Reduced or Summated models when applied to the Validation cohort.

	Derivation cohort	**Validation cohort**
Reduced Model		
Logit Coefficients		
Intercept	-2.93681	
[1]*AgeLte50*	1.04413	
PFDI5	0.54783	
GUPI5	0.32824	
[2]*GUPI2B*	1.24367	
AUC (95% CI)	0.80 (0.73, 0.87)	0.74 (0.69, 0.79)
Summated Score Model		
Logit Coefficients		
Intercept	-2.89321	
[1,2]*Sum Score*	0.39878	
AUC (95% CI)	0.79 (0.72, 0.87)	0.74 (0.69, 0.79)

[1]Value of 3 assigned in sum score when Age ≤ 50
[2]Value of 3 assigned in sum score when GUPI2B endorsed

Validated Questionnaires: ICSI: Interstitial Cystitis Symptoms Index; ICPI: interstitial Cystitis Problem Index; fGUPI: female Genitourinary pain index; UDI-6: Urinary Distress Inventory Short Form; CRADI-8: Colorectal-Anal Distress Inventory; Pelvic Organ Prolapse Distress Inventory.

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Supplemental Table 6. ***Sensitivity, Specificity, and Accuracy for the range of thresholds for the PI.*** A threshold of 7 was chosen as the optimal balance for a screening measure, but prioritizing sensitivity to avoid missing those with true MFS.

Summated Score Cut point	**Sensitivity**	**Specificity**	**Accuracy**
≥ 0	100%	0%	22%
≥ 1	98%	9%	28%
≥ 2	98%	14%	32%
≥ 3	97%	18%	36%
≥ 4	93%	34%	47%
≥ 5	90%	42%	53%
≥ 6	86%	50%	58%
*≥ 7	80%	61%	65%
≥ 8	69%	68%	68%
≥ 9	58%	76%	72%
≥ 10	48%	82%	74%
≥ 11	37%	85%	75%
≥ 12	33%	88%	76%
≥ 13	19%	94%	77%
≥ 14	11%	97%	78%
≥ 15	5%	98%	78%

*Denotes cut point threshold that maximizes both sensitivity and specificity per Youden's Index

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Supplementary Table 7: ***Symptomatic Features of the Validation Cohort by Diagnosis*.**

	Question	Scale	MFS (n=111)	Cont (n=209)	OAB (n=285)	IC/BPS (n=53)	Adjusted *P* value (MFS vs. Cont	OAB	IC/BPS
*Age**		0-95	41.75 (16.28)	59.04 (17.83)	58.06 (19.35)	44.75 (17.72)	<0.001	<0.001	0.53
OABq1	Frequent urination during the daytime hours	1-6	2.92 (1.79)	1.75 (1.26)	3.08 (1.58)	3.74 (1.57)	<0.001	0.80	0.56
OABq2	**An uncomfortable urge to urinate**	1-6	3.91 (1.47)	2.20 (1.46)	3.55 (1.64)	3.87 (1.65)	<0.001	0.16	>0.999
OABq3	A sudden urge to urinate	1-6	2.65 (1.74)	2.00 (1.34)	3.47 (1.64)	2.70 (1.75)	0.004	<0.001	0.93
OABq4	Accidental loss of small amounts of urine	1-6	1.25 (0.53)	2.01 (1.30)	3.62 (1.54)	1.43 (0.60)	<0.001	<0.001	0.02
OABq5	Nighttime urination	1-6	2.83 (1.86)	2.43 (1.57)	3.49 (1.69)	2.98 (1.62)	0.28	0.003	0.37
OABq6	Waking at night because you had to urinate	1-6	3.03 (1.82)	2.80 (1.58)	3.80 (1.63)	3.36 (1.58)	0.44	<0.001	0.32
OABq7	An uncontrollable urge to urinate	1-6	2.98 (1.75)	1.30 (1.28)	3.53 (1.72)	3.12 (1.64)	<0.001	0.02	0.44
OABq8	Urine loss associated with a strong desire to urinate	1-6	1.19 (0.51)	1.84 (1.25)	3.52 (1.51)	1.21 (0.45)	<0.001	<0.001	0.45
ICSI1	Strong need to urinate with little or no warning	0-5	1.81 (1.66)	0.96 (1.24)	2.59 (1.67)	2.10 (1.73)	<0.001	<0.001	0.32
ICSI2	Urinate less than 2 hours after you finished urinating	0-5	3.15 (1.64)	1.50 (1.46)	3.26 (1.51)	3.13 (1.63)	<0.001	0.99	>0.999
ICSI3	How often typically up at night to urinate	0-5	1.45 (1.43)	1.25 (1.18)	2.10 (1.30)	1.72 (1.06)	0.42	<0.001	0.11
ICSI4	Experienced pain or burning in your bladder	0-4	0.56 (0.73)	0.46 (0.76)	0.77 (1.04)	2.21 (1.38)	0.26	0.26	<0.001
ICPI1	Frequent urination during the day	0-4	2.25 (1.45)	1.03 (1.25)	2.69 (1.26)	2.64 (1.24)	<0.001	0.02	0.23
ICPI2	Getting up at night to urinate	0-4	1.70 (1.55)	1.25 (1.27)	2.30 (1.41)	2.04 (1.21)	0.07	0.002	0.27
ICPI3	Need to urinate with little warning	0-4	1.43 (1.49)	0.75 (1.11)	2.28 (1.42)	1.70 (1.51)	<0.001	<0.001	0.27
ICPI4	Burning, pain, discomfort or pressure in your bladder	0-4	1.13 (1.49)	0.60 (1.06)	1.47 (1.61)	3.21 (1.13)	0.008	0.06	<0.001
fGUPI1a†	Pain/discomfort at the entrance to the vagina	0-1	0.38	0.12	0.24	0.57	<0.001	0.01	0.03
fGUPI1b†	Pain/discomfort in the vagina	0-1	0.35	0.10	0.28	0.60	<0.001	0.17	0.007
fGUPI1c†	Pain/discomfort in the urethra	0-1	0.27	0.09	0.29	0.71	<0.001	0.73	<0.001
fGUPI1d†	Pain/discomfort below the waist, in pubic or bladder area	0-1	0.43	0.12	0.35	0.84	<0.001	0.13	<0.001
fGUPI2a†	Pain or burning during urination	0-1	0.21	0.08	0.31	0.63	0.002	0.05	<0.001
fGUPI2b†*	*Pain or discomfort during or after sexual intercourse*	0-1	0.38	0.19	0.28	0.63	<0.001	0.07	0.007
fGUPI2c†	Pain or discomfort as your bladder fills	0-1	0.07	0.06	0.29	0.87	0.74	<0.001	<0.001
fGUPI2d†	Pain or discomfort relieved by voiding	0-1	0.18	0.10	0.29	0.82	0.07	0.07	<0.001
fGUPI3	Frequency of pain or discomfort over the last week	0-5	2.85 (1.31)	0.97 (1.20)	1.93 (1.55)	4.00 (1.10)	<0.001	<0.001	<0.001
fGUPI4	Number that best describes average pain/discomfort	0-10	2.33 (2.22)	1.02 (1.64)	3.26 (3.00)	5.77 (1.78)	<0.001	0.03	<0.001
*fGUPI5**	***Frequency of sensation of incomplete emptying***	0-5	3.12 (1.39)	1.15 (1.30)	2.30 (1.68)	2.13 (1.69)	<0.001	<0.001	<0.001
fGUPI6	**Need to urinate <2 hours after last urinating**	0-5	3.52 (1.27)	1.58 (1.27)	3.01 (1.50)	3.23 (1.54)	<0.001	0.01	0.6
fGUPI7	Have your symptoms kept you from doing the kinds of things you would usually do	0-3	1.68 (1.01)	0.44 (0.71)	1.74 (1.08)	1.87 (1.04)	<0.001	0.9	0.86
fGUPI8	How much did you think about your symptoms	0-3	2.52 (0.67)	0.75 (0.78)	2.46 (0.77)	2.66 (0.68)	<0.001	0.4	0.27
fGUPI9	Satisfaction with current symptoms	0-6	4.69 (1.03)	1.59 (1.09)	4.50 (1.18)	5.04 (1.09)	<0.001	0.2	0.07
POPDI-1	Pressure in the lower abdomen	0-4	1.70 (1.42)	0.59 (1.03)	1.48 (1.52)	2.17 (1.59)	<0.001	0.2	0.09
POPDI-2	Heaviness or dullness in the lower abdomen	0-4	1.21 (1.40)	0.37 (0.82)	1.06 (1.41)	1.80 (1.59)	<0.001	0.32	0.04
POPDI-3	**A bulge or something falling out that can see or feel in the vaginal area**	0-4	0.60 (1.19)	0.33 (0.83)	0.55 (1.16)	0.51 (1.08)	0.36	>0.999	>0.999
POPDI-4	A need to push on the vagina or around the rectum to have a complete bowel movement	0-4	0.75 (1.27)	0.37 (0.81)	0.66 (1.21)	0.77 (1.30)	0.09	>0.999	>0.999
*POPDI-5**	***A feeling of incomplete bladder emptying***	0-4	2.68 (1.35)	0.91 (1.17)	1.67 (1.51)	1.87 (1.58)	<0.001	<0.001	0.005
POPDI-6	A need to push up in the vagina area to start or complete urination	0-4	0.37 (0.89)	0.17 (0.60)	0.37 (0.90)	0.17 (0.58)	0.12	>0.999	0.37
CRADI-8-1	**A need to strain too hard to have a bowel movement**	0-4	1.32 (1.43)	0.51 (0.96)	1.00 (1.26)	0.91 (1.33)	<0.001	0.22	0.22

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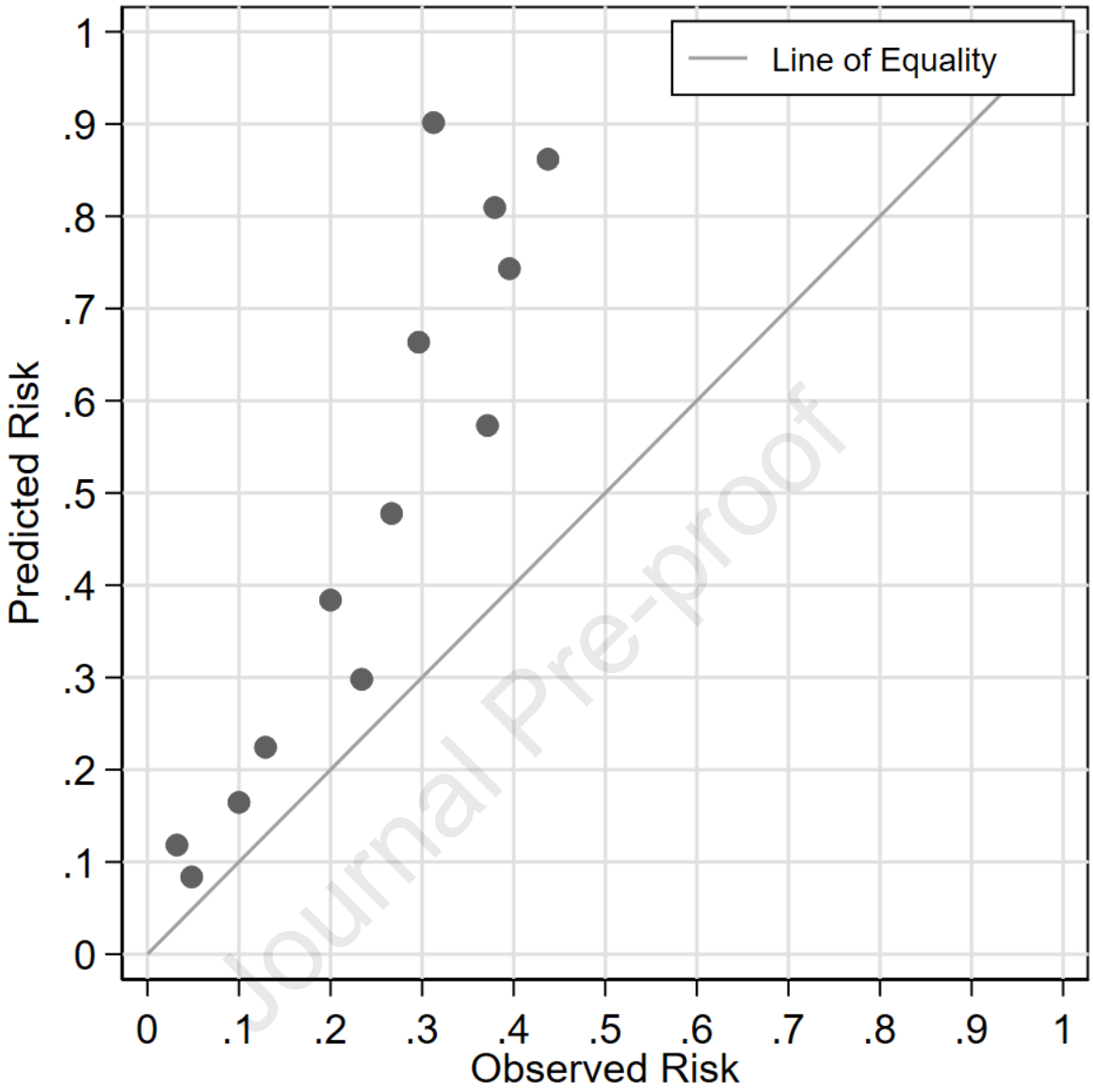
CRADI-8-2	**A feeling that you have not completely emptied your bowels after a bowel movement**	0-4	1.16 (1.40)	0.59 (0.98)	1.11 (1.30)	0.94 (1.27)	0.002	0.99	0.99
CRADI-8-3	Losing stool without control when stools are well formed	0-4	0.28 (0.72)	0.16 (0.55)	0.41 (0.98)	0.10 (0.46)	0.20	0.76	0.20
CRADI-8-4	Losing stool without control when stool is loose or liquid	0-4	0.46 (0.95)	0.26 (0.77)	0.82 (1.31)	0.42 (0.87)	0.10	0.10	0.77
CRADI-8-5	Losing gas from the rectum without control	0-4	0.70 (1.23)	0.41 (0.88)	1.08 (1.44)	0.58 (1.12)	0.20	0.06	0.94
CRADI-8-6	**Pain with passing stools**	0-4	0.75 (1.23)	0.20 (0.62)	0.48 (1.04)	0.63 (1.24)	<0.001	0.04	0.76
CRADI-8-7	**A strong sense of urgency and have to rush to the bathroom to have a bowel movement**	0-4	1.31 (1.41)	0.51 (1.01)	1.12 (1.45)	0.83 (1.24)	<0.001	0.34	0.12
CRADI-8-8	Stool passes through the rectum and bulges outside during or after a bowel movement	0-4	0.51 (1.00)	0.23 (0.63)	0.58 (1.22)	0.27 (0.72)	0.02	>0.999	0.37
UDI-6-1	Bothered by frequent urination	0-4	2.04 (1.54)	0.95 (1.27)	2.41 (1.46)	2.19 (1.61)	<0.001	>0.999	0.79
UDI-6-2	Bothered by leakage related to feeling of urgency	0-4	0.60 (1.11)	0.70 (1.13)	2.06 (1.50)	0.21 (0.57)	0.48	<0.001	0.03
UDI-6-3	Bothered by leakage related to physical activity, coughing, or sneezing	0-4	0.78 (1.29)	0.75 (1.10)	1.82 (1.57)	0.43 (0.84)	0.68	<0.001	0.19
UDI-6-4	Bothered by small amounts of leakage (drops)	0-4	0.55 (1.03)	0.49 (0.92)	1.88 (1.56)	0.29 (0.67)	0.78	<0.001	0.37
UDI-6-5	**Bothered by difficulty emptying bladder**	0-4	1.31 (1.46)	0.35 (0.78)	0.98 (1.43)	1.17 (1.53)	<0.001	0.09	0.88
UDI-6-6	Bothered by pain or discomfort in the lower abdominal or genital area	0-4	1.25 (1.28)	0.41 (0.83)	1.34 (1.46)	2.68 (1.36)	<0.001	0.98	<0.001

Means (standard deviation) are shown for all interval variables, except for the binary variables which document the population proportions scoring positive for each individual feature. Pairwise comparison of interval variables were compared using Welch's t test, while binary variables (designated with †) were examined using the Chi-square test. MFS: Myofascial Frequency Syndrome; Cont: Asymptomatic Controls; OAB: Overactive Bladder; IC/BPS: Interstitial Cystitis/Bladder Pain Syndrome; OABq: Overactive Bladder Questionnaire; ICSI: Interstitial Cystitis Symptoms Index; ICPI: interstitial Cystitis Problem Index; fGUPI: female Genitourinary pain index; UDI-6: Urinary Distress Inventory Short Form; CRADI-8: Colorectal-Anal Distress Inventory; POPDI-6: Pelvic Organ Prolapse Distress Inventory**;** ns: Not significant.

* Variables used to create the Persistency Index

† Binary Variables: the values noted are proportions of each population answering "yes" to the symptomatic feature.

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Supplemental Figure 2. ***Phenotyping Comprehensive Lower Urinary Symptoms (p-CLUS) nomogram***

Applying the Nomogram:

1. Calculate the patient's Bother Score using the fGUPI QoL:

    a. Bother = GUPI7 + GUPI8 + GUPI9 Bother = _____ *

* Only proceed for patients with Bother score over 5

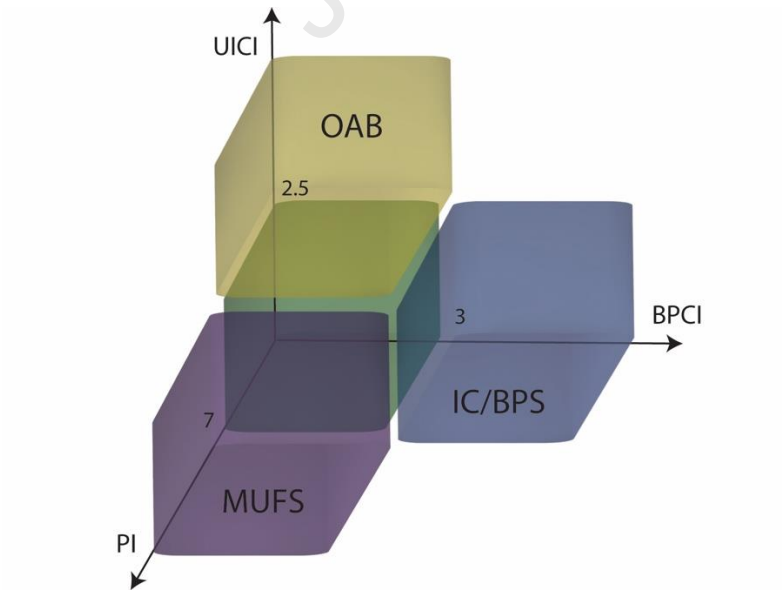
2. Determine the patient's BPCI (Bladder Pain Composite Index) and UICI (Urgency Incontinence Composite Index) based on their ICSI/ICPI, OABq, and fGUPI responses as follows:

    a. BPCI = ([(ICSI4+1)/5]+GUPI2C) X 3 BPCI = _____
    b. UICI = (OABq4+OABq8+OABq25)/3 UICI = _____
    c. PI = PFDI20q5 + GUPI5 + (GUPI2B*3) + AgeP PI = _____
    AgeP = 3 IF Age < 50 years

3. Determine Nomogram Quadrant
    a. If BPCI > 3, Classify patient as IC/BPS
    b. If BPCI < 3 and UICI > 2.5, Classify patient as OAB
    c. IF BPCI < 3, UICI < 2.5 and PI > 7, Classify patient as MFS

Graphing the result:

If Bother >5, location on graph of X (UICI) vs. y (BPCI) vs. z (PI) determines diagnosis:



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Development and Validation of a Machine Learning Algorithm to Classify Lower Urinary Tract Symptoms

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Abbreviations: Lower urinary tract urinary symptoms (LUTS), overactive bladder (OAB), interstitial cystitis/painful bladder syndrome (IC/BPS), machine learning (ML), pelvic organ prolapse (POP), female Genitourinary Pain Index (fGUPI), Overactive Bladder Questionnaire (OABq, Pelvic Floor Distress Inventory (PFDI-20), Interstitial Cystitis Symptom and Problem Indices (ICSI/ICPI), urinary tract infection (UTI), Uniform manifold approximation and projection (UMAP), (pelvic floor disorders [*PFD*]), urgency urinary incontinence (*UUI*), mixed urinary incontinence (*MUI*), fecal incontinence/mixed urinary incontinence (*FI/MUI*), myofascial frequency syndrome (*MFS*), pelvic organ prolapse (*POP*), myofascial pelvic pain (*MPP*), controls/stress urinary incontinence (*Controls/SUI*), non-urologic pelvic pain (*NUPP*), stress urinary incontinence (SUI), urgency urinary incontinence (UUI),

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Abstract

Objective: Lower urinary tract symptoms (LUTS), such as urinary urgency, frequency, and incontinence, affect the majority of the population, causing substantial morbidity, yet few receive effective care. Sizeable symptomatic overlap between LUTS categories leads to high rates of misdiagnosis. To improve diagnostic accuracy, we sought to employ machine learning approaches to LUTS categorization to generate diagnostic groupings based on patient-reported clinical data, creating a novel tool for diagnosis of patients with voiding complaints.

Methods: Questionnaire responses in a Development Dataset of 514 female subjects were used for model development, identifying 4 major clusters and 9 specific phenotypes of LUTS using agglomerative hierarchical clustering. Each cluster and phenotype was assigned a clinical identity consistent with recognized causes of voiding dysfunction by the consensus of two urologic specialists. Then, a random forest classifier was trained to assign unseen patients into these phenotypes. That model was then applied to a Validation Dataset of 571 additional subjects to confirm the diagnostic algorithm.

Results: This data-driven, hierarchical clustering approach captured overlapping symptoms inherent in typical patients, recognizing common uncomplicated diagnoses (i.e., overactive bladder) as well as several underrecognized diagnostic categories (i.e., myofascial pelvic pain). A diagnostic algorithm derived by supervised machine learning to assign unseen subjects into these phenotypes demonstrated good reproducibillty of the phenotypes and their symptomatic patterns in an independent Validation Dataset.

Conclusions: We describe the generation of a machine learning algorithm relying only on validated, patient-reported symptoms for diagnostic classification. Given a growing physician shortage and increasing challenges for patients accessing specialist care, this type of digital technology holds great potential to improve the recognition and diagnosis of functional urologic conditions.

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Introduction:

Half of adult women are incontinent; more than 75% of women at some point in the lifespan report disruptions in daily activities by at least one lower urinary tract symptom (LUTS), such as *urinary urgency, frequency, nocturia, painful urination, bladder pain or discomfort, or incontinence*.[1,2] When severe, these urinary symptoms degrade health-related quality of life to levels worse than chronic dialysis.[3] Incontinence and urinary complaints are one of the most common causes for the long-term institutionalization of older adults.[4] Further, these disorders represent substantial economic burden, with annual costs estimated to approach 100 billion dollars.[5] Yet despite this large burden of illness, most women do not seek care, due to embarrassment, resignation, or misconceptions that these symptoms are normal or cannot be treated.[6]

Even for those who do seek care, many will not receive an accurate diagnosis.[7] While patients presenting with urinary symptoms are categorized into several unique conditions, appropriate diagnosis and treatment is complicated by subjectivity of language used to describe symptoms and sizeable symptomatic overlap.[8] While classified as separate conditions, diagnoses such as overactive bladder (OAB) and interstitial cystitis/painful bladder syndrome (IC/BPS) are not diseases, but symptom complexes without a known pathophysiology that share many overlapping symptoms. Clinicians typically assign a diagnosis according to patients' most bothersome complaints, but as there are currently no definitive tests or biomarkers available, diagnosis and treatment assignment are subjective, based entirely on clinician judgement.[9,10] Due to poor efficacy and treatment side effects, more than 90% of patients will abandon medical therapies within a year.[11]

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A data-driven approach may address many of the current obstacles to LUTS care. Virtual screening approaches would allow anonymized recognition of symptoms without requiring in-person or specialist visits. Given the high degree of overlapping symptoms, but distinctive patterns of combined symptoms, algorithms identifying more specific phenotypes of LUTS may recognize subtle distinctions indicative of unique causes of convergent symptomatologies that clinicians may have difficulty recognizing. While symptoms of LUTS diagnoses may be similar, the underlying etiologies of these symptoms may be quite different and require different approaches to treatment. To this end, multiple studies have attempted to utilize a range of unsupervised machine learning (ML) methods to improve phenotypic classification of lower urinary tract disorders. However, most have examined only a subset of symptoms, typically excluding patients with complex symptoms or confounding factors such as pelvic organ prolapse (POP). However, “as often patients present with multiple urinary symptoms that do not perfectly fit the pre-established diagnoses,”[12] the intentional exclusion in these studies of patients with complex or overlapping symptoms or co-existing pelvic organ prolapse may underlie the lack of practical progress in improving current diagnostic schema.

For most ML methods, data objects are divided into non-overlapping, mutually-exclusive clusters of a fixed number. In contrast, hierarchical clustering generates a set of nested clusters that are arranged as a tree/dendrogram. Hierarchical clustering is best used when the number of classes is not known; once the structure of the data is defined, one can stop at any number of clusters. A strength of hierarchical clustering is the ability for the resulting dendrogram to provide insights as to the structure of the data, which in turn informs about the number of logical clusters. Given the nature of functional urologic symptoms, we believe that hierarchical clustering presents a more complete picture of the underlying patterns of lower urinary tract symptoms than other methods of machine learning. In addition, It may provide a more useful framework to determine what level of phenotypic classification is useful in clinical practice.

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Given the known obstacles and clinical dilemmas in diagnosing LUTS, we aimed to create an unsupervised ML algorithm encompassing all patients presenting with LUTS. This novel tool for the diagnosis of patients with voiding complaints utilized agglomerative hierarchical clustering to generate diagnostic groupings based on patient-reported clinical data.

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Methods:

Study Cohorts

After Institutional Review Board (IRB#00040261) approval, the *Development Dataset* of 514 female subjects with a wide range of symptoms, seen consecutively for evaluation in a tertiary urogynecology practice between January and December 2018, was used for model development. A second *Validation Dataset* of 571 subjects recruited from the same practice consequtively between January 2019 and March 2020 was used to validate the diagnostic ML algorithm. For each cohort, subjects were administered four, validated questionnaires at initial evaluation: the female Genitourinary Pain Index (fGUPI)[13], Overactive Bladder Questionnaire (OABq)[14], Pelvic Floor Distress Inventory (PFDI-20)[15] and O'Leary-Sant Indices, including the Interstitial Cystitis Symptom and Problem Indices (ICSI/ICPI).[16] The fGUPI measures the nature and severity of genitourinary pain, and contains subscales assessing pain, urinary symptoms, and quality of life.[13] The OABq measures continent and incontinent OAB symptoms, symptom bother, coping behaviors, concern/worry, social interaction, sleep, and health-related quality of life.[14] Only the symptom-based questions (1-8) were utilized in this analysis. The PFDI-20 measures urinary, defecatory, and prolapse symptoms commonly associated with pelvic floor disorders such as POP.[15] The ICSI/ICPI are used together to measure the severity and bother of urinary frequency, urgency, nocturia, and bladder pain.[16] Patients with active urinary tract infection (UTI), prior pelvic reconstructive surgeries (such as prolapse repairs, bladder augmentation, incontinence procedures), current pregnancy, or neurogenic bladder were excluded from the study. Patients with cyclic pain at menses were excluded, however, patients with prior history of UTI or comorbid functional pain syndromes, such as irritable bowel syndrome or fibromyalgia, were allowed to participate. Patients with asymptomatic complaints (e.g., microscopic hematuria) were included in both datasets.

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Hierarchical Clustering

Agglomerative hierarchical clustering was applied to the *Development Dataset* to identify patient groups on the basis of patient age and questionnaire responses. This unsupervised approach recursively builds a hierarchical representation from the "bottom up" by grouping pairs of samples according to a distance metric and linkage criterion. This algorithm was applied using the Ward linkage criterion, which aims to create groupings which have minimum intra-group variance.[17] Similarity between samples was calculated using the Euclidean (i.e., squared) distance between symptoms. After the hierarchical representation was constructed using the agglomerative algorithm, clusters were created by truncating the depth of the hierarchical representation, thereby grouping patients into a fixed number of clusters (e.g., **Fig. 1**). Mean silhouette scores[18] were computed to measure cluster assignment performance to select the optimal cluster assignment between 2 and 15 clusters. Using this criterion, four and nine cluster solutions were selected.

Phenotypic group descriptive assignments

Age and survey response scores were scaled to a set range before plotting as a heat map. ANOVA assessed significant differences between cluster groups in intragroup means for each variable. The dominant features for each cluster and phenotype were examined independently by two urogynecologists, who each assigned a clinical identity based on their expert opinion. For any disagreement, discussion between the two evaluators and a third moderating urogynecologist allowed for refinement of the group clinical identity until consensus was reached.

Generation of the diagnostic algorithm

Unsupervised algorithms, such as agglomerative clustering, are not reliably applicable to new data as they require the entire hierarchical representation to be re-generated each time the

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algorithm is run. After manually validating cluster assignments and assigning phenotypic group descriptions, a supervised machine learning model was trained to assign unseen patients into existing clusters. Using the Development Dataset, random forest models were trained to predict the machine-generated cluster assignment on the same symptoms used for clustering. Random forests are generally robust to overfitting and outliers, and outperform other methods when representing tabular data.[19] Two models were generated which assigned patients into the four and nine cluster labels, respectively. These models were assessed using the validation dataset with balanced accuracy[20] (defined as the average sensitivity score for each class) – which has been used to deal with imbalanced data.

Uniform manifold approximation and projection (UMAP) visualization

UMAP is a nonlinear dimension reduction technique used to visualize high-dimensionality data for qualitative inspection.[21] Using the development dataset, the algorithm was applied to represent patients in two data-generated axes. As in the clustering analysis, the projection axes were optimized with respect to the Euclidean distance between patient responses. Then, Validation Dataset patients were transformed into the same space and all patients visualized together. Each patient was colored according to the phenotype assigned by the nine-cluster model.

Statistical analysis

Cluster fitting and optimization, machine learning model development and evaluation, and UMAP were performed with Python using the scikit-learn and UMAP-learn packages. All other analyses and visualization were performed in R version 4.2.1. Differences in demographic and clinical characteristics were compared by using Wilcoxon signed rank tests for paired data and the Pearson chi square, Fisher exact, or Mann-Whitney U-tests for independent data as

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appropriate (2-tailed). Differences in proportions were compared using the two-sample z-test.

Results were considered significant at an alpha level <0.05.

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Results

Unsupervised clustering of subjects presenting with LUTS.

The *Development Dataset* of 514 female patients with a mean age of 58.7 years completed a panel of validated symptomatic questionnaires assessing genitourinary symptoms between June 2017 and December 2018. Using only age and patient-reported symptoms, subjects were classified into symptomatic clusters according to an agglomerative hierarchical clustering algorithm (**Fig. 1**). Examination of the resulting dendrogram (**Fig. 1**, blue line) revealed four clear branches, confirmed as the optimal number of clusters using the silhouette method (global maximum, **Fig. 2**).

Data-driven hierarchical clustering reveals the global patterns in phenotypes.

The symptom patterns associated with each cluster (**Table 1**) reflected the overall categories of subjects seeking urogynecologic care: 1) subjects with mild symptoms who are only moderately bothered (*Mild symptoms/controls*), 2) subjects with predominantly lower urinary tract symptoms, such as urinary frequency, urgency, and incontinence (*LUTS*), 3) subjects with pain as their predominant complaint (*Pain*), and 4) subjects with pelvic floor complaints (pelvic pressure, vaginal bulge) who also exhibit urinary symptoms and discomfort (pelvic floor disorders [*PFD*]). These patterns are more clearly visualized in a heat map (**Fig. 3**) demonstrating which features are prominent in each group. The *PFD* group had globally elevated symptom scores across all symptomatic domains, with unique complaints attributable to the pelvic floor, such as defecatory dysfunction (PFDI20 q7-8), vaginal bulge (PFDI20 q3), pelvic pressure (PFDI20 q2), and a need to splint to defecate or void (PFDI20 q4, PFDI20 q6). The *Pain* group was the youngest group overall and displayed similarly high scores to the *PFD* group only on questions assessing pelvic and genitourinary pain (fGUPI q1-4, PFDI20 q20, ICSI q4, ICPI q4). The *LUTS* group was generally older than the other groups and exhibited elevated

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urinary incontinence related to both urgency (PFDI20 q16, OABq q8) and stress (activities that increase intraabdominal pressure) (OABq q4, PFDI20 q17). While these subjects commonly exhibited urinary urgency (OABq q3, ICPI q3, ICSI q1), frequency (ICSI q2, ICPI q1, GUPI q6), and nocturia (ICPI q2, OABq q5) at levels greater than the controls, symptom severities of the *LUTS* group only surpassed the *PFD* group in the domain of fecal incontinence (PFDI20 q9-11).

Discrimination of symptomatic phenotypes.

While the four-cluster classification provides a general categorization of women presenting for urogynecologic care, the resulting groups encapsulate only the most basic symptomatic categorization, failing to distinguish patients for whom different treatments are typically selected, such as stress and urgency incontinence, vestibulodynia and interstitial cystitis/bladder pain syndrome, or pelvic organ prolapse and myofascial pelvic pain. We therefore examined the next most optimal range of clusters. The silhouette score reached a local maximum in the range of 9-11 clusters (**Fig. 2**, local maximum); in the dendrogram, the nine-cluster division best captured the major subdivisions in the data (**Fig. 1**, gold line). Again visualized as a heat map, patterns of dominant symptoms provide characterization of each cluster phenotype (**Table 2**), each of which was assigned a phenotypic designation by specialist consensus (**Fig. 4**).

The *LUTS* cluster was subdivided into three phenotypes: 1) urgency urinary incontinence (*UUI*), who lacked other bothersome sypmtoms, 2) mixed urinary incontinence (*MUI*), who exhibited both UUI and SUI, and 3) fecal incontinence/mixed urinary incontinence (*FI/MUI*), who were profoundly impacted by both fecal urgency and incontinence in addition to their urinary symptoms. The *Pain* cluster was subdivided into an *IC/BPS* phenotype, who were bothered by classic bladder pain with bladder filling, relieved by bladder emptying, and a second phenotype whose symptoms were described more as bladder pressure and discomfort. The co-existence of these symptoms with a strong sensation of incomplete bladder emptying identified this group

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as myofascial frequency syndrome (*MFS*), a condition in which urinary symptoms are caused by pelvic floor myofascial dysfunction. The *PFD* cluster was further divided into subjects with clear pelvic organ prolapse (*POP*), who described both a bothersome vaginal bulge and needing to reduce the prolapse to urinate or defecate, and a myofascial pelvic pain (*MPP*) group, who have both genitourinary pain and global urinary, defecatory, and sexual dysfunction, similar to the POP group, but who lack any evidence of vaginal bulge. The last cluster (*Mild symptoms/controls*) included two phenotypes of subjects: those with stress urinary incontinence (*Controls/SUI*) who were often only minimally bothered, and those with focal genital pain unrelated to bladder filling or voiding, known as non-urologic pelvic pain (*NUPP*).

Development of a classification algorithm

We next sought to create a diagnostic tool for the phenotypic classification of new patients. We trained a random forest classifier using the phenotypic assignments of the Development Dataset to create a classification algorithm, which we then applied to the independent Validation Dataset of 571 individuals with urologic complaints. Phenotypic assignment using the random forest classifier resulted in groups that were highly similar to the development dataset phenotypes, exhibiting the same patterns of distinctive symptoms. We plotted the similarity of the development and validation phenotypes graphically using a uniform manifold approximation and projection (UMAP) method (**Fig. 5**). Proximity in UMAP space signifies similarity between groups, in this case capturing the overlap in symptom profiles between phenotypes from the validation and development cohorts as well as the relationships between groups. For example, the mixed urinary incontinence (MUI) group, which exhibits incontinence elicited by urgency and stress, exists at the interface between the urgency urinary incontinence (UUI) and stress urinary incontinence (SUI) groups, sharing features of both while still occupying a unique space.

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Discussion

We successfully applied machine learning algorithms to the diagnostic classification of women with a wide range of symptoms presenting for urologic care. This classification generated logical, phenotypic groups based on validated, patient-reported symptoms alone. Symptomatic patterns could be grouped into four general clusters: minimal/mild symptoms, urogenital pain, urinary complaints, and pelvic floor disorders. Validation of these clusters revealed high reproducibility in an independent cohort. These groups are analogous to the general clinical categories currently used; most patients presenting for urologic care will be diagnosed with either incontinence, genitourinary pain, or pelvic organ prolapse. As unsupervised machine learning brings no assumptions to cluster derivation, agreement of the overall diagnostic categories with well-accepted clinical categorization validates the ability of data-driven methods to derive clinically meaningful diagnostic categories.

Several groups have tried to subclassify urologic phenotypes, but have typically examined only one symptom cluster in isolation (e.g., overactive bladder[12,22-24] or genitourinary pain[25-28]). Substantial work, however, documents that these divisions are artificial; many patients carrying an OAB diagnosis suffer from significant bladder pain (35%) while more than 30% of IC/BPS patients have urge incontinence.[29,30] In addition, OAB symptoms are common in patients desiring surgical repairs for POP.[31] Given the high prevalence of prolapse in the population (24-49%),[32-34] it is unclear how co-existing POP should influence our clinical management of patients presenting primarily with urinary complaints.

To overcome this obstacle, broad inclusion of all patients consecutively presenting for urogynecologic care combined with unsupervised clustering using patient complaints alone allowed us to derive nine unique phenotypes encompassing the range of overlapping symptoms

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without bias. Distinction between groups was based on unique combinations of symptoms rather than individual, pathognomonic features.[23] These nine phenotypic diagnoses included the range of common urologic diagnoses (SUI, UUI, MUI, IC/BPS), but also incorporated several less common, emerging pathologies that have only recently been suspected in the etiology of LUTS (MFS, MPP, NUPP).[28,35-37] The classifier also distinguished between subjects with mixed urinary incontinence in whom a correctable, anatomic cause (POP) to their symptoms should be suspected, which may influence treatment choices. Lastly, the classifier was capable of recognizing highly impactful symptoms like FI, which are frequently unaddressed as patients are often too embarrassed to express them. Thus, these resulting groups captured the ranges of coexisting symptoms while still accounting for the complicated symptomatic overlap of real-world patients, something no other ML categorization system has done thus far.

Our findings here are novel and timely, with the potential to improve diagnosis and treatment and overcome the significant burden these conditions place on patients and the healthcare system. While various approaches to subclassifying urinary symptoms and genitourinary pain exist,[12,22-27] most require detailed information (patient demographics, physical exam findings, imaging, genetic or biochemical markers, or other diagnostic testing results) unavailable or unfamiliar to most practioners outside of specialized clinical settings. In addition, most of these categorization schema evaluated narrow populations without overlapping symptoms, which ignores a large subset of real-world patients. Here, we generate a diagnostic algorithm based on our novel ML-based phenotypic classification that can be used for treatment assignment of a broad care-seeking population with a wide range of urinary and pelvic complaints. By relying only on patient-reported symptoms, this algorithm can be applied by any type of practitioner in any care delivery setting, including telemedicine.

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Providing adequate care for the enormous population of women affected by urinary complaints faces numerous obstacles, both at the health system and individual levels. First is the lack of recognition of these symptoms. Patients, even when highly bothered, may not seek care for urinary complaints due to shame, embarrassment, or a feeling that symptoms are unavoidable. Doctors may not ask about these issues, and even if they do, may not be able to address them due to time constraints or knowledge gaps. The prevalence of urinary symptoms recognized in the primary care setting increases dramatically when validated questionnaires are routinely administered,[38] stressing the need for better, more pervasive, and perhaps more anonymized screening. As a result of these numerous barriers, however, few women seek or receive care.[39] The development of a digital resource providing diagnostic assistance has the potential to dramatically improve the quality of life of the population, not only through more accurate diagnostics but by allowing rapid implementation of first-line, low-risk treatments and earlier access to specialty care.

Although our results are promising, our algorithm is based on data from a single center; thus, our findings may not be scalable to the population at large. Further, accurate classification of patients is only of clinical value if the treatment based on these diagnostic groupings correlates with clinical improvement, which will need to be addressed in future prospective studies. Also, the current modeling requires patients to answer nearly 50 questions, which may not be achievable in most clinical scenarios. Finally, our approach to classifying patients may not be generalizable to populations in different clinical scenarios, such as those not presenting for urologic care.

Despite these limitations, this study examined a large number of patients (over 500 in each cohort, totaling over 1,000 subjects) who were consecutively included regardless of referral diagnosis or presenting complaints. This means that our cohort not only included a control

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group, but is likely representative of the true patient population referred for urologic care. Furthermore, this algorithm relies only on validated questionnaire responses. Thus, this novel LUTS classification algorithm can be utilized to assign diagnoses without the need for either sub-specialist evaluation, to which access can be limited, or physical examination, which can be challenging for patients in underserved areas. Given a growing physician shortage and increasing challenges for patients accessing specialist care, digital technology holds great potential to improve the early recognition, diagnosis, and early treatment of functional urologic conditions. Future prospective work with a larger, multi-institutional cohort is needed to improve these algorithms and to allow accurate diagnosis and treatment assignment based on the machine learning-suggested phenotypes. In addition, reduction of the number of questions to the minimum subset possible is needed to make this feasible to perform in a clinical setting. With refinement, however, this approach to care delivery is capable of increasing both the equity and rapidity of access to effective urologic care.

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Conclusions

A data-driven approach to the phenotyping of lower urinary tract syptoms using unsupervised and supervised machine learning approaches is capable of recognizing both simple and highly complex phenotypic patterns in patients seeking care for urinary complaints. The development in this report of a digital tool trained to classify a broad range of subjects with urologic symptoms that can be administered virtually shows promise to improve the recognition and accurate diagnosis of such disorders.

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Figures

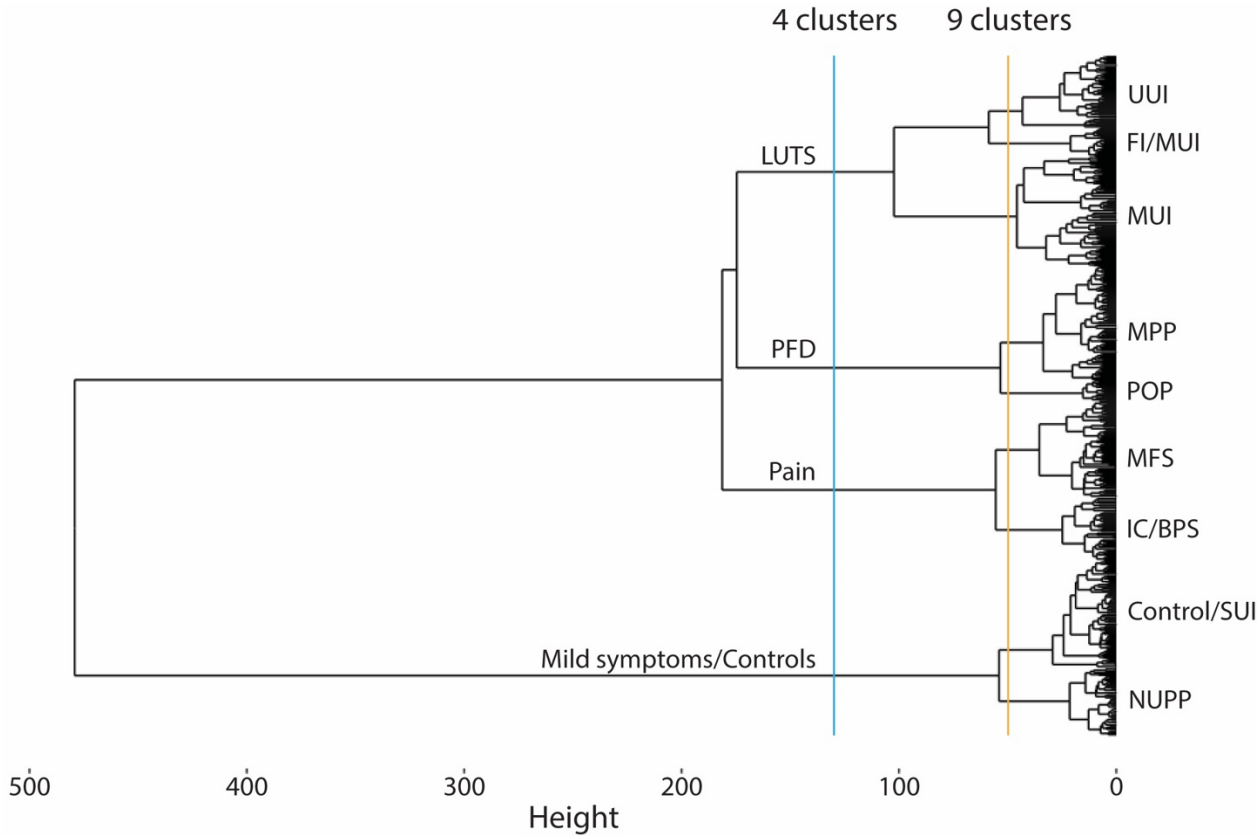


Figure 1. ***Dendrogram indicating the hierarchical relationships between clusters.*** The different lines indicate different possible cut-off points used to subclassify subjects with LUTS, with the blue line indicating the major symptomatic divisions in subjects presenting for care in a urogynecology clinic (*LUTS*: lower urinary tract symptoms; *PFD*: pelvic floor disorders; *Pain*: pelvic pain complaints; *Mild symptoms/controls*: patients with mild or minimal complaints). The yellow line indiciates the location in the dendrogram at which subjects are separated into 9 unique clusters, with each of the major categories further divided into 2-3 subclusters (UUI: urgency urinary incontinence; MUI: mixed urinary incontinence; FI/MUI: fecal incontinence/UUI; MFS: myofascial frequency syndrome; POP: pelvic organ prolapse; MPP: myofascial pelvic pain; IC/BPS: interstitial cystitis/bladder pain syndrome; NUPP: non-urologic pelvic pain; Control/SUI: Asymptomatic subject/stress urinary incontinence).

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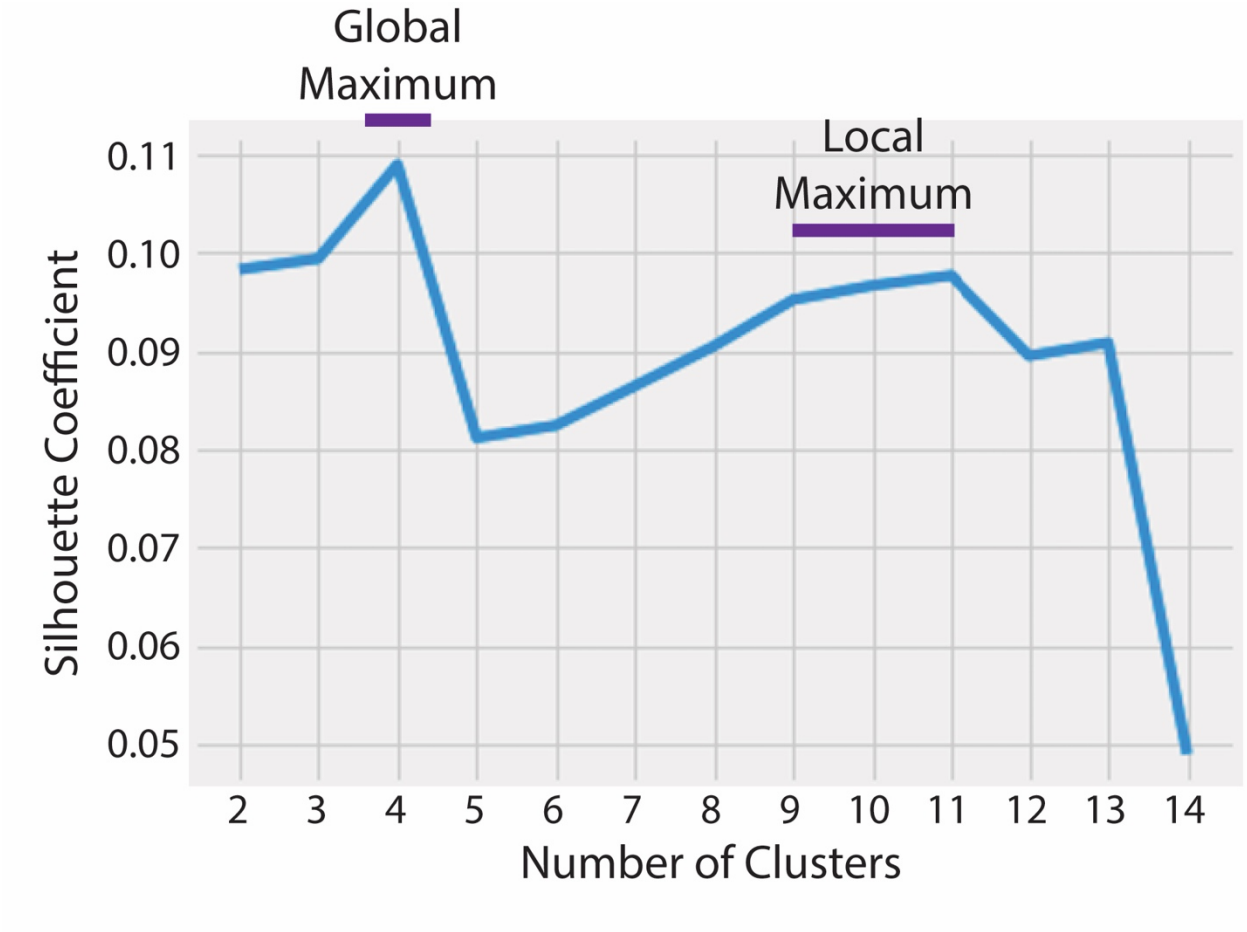


Figure 2: ***Optimal number of clusters for the hierarchical clustering by the silhouette method.*** The Silhouette score serves as a measure of the goodness of a clustering technique, encompassing both how similar each individual is to others in the same cluster (cohesion) compared to others in other distinct clusters (separation). Higher value scores indicate that each individual is well matched to their own cluster and poorly matched to neighboring clusters.

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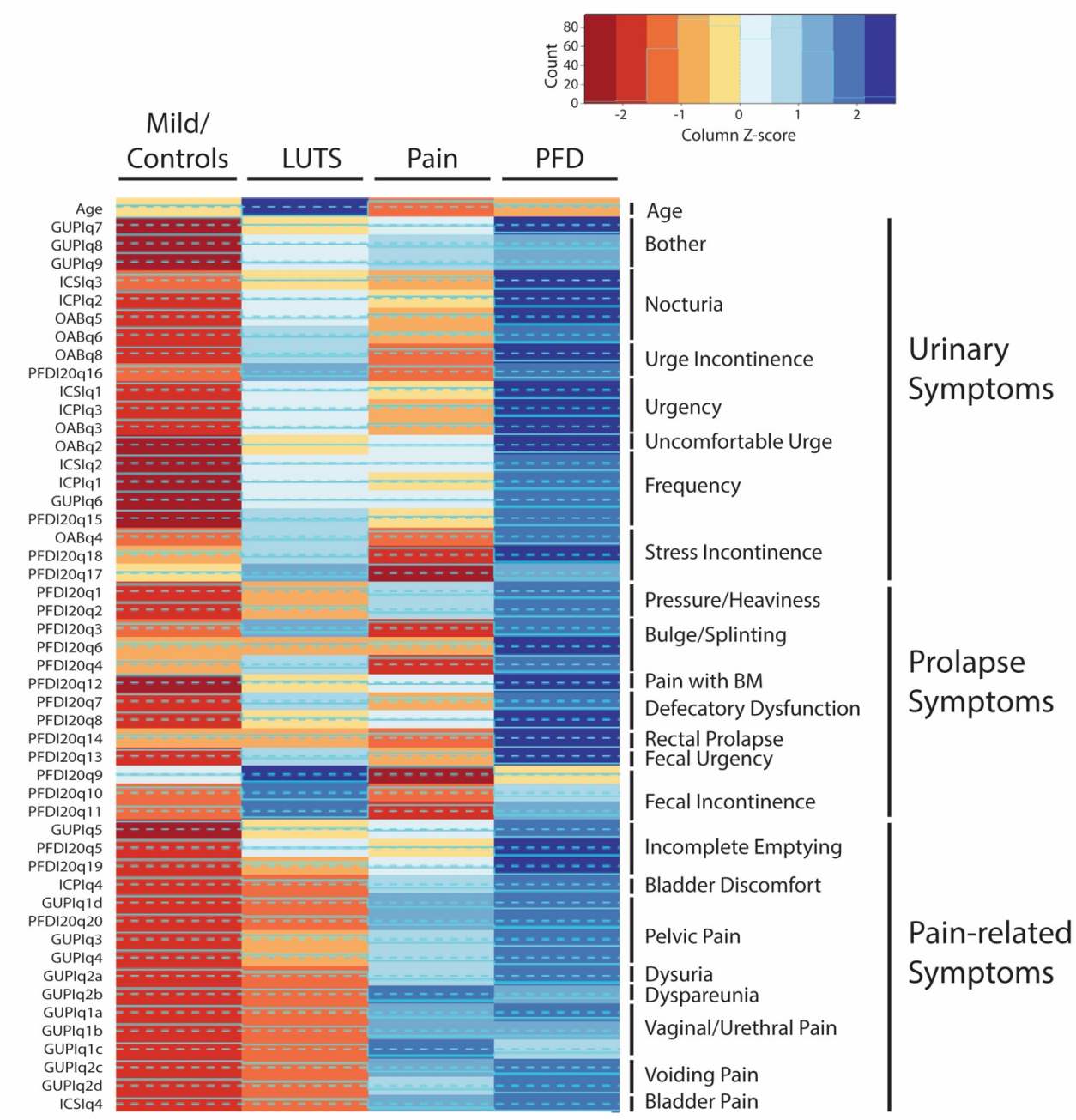


Figure 3. ***Heatmap of survey responses and patient characteristics for each of the machine learning generated clusters for the 4 major clusters.*** Specific symptomatic patterns for the 4 clusters (blue in Figure A), with deepening blues indicating scores increasingly elevated over the population mean and deeper shades of red indicating scores increasingly lower than the population mean. (*LUTS*: lower urinary tract symptoms; *PFD*: pelvic floor disorders; *Pain*: pelvic pain complaints; *Mild symptoms/controls*: patients with mild or minimal complaints).

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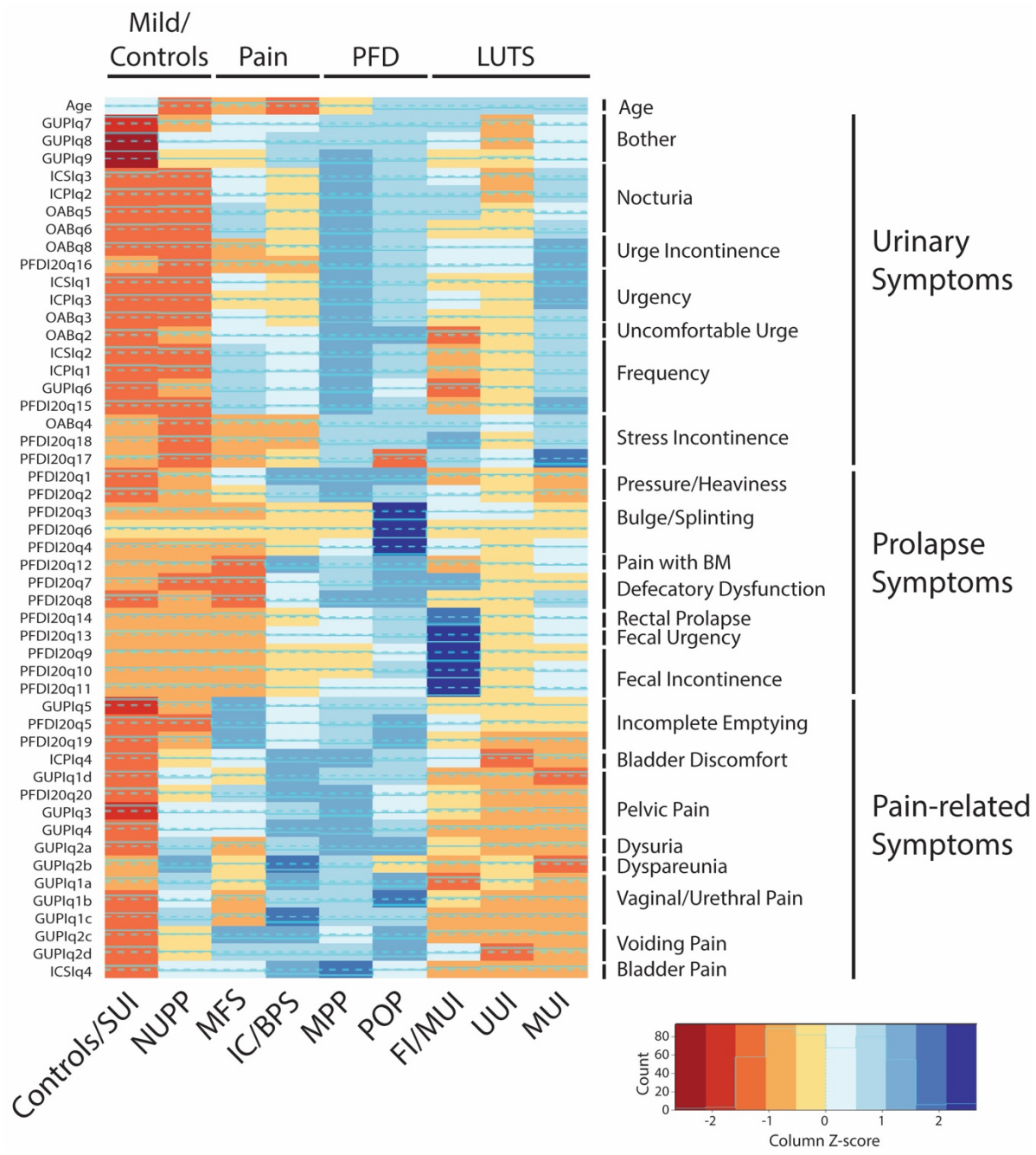


Figure 4: ***Heatmap of survey responses and patient characteristics for each of the machine learning generated clusters.*** Specific symptomatic patterns for the nine clusters shown in Figure A, with deepening blues indicating scores increasingly elevated over the population mean and deeper shades of red indicating scores increasingly lower than the population mean. (UUI: urgency urinary incontinence; FI/UUI: fecal incontinence/UUI; MUI: mixes urinary incontinence;' HT PFD: high-tone pelvic floor dysfuction; POP: pelvic organ prolapse; MPP: myofascial pelvic pain; IC/BPS: interstitial cystitis/bladder pain syndrome; NUPP: non-urologic pelvic pain; Control/SUI: Asymptomatic subject/stress urinary incontinence).

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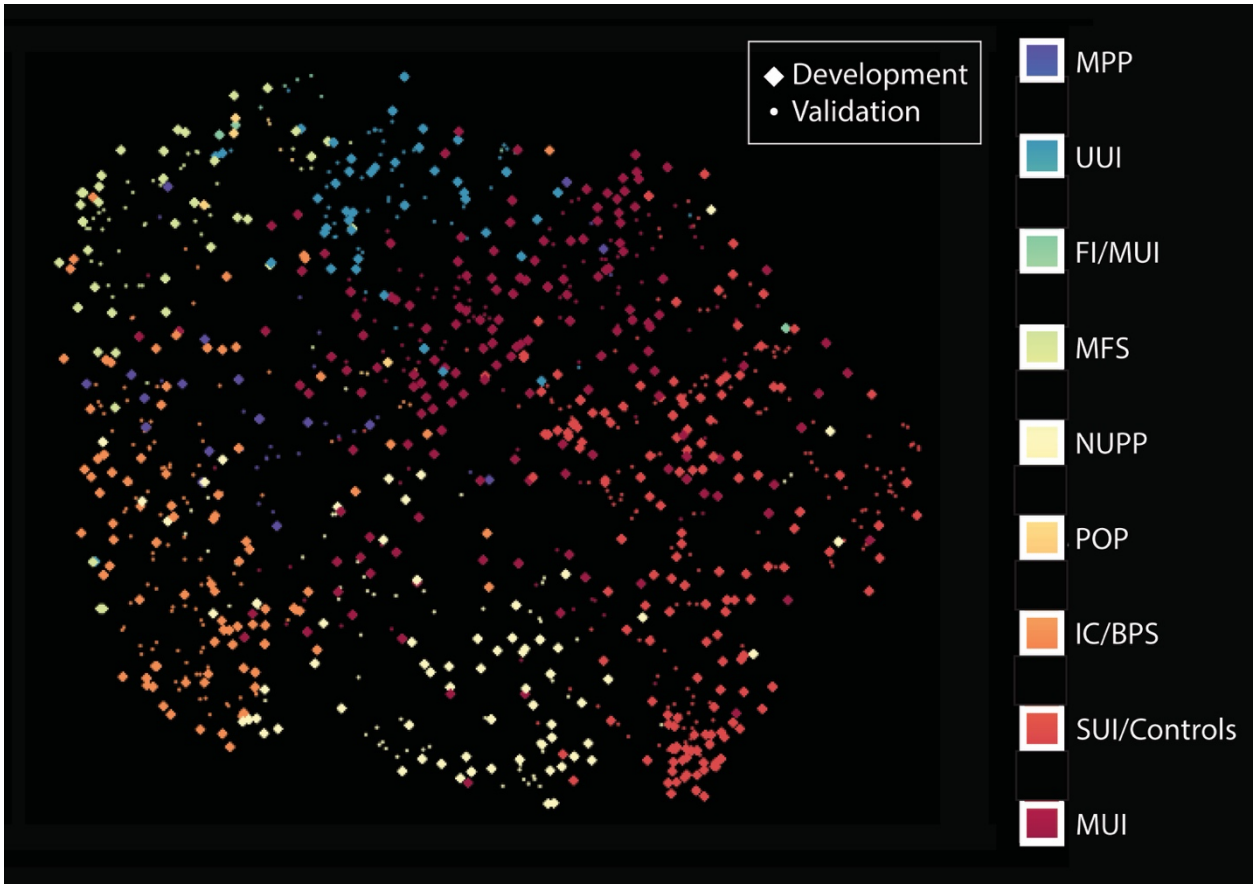


Figure 5: ***Uniform Manifold Approximation and Projection (UMAP) plot visualizing the overlap in clusters with respect to the symptomatic features between the development and validation populations.*** Good overlap was seen between the clusters in the development (larger diamonds) and validation (smaller circles) cohorts.

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Mean (SD)	Pain n = 173	PFD n = 46	LUTS n = 152	Mild Symptoms/ Controls n = 143	*p*	SMD
Age	54.38 (16.41)	57.10 (14.98)	65.37 (14.61)	57.47 (15.70)	<0.001	0.363
ICSI1	1.68 (1.44)	4.03 (1.27)	2.23 (1.64)	0.49 (0.69)	<0.001	1.537
ICSI2	3.02 (1.50)	4.43 (0.96)	3.09 (1.42)	1.50 (1.34)	<0.001	1.168
ICSI3	1.61 (1.19)	3.33 (1.19)	2.05 (1.35)	1.32 (1.19)	<0.001	0.885
ICSI4	2.04 (1.61)	2.55 (1.66)	0.44 (0.79)	0.27 (0.61)	<0.001	1.120
ICPI1	2.24 (1.25)	3.75 (0.51)	2.44 (1.22)	0.75 (0.99)	<0.001	1.627
ICPI2	1.78 (1.25)	3.46 (0.93)	2.23 (1.41)	0.88 (1.02)	<0.001	1.236
ICPI3	1.24 (1.14)	3.39 (0.69)	2.18 (1.33)	0.38 (0.69)	<0.001	1.862
ICPI4	2.67 (1.35)	3.41 (0.95)	0.90 (1.14)	0.28 (0.65)	<0.001	1.867
OABq2	3.51 (1.44)	5.35 (0.94)	3.37 (1.60)	1.54 (0.87)	<0.001	1.736
OABq3	2.37 (1.33)	5.11 (1.10)	3.40 (1.63)	1.35 (0.66)	<0.001	1.825
OABq4	1.85 (1.19)	3.96 (1.93)	3.27 (1.62)	1.81 (1.12)	<0.001	0.856
OABq5	2.85 (1.54)	4.86 (1.34)	3.61 (1.68)	1.91 (1.15)	<0.001	1.156
OABq6	3.11 (1.52)	4.90 (1.37)	3.85 (1.69)	2.06 (1.31)	<0.001	1.070
OABq8	1.73 (1.16)	4.25 (1.84)	3.16 (1.67)	1.31 (0.65)	<0.001	1.214
PFDI20 1	1.93 (1.19)	2.35 (1.26)	0.97 (1.10)	0.45 (0.54)	<0.001	1.083
PFDI20 2	1.49 (1.25)	1.90 (1.31)	0.82 (1.06)	0.38 (0.47)	<0.001	0.844
PFDI20 3	0.23 (0.45)	0.63 (0.94)	0.56 (1.06)	0.30 (0.37)	<0.001	0.327
PFDI20 4	0.41 (0.72)	0.82 (1.02)	0.69 (1.03)	0.52 (0.70)	0.003	0.270
PFDI20 5	1.37 (1.21)	2.18 (1.34)	1.44 (1.17)	0.70 (0.69)	<0.001	0.691
PFDI20 6	0.05 (0.12)	0.58 (1.18)	0.09 (0.26)	0.07 (0.17)	<0.001	0.368
PFDI20 7	0.73 (0.94)	1.28 (1.12)	1.01 (1.16)	0.50 (0.61)	<0.001	0.454
PFDI20 8	1.06 (1.04)	1.43 (1.22)	0.98 (1.05)	0.72 (0.70)	<0.001	0.364
PFDI20 9	0.09 (0.29)	0.20 (0.60)	0.31 (0.85)	0.20 (0.28)	0.007	0.208
PFDI20 10	0.30 (0.55)	0.56 (0.91)	0.66 (1.11)	0.30 (0.45)	<0.001	0.270
PFDI20 11	0.46 (0.75)	0.87 (1.00)	0.95 (1.19)	0.53 (0.55)	<0.001	0.333
PFDI20 12	0.35 (0.71)	0.51 (0.88)	0.29 (0.68)	0.13 (0.22)	0.001	0.311
PFDI20 13	0.61 (0.87)	1.09 (1.09)	0.86 (1.10)	0.49 (0.57)	<0.001	0.375
PFDI20 14	0.17 (0.51)	0.81 (1.70)	0.23 (0.61)	0.24 (0.47)	<0.001	0.281
PFDI20 15	1.93 (1.15)	2.86 (0.94)	2.32 (1.30)	1.27 (0.95)	<0.001	0.824
PFDI20 16	0.76 (0.89)	2.02 (1.43)	1.84 (1.28)	0.73 (0.68)	<0.001	0.740
PFDI20 17	0.97 (0.92)	1.55 (1.27)	1.48 (1.31)	1.29 (1.04)	<0.001	0.290
PFDI20 18	0.68 (0.78)	2.01 (1.39)	1.50 (1.36)	1.04 (0.94)	<0.001	0.651
PFDI20 19	1.02 (1.16)	1.51 (1.31)	0.67 (0.95)	0.44 (0.54)	<0.001	0.578
PFDI20 20	1.95 (1.33)	2.32 (1.19)	0.65 (0.96)	0.33 (0.39)	<0.001	1.214
fGUPI1a	0.47 (0.48)	0.50 (0.46)	0.14 (0.32)	0.06 (0.22)	<0.001	0.730
fGUPI1b	0.52 (0.48)	0.51 (0.47)	0.12 (0.28)	0.03 (0.13)	<0.001	0.874
fGUPI1c	0.57 (0.47)	0.44 (0.44)	0.09 (0.23)	0.03 (0.13)	<0.001	0.960
fGUPI1d	0.77 (0.40)	0.85 (0.31)	0.23 (0.39)	0.06 (0.21)	<0.001	1.505
fGUPI2a	0.55 (0.48)	0.72 (0.42)	0.16 (0.35)	0.02 (0.10)	<0.001	1.189
fGUPI2b	0.52 (0.46)	0.43 (0.41)	0.12 (0.29)	0.09 (0.27)	<0.001	0.717
fGUPI2c	0.55 (0.48)	0.67 (0.44)	0.13 (0.32)	0.02 (0.12)	<0.001	1.109
fGUPI2d	0.51 (0.47)	0.68 (0.44)	0.16 (0.34)	0.06 (0.22)	<0.001	0.984
fGUPI3	3.13 (1.27)	3.94 (1.14)	1.25 (1.32)	0.44 (0.70)	<0.001	1.904
fGUPI4	5.08 (2.38)	6.57 (1.97)	2.18 (2.50)	0.56 (1.14)	<0.001	1.802

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fGUPI5	2.34 (1.72)	3.59 (1.70)	1.90 (1.50)	0.55 (0.81)	<0.001	1.134
fGUPI6	2.88 (1.48)	4.11 (1.03)	2.85 (1.43)	1.22 (1.14)	<0.001	1.197
fGUPI7	1.30 (1.08)	2.26 (0.80)	1.18 (1.14)	0.18 (0.49)	<0.001	1.305
fGUPI8	2.41 (0.75)	2.67 (0.55)	2.05 (0.98)	0.55 (0.77)	<0.001	1.486
fGUPI9	4.69 (1.21)	5.34 (0.90)	4.33 (1.25)	2.01 (1.58)	<0.001	1.327

Table 1. ***Patient survey scores for subjects seeking care in a urogynecology clinic by*** **4-cluster machine learning diagnostic groups.** Means and standard deviations are reported for each group. *LUTS*: lower urinary tract symptoms; *PFD*: pelvic floor disorders; *Pain*: pelvic pain complaints; *Mild symptoms/controls*: patients with mild or minimal complaints. *SMD*: standard mean difference.

Mean (SD)	MUI n = 100	SUI/Control n = 143	IC/BPS n = 91	POP n = 6	NUPP n = 60	MPP n = 40	FI/MUI n = 7	UUI n = 45	MFS n = 22	*p*	SMD
Age	65.8 (15.1)	57.5 (15.7)	50.1 (15.5)	55.8 (15.8)	59.2 (16.1)	57.3 (15.1)	57.9 (11.4)	65.5 (13.9)	59.0 (17.0)	<0.001	0.361
ICSI1	1.77 (1.30)	0.49 (0.69)	1.97 (1.48)	3.18 (0.74)	1.05 (1.17)	4.16 (1.29)	1.43 (1.90)	3.38 (1.72)	2.21 (1.42)	<0.001	1.152
ICSI2	2.65 (1.34)	1.50 (1.34)	3.50 (1.28)	4.00 (0.89)	1.95 (1.37)	4.50 (0.96)	2.22 (0.91)	4.21 (0.99)	3.99 (0.99)	<0.001	1.163
ICSI3	1.76 (1.26)	1.32 (1.19)	1.96 (1.23)	2.75 (0.42)	0.91 (0.76)	3.41 (1.24)	2.29 (1.11)	2.66 (1.40)	2.02 (1.18)	<0.001	0.864
ICSI4	0.48 (0.86)	0.27 (0.61)	2.52 (1.76)	0.89 (0.45)	1.64 (1.18)	2.80 (1.64)	0.43 (0.79)	0.33 (0.60)	1.14 (1.34)	<0.001	0.961
ICPI1	2.07 (1.14)	0.75 (0.99)	2.57 (1.01)	3.05 (0.83)	1.45 (1.29)	3.85 (0.36)	1.47 (1.39)	3.40 (0.72)	3.05 (0.90)	<0.001	1.307
ICPI2	1.86 (1.39)	0.88 (1.02)	2.18 (1.12)	3.02 (0.87)	0.88 (0.84)	3.52 (0.93)	3.00 (1.15)	2.92 (1.19)	2.59 (1.30)	<0.001	1.053
ICPI3	1.74 (1.16)	0.38 (0.69)	1.48 (1.15)	2.96 (0.95)	0.69 (0.87)	3.45 (0.64)	1.97 (1.32)	3.18 (1.15)	1.71 (1.20)	<0.001	1.338
ICPI4	0.77 (1.04)	0.28 (0.65)	3.15 (1.13)	2.44 (0.89)	2.11 (1.28)	3.55 (0.88)	1.81 (1.51)	1.05 (1.24)	2.23 (1.68)	<0.001	1.218
OABq2	2.91 (1.45)	1.54 (0.87)	3.87 (1.27)	5.00 (0.89)	2.74 (1.45)	5.40 (0.94)	2.14 (1.57)	4.58 (1.21)	4.15 (1.23)	<0.001	1.373
OABq3	2.96 (1.48)	1.35 (0.66)	2.44 (1.40)	4.33 (1.63)	1.99 (1.07)	5.22 (0.97)	3.00 (1.91)	4.44 (1.44)	3.09 (1.41)	<0.001	1.198
OABq4	2.85 (1.46)	1.81 (1.12)	1.91 (1.30)	3.83 (2.14)	1.75 (1.00)	3.98 (1.93)	4.00 (1.83)	4.08 (1.61)	1.84 (1.27)	<0.001	0.798
OABq5	3.25 (1.68)	1.91 (1.15)	3.08 (1.50)	4.33 (1.86)	1.99 (1.13)	4.94 (1.25)	4.71 (1.25)	4.25 (1.50)	4.23 (1.38)	<0.001	0.972
OABq6	3.48 (1.73)	2.06 (1.31)	3.44 (1.41)	4.33 (1.37)	2.14 (1.12)	4.99 (1.37)	3.57 (1.81)	4.71 (1.24)	4.36 (1.43)	<0.001	0.892
OABq8	2.70 (1.54)	1.31 (0.65)	1.88 (1.33)	3.33 (2.25)	1.43 (0.66)	4.38 (1.76)	2.68 (1.48)	4.26 (1.49)	1.96 (1.35)	<0.001	0.967
PFDI20 1	0.94 (1.04)	0.45 (0.54)	2.31 (1.03)	2.50 (1.64)	1.42 (1.13)	2.33 (1.21)	1.14 (1.57)	1.00 (1.19)	1.73 (1.45)	<0.001	0.741
PFDI20 2	0.82 (0.97)	0.38 (0.47)	2.01 (1.13)	1.67 (1.97)	0.85 (1.05)	1.93 (1.21)	1.57 (1.62)	0.71 (1.15)	1.05 (1.25)	<0.001	0.602
PFDI20 3	0.68 (1.20)	0.30 (0.37)	0.34 (0.55)	1.92 (1.63)	0.16 (0.26)	0.43 (0.62)	0.71 (0.95)	0.29 (0.58)	0.02 (0.10)	<0.001	0.652
PFDI20 4	0.66 (0.99)	0.52 (0.70)	0.57 (0.85)	2.17 (1.83)	0.23 (0.41)	0.62 (0.66)	1.43 (1.51)	0.65 (1.04)	0.18 (0.66)	<0.001	0.579
PFDI20 5	1.35 (1.07)	0.70 (0.69)	1.32 (0.99)	2.83 (0.98)	0.72 (0.84)	2.09 (1.37)	2.14 (1.21)	1.53 (1.34)	3.29 (0.84)	<0.001	1.070
PFDI20 6	0.07 (0.20)	0.07 (0.17)	0.06 (0.12)	3.33 (0.82)	0.05 (0.14)	0.17 (0.44)	0.14 (0.38)	0.12 (0.36)	0.00 (0.00)	<0.001	1.410
PFDI20 7	0.96 (1.11)	0.50 (0.61)	0.87 (0.92)	1.86 (1.71)	0.49 (0.73)	1.19 (1.01)	2.00 (1.73)	0.96 (1.13)	0.82 (1.33)	<0.001	0.498
PFDI20 8	0.91 (1.04)	0.72 (0.70)	1.33 (1.01)	1.67 (1.63)	0.71 (0.82)	1.40 (1.17)	1.19 (1.68)	1.09 (0.99)	0.91 (1.38)	<0.001	0.333
PFDI20 9	0.05 (0.20)	0.20 (0.28)	0.14 (0.39)	0.73 (1.61)	0.06 (0.11)	0.12 (0.18)	3.57 (0.79)	0.35 (0.68)	0.00 (0.00)	<0.001	1.560
PFDI20 10	0.25 (0.59)	0.30 (0.45)	0.37 (0.57)	1.25 (1.94)	0.28 (0.54)	0.46 (0.63)	3.71 (0.76)	1.10 (1.16)	0.11 (0.43)	<0.001	1.366
PFDI20 11	0.80 (1.09)	0.53 (0.55)	0.49 (0.73)	1.00 (1.67)	0.46 (0.72)	0.85 (0.90)	2.38 (1.57)	1.07 (1.21)	0.38 (0.97)	<0.001	0.532
PFDI20 12	0.34 (0.78)	0.13 (0.22)	0.56 (0.89)	0.77 (1.60)	0.17 (0.37)	0.47 (0.74)	0.14 (0.38)	0.18 (0.44)	0.00 (0.00)	<0.001	0.427
PFDI20 13	0.75 (1.00)	0.49 (0.57)	0.80 (0.90)	1.42 (1.86)	0.37 (0.62)	1.04 (0.96)	2.57 (1.81)	0.83 (0.98)	0.50 (1.10)	<0.001	0.569
PFDI20 14	0.14 (0.39)	0.24 (0.47)	0.16 (0.34)	0.97 (1.07)	0.12 (0.28)	0.79 (1.79)	1.43 (1.62)	0.26 (0.58)	0.36 (1.18)	<0.001	0.492
PFDI20 15	2.01 (1.22)	1.27 (0.95)	2.21 (0.84)	3.25 (0.88)	1.15 (1.05)	2.81 (0.95)	1.43 (1.81)	3.16 (0.97)	2.86 (1.32)	<0.001	0.906
PFDI20 16	1.52 (1.16)	0.73 (0.68)	0.91 (0.91)	1.58 (1.86)	0.57 (0.66)	2.08 (1.37)	1.74 (1.37)	2.58 (1.27)	0.70 (1.26)	<0.001	0.711

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PFDI20 17	1.30 (1.28)	1.29 (1.04)	1.21 (0.93)	0.42 (1.02)	0.72 (0.79)	1.72 (1.23)	2.00 (1.91)	1.80 (1.21)	0.64 (0.95)	<0.001	0.567
PFDI20 18	1.20 (1.15)	1.04 (0.94)	0.79 (0.77)	2.25 (0.99)	0.61 (0.74)	1.97 (1.45)	2.89 (1.64)	1.95 (1.51)	0.45 (0.86)	<0.001	0.870
PFDI20 19	0.65 (0.90)	0.44 (0.54)	0.95 (0.92)	2.75 (0.76)	0.42 (0.62)	1.33 (1.28)	1.00 (1.41)	0.68 (1.00)	2.95 (1.17)	<0.001	1.106
PFDI20 20	0.69 (0.96)	0.33 (0.39)	2.34 (1.13)	1.92 (1.56)	1.40 (1.27)	2.38 (1.13)	1.00 (1.53)	0.50 (0.85)	1.84 (1.70)	<0.001	0.836
fGUPI1a	0.21 (0.37)	0.06 (0.22)	0.52 (0.48)	0.61 (0.44)	0.51 (0.48)	0.48 (0.47)	0.03 (0.07)	0.01 (0.06)	0.16 (0.35)	<0.001	0.810
fGUPI1b	0.15 (0.31)	0.03 (0.13)	0.58 (0.47)	0.61 (0.44)	0.55 (0.48)	0.49 (0.48)	0.17 (0.37)	0.04 (0.16)	0.16 (0.35)	<0.001	0.774
fGUPI1c	0.11 (0.26)	0.03 (0.13)	0.72 (0.43)	0.44 (0.46)	0.50 (0.47)	0.44 (0.45)	0.07 (0.11)	0.04 (0.16)	0.14 (0.30)	<0.001	0.857
fGUPI1d	0.28 (0.42)	0.06 (0.21)	0.92 (0.25)	0.66 (0.41)	0.70 (0.42)	0.87 (0.29)	0.14 (0.38)	0.12 (0.30)	0.30 (0.45)	<0.001	1.207
fGUPI2a	0.18 (0.36)	0.02 (0.10)	0.71 (0.44)	0.57 (0.50)	0.43 (0.48)	0.75 (0.41)	0.29 (0.49)	0.10 (0.29)	0.18 (0.35)	<0.001	0.842
fGUPI2b	0.15 (0.31)	0.09 (0.27)	0.65 (0.44)	0.32 (0.40)	0.43 (0.46)	0.45 (0.41)	0.14 (0.38)	0.06 (0.21)	0.24 (0.38)	<0.001	0.619
fGUPI2c	0.08 (0.24)	0.02 (0.12)	0.76 (0.42)	0.55 (0.50)	0.25 (0.41)	0.68 (0.43)	0.14 (0.38)	0.23 (0.42)	0.52 (0.49)	<0.001	0.854
fGUPI2d	0.14 (0.31)	0.06 (0.22)	0.64 (0.46)	0.73 (0.44)	0.37 (0.45)	0.67 (0.44)	0.43 (0.53)	0.17 (0.37)	0.37 (0.45)	<0.001	0.731
fGUPI3	1.34 (1.33)	0.44 (0.70)	3.39 (1.16)	2.79 (0.98)	2.91 (1.25)	4.11 (1.07)	1.49 (1.80)	1.01 (1.21)	2.69 (1.53)	<0.001	1.250
fGUPI4	2.47 (2.67)	0.56 (1.14)	5.80 (1.93)	4.52 (2.07)	4.56 (2.54)	6.88 (1.79)	2.14 (2.85)	1.55 (1.93)	3.48 (2.55)	<0.001	1.220
fGUPI5	1.95 (1.46)	0.55 (0.81)	2.64 (1.66)	3.41 (1.57)	1.33 (1.36)	3.62 (1.74)	2.00 (1.63)	1.77 (1.59)	3.82 (1.26)	<0.001	0.950
fGUPI6	2.40 (1.25)	1.22 (1.14)	3.48 (1.18)	3.01 (1.21)	1.62 (1.23)	4.28 (0.91)	1.71 (1.38)	4.04 (1.04)	3.79 (0.94)	<0.001	1.208
fGUPI7	0.83 (0.91)	0.18 (0.49)	1.45 (1.05)	2.02 (1.25)	1.11 (1.13)	2.29 (0.72)	2.14 (1.46)	1.82 (1.19)	1.24 (0.97)	<0.001	0.860
fGUPI8	1.88 (0.94)	0.55 (0.77)	2.49 (0.67)	2.55 (0.50)	2.25 (0.84)	2.69 (0.56)	2.43 (1.13)	2.35 (0.98)	2.47 (0.77)	<0.001	0.793
fGUPI9	3.99 (1.20)	2.01 (1.58)	4.91 (1.07)	4.93 (1.11)	4.35 (1.43)	5.40 (0.86)	4.43 (1.62)	5.06 (0.96)	4.68 (0.88)	<0.001	0.812

Table 2. ***Group symptom means and differences for 9 symptom subclusters of subjects seeking care in a urogynecology clinic***. Groups means and standard deviations are reported for each group. MUI: mixes urinary incontinence; Control/SUI: Asymptomatic subject/stress urinary incontinence; IC/BPS: interstitial cystitis/bladder pain syndrome; POP: pelvic organ prolapse; NUPP: non-urologic pelvic pain; MPP: myofascial pelvic pain; FI/MUI: fecal incontinence/mixed urinary incontinence; UUI: urgency urinary incontinence; MFS: myofascial frequency syndrome. SMD: Standard mean difference.

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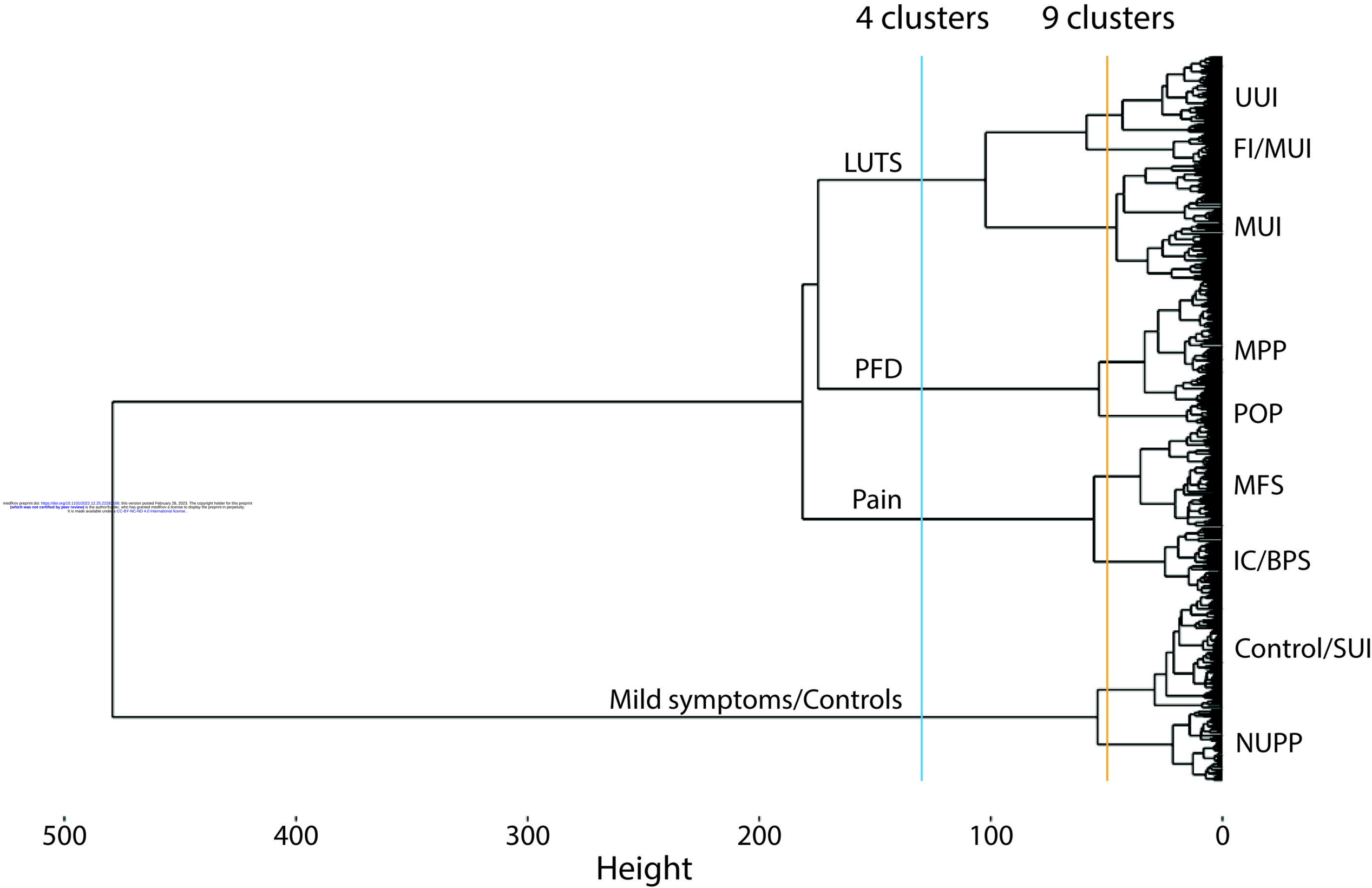
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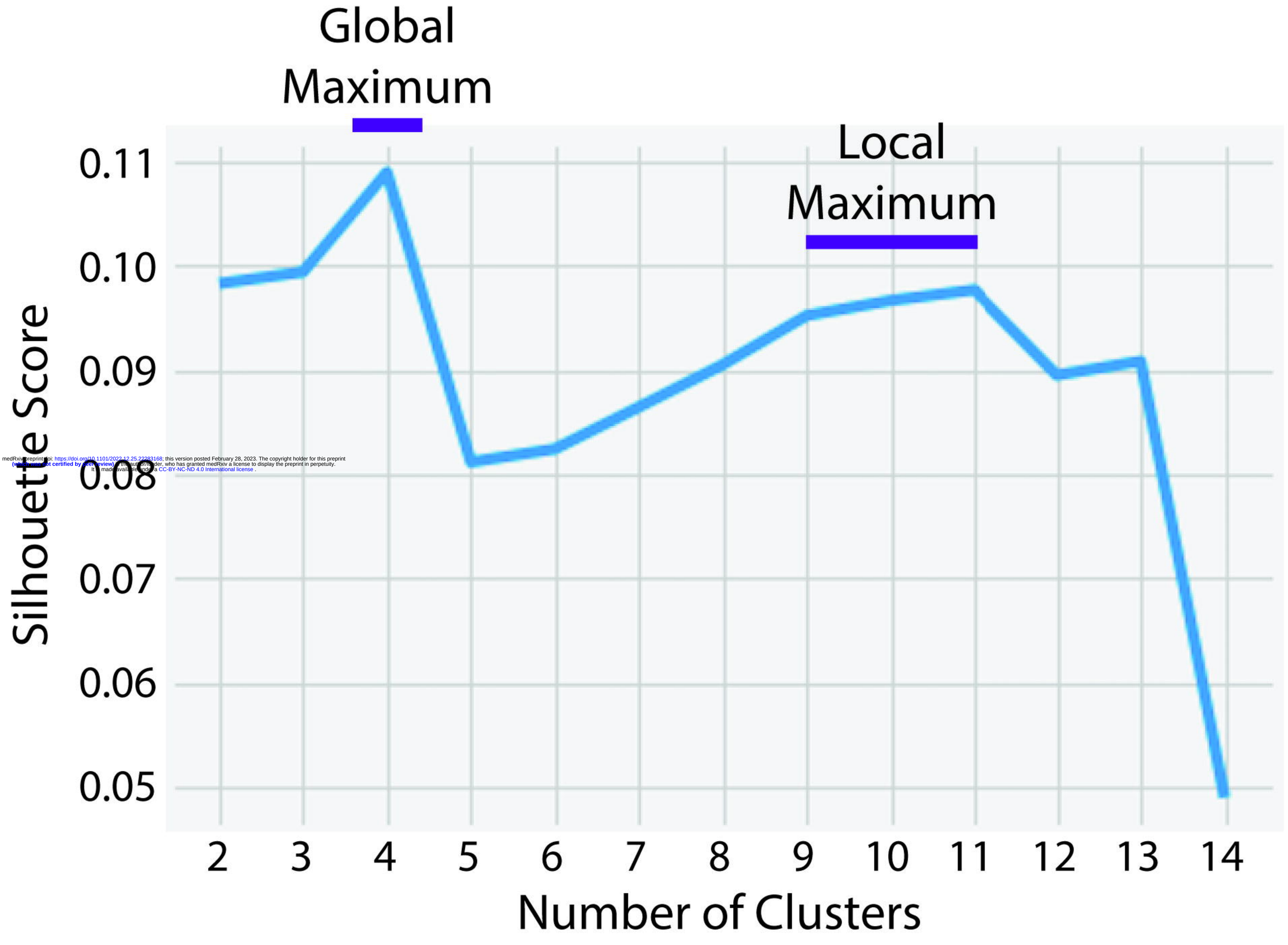
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Mild/
Controls | Pain | PFD | LUTS

Age
GUPIq7
GUPIq8
GUPIq9
ICSIq3
ICPIq2
OABq5
OABq6
OABq8
PFDI20q16
ICSIq1
ICPIq3
OABq3
OABq2
ICSIq2
ICPIq1
GUPIq6
PFDI20q15
OABq4
PFDI20q18
PFDI20q17
PFDI20q1
PFDI20q2
PFDI20q3
PFDI20q6
PFDI20q4
PFDI20q12
PFDI20q7
PFDI20q8
PFDI20q14
PFDI20q13
PFDI20q9
PFDI20q10
PFDI20q11
GUPIq5
PFDI20q5
PFDI20q19
ICPIq4
GUPIq1d
PFDI20q20
GUPIq3
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ICSIq4

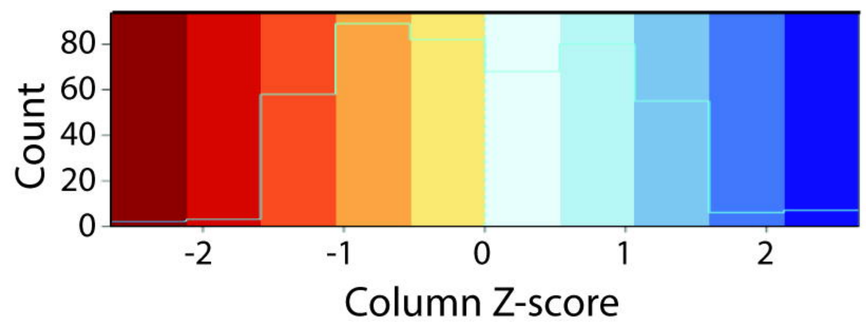
Controls/SUI
NUPP
MFS
IC/BPS
MPP
POP
FI/MUI
UUI
MUI

Age
Bother
Nocturia
Urge Incontinence
Urgency
Uncomfortable Urge
Frequency
Stress Incontinence
Pressure/Heaviness
Bulge/Splinting
Pain with BM
Defecatory Dysfunction
Rectal Prolapse
Fecal Urgency
Fecal Incontinence
Incomplete Emptying
Bladder Discomfort
Pelvic Pain
Dysuria
Dyspareunia
Vaginal/Urethral Pain
Voiding Pain
Bladder Pain

Urinary Symptoms
Prolapse Symptoms
Pain-related Symptoms

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Count
80
60
40
20
0
-2
-1
0
1
2
Column Z-score



Mild/ Controls

LUTS

Pain

PFD

Age
GUPIq7
GUPIq8
GUPIq9
ICSIq3
ICPIq2
OABq5
OABq6
OABq8
PFDI20q16
ICSIq1
ICPIq3
OABq3
OABq2
ICSIq2
ICPIq1
GUPIq6
PFDI20q15
OABq4
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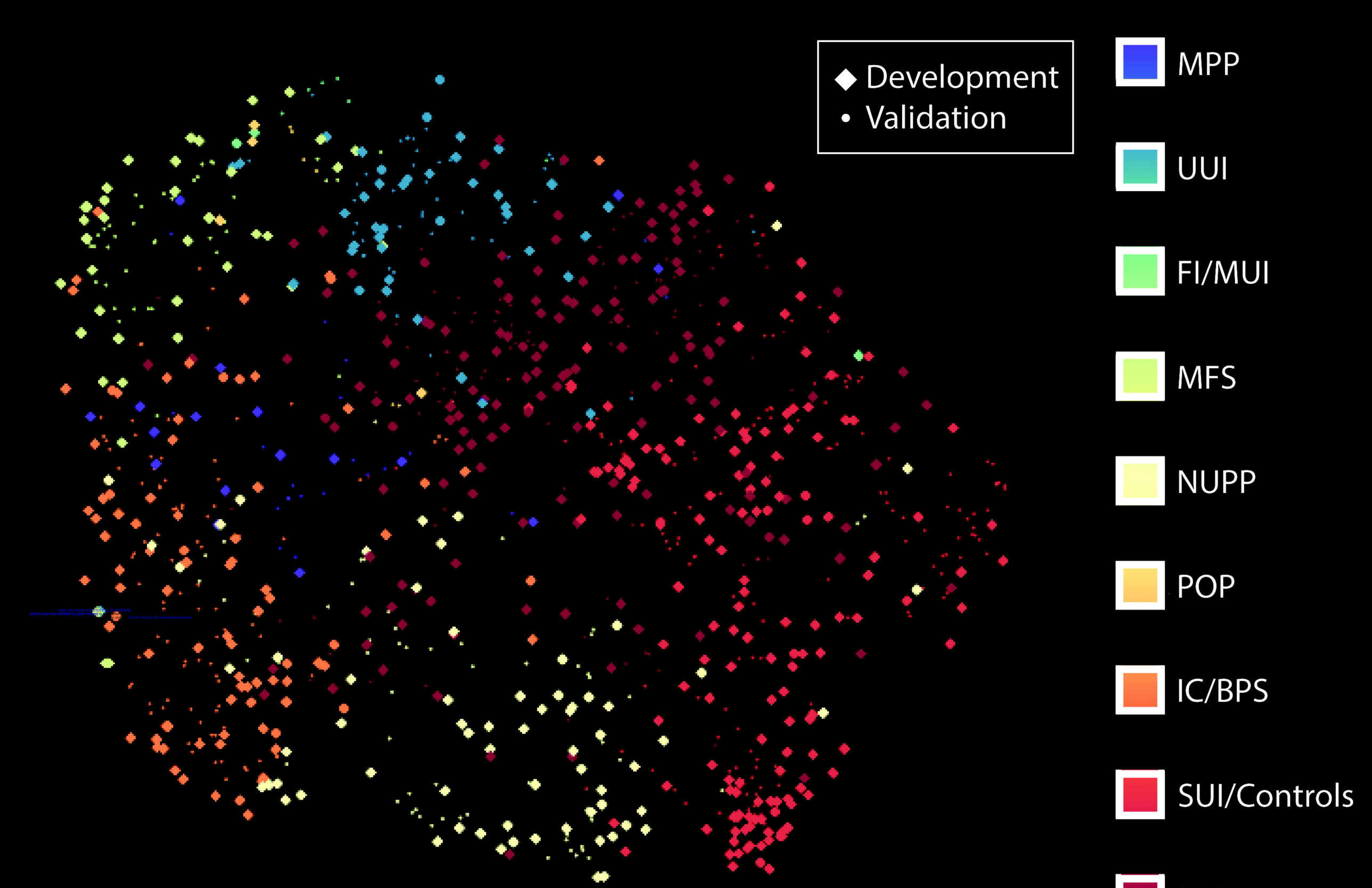
Age
Bother
Nocturia
Urge Incontinence
Urgency
Uncomfortable Urge
Frequency
Stress Incontinence
Pressure/Heaviness
Bulge/Splinting
Pain with BM
Defecatory Dysfunction
Rectal Prolapse
Fecal Urgency
Fecal Incontinence
Incomplete Emptying
Bladder Discomfort
Pelvic Pain
Dysuria
Dyspareunia
Vaginal/Urethral Pain
Voiding Pain
Bladder Pain

Urinary Symptoms

Prolapse Symptoms

Pain-related Symptoms

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Mean (SD)	Pain n = 173	PFD n = 46	LUTS n = 152	Mild Symptoms/ Controls n = 143	*p*	SMD
Age	54.38 (16.41)	57.10 (14.98)	65.37 (14.61)	57.47 (15.70)	<0.001	0.363
ICSI1	1.68 (1.44)	4.03 (1.27)	2.23 (1.64)	0.49 (0.69)	<0.001	1.537
ICSI2	3.02 (1.50)	4.43 (0.96)	3.09 (1.42)	1.50 (1.34)	<0.001	1.168
ICSI3	1.61 (1.19)	3.33 (1.19)	2.05 (1.35)	1.32 (1.19)	<0.001	0.885
ICSI4	2.04 (1.61)	2.55 (1.66)	0.44 (0.79)	0.27 (0.61)	<0.001	1.120
ICPI1	2.24 (1.25)	3.75 (0.51)	2.44 (1.22)	0.75 (0.99)	<0.001	1.627
ICPI2	1.78 (1.25)	3.46 (0.93)	2.23 (1.41)	0.88 (1.02)	<0.001	1.236
ICPI3	1.24 (1.14)	3.39 (0.69)	2.18 (1.33)	0.38 (0.69)	<0.001	1.862
ICPI4	2.67 (1.35)	3.41 (0.95)	0.90 (1.14)	0.28 (0.65)	<0.001	1.867
OABq2	3.51 (1.44)	5.35 (0.94)	3.37 (1.60)	1.54 (0.87)	<0.001	1.736
OABq3	2.37 (1.33)	5.11 (1.10)	3.40 (1.63)	1.35 (0.66)	<0.001	1.825
OABq4	1.85 (1.19)	3.96 (1.93)	3.27 (1.62)	1.81 (1.12)	<0.001	0.856
OABq5	2.85 (1.54)	4.86 (1.34)	3.61 (1.68)	1.91 (1.15)	<0.001	1.156
OABq6	3.11 (1.52)	4.90 (1.37)	3.85 (1.69)	2.06 (1.31)	<0.001	1.070
OABq8	1.73 (1.16)	4.25 (1.84)	3.16 (1.67)	1.31 (0.65)	<0.001	1.214
PFDI20 1	1.93 (1.19)	2.35 (1.26)	0.97 (1.10)	0.45 (0.54)	<0.001	1.083
PFDI20 2	1.49 (1.25)	1.90 (1.31)	0.82 (1.06)	0.38 (0.47)	<0.001	0.844
PFDI20 3	0.23 (0.45)	0.63 (0.94)	0.56 (1.06)	0.30 (0.37)	<0.001	0.327
PFDI20 4	0.41 (0.72)	0.82 (1.02)	0.69 (1.03)	0.52 (0.70)	0.003	0.270
PFDI20 5	1.37 (1.21)	2.18 (1.34)	1.44 (1.17)	0.70 (0.69)	<0.001	0.691
PFDI20 6	0.05 (0.12)	0.58 (1.18)	0.09 (0.26)	0.07 (0.17)	<0.001	0.368
PFDI20 7	0.73 (0.94)	1.28 (1.12)	1.01 (1.16)	0.50 (0.61)	<0.001	0.454
PFDI20 8	1.06 (1.04)	1.43 (1.22)	0.98 (1.05)	0.72 (0.70)	<0.001	0.364
PFDI20 9	0.09 (0.29)	0.20 (0.60)	0.31 (0.85)	0.20 (0.28)	0.007	0.208
PFDI20 10	0.30 (0.55)	0.56 (0.91)	0.66 (1.11)	0.30 (0.45)	<0.001	0.270
PFDI20 11	0.46 (0.75)	0.87 (1.00)	0.95 (1.19)	0.53 (0.55)	<0.001	0.333
PFDI20 12	0.35 (0.71)	0.51 (0.88)	0.29 (0.68)	0.13 (0.22)	0.001	0.311
PFDI20 13	0.61 (0.87)	1.09 (1.09)	0.86 (1.10)	0.49 (0.57)	<0.001	0.375
PFDI20 14	0.17 (0.51)	0.81 (1.70)	0.23 (0.61)	0.24 (0.47)	<0.001	0.281
PFDI20 15	1.93 (1.15)	2.86 (0.94)	2.32 (1.30)	1.27 (0.95)	<0.001	0.824
PFDI20 16	0.76 (0.89)	2.02 (1.43)	1.84 (1.28)	0.73 (0.68)	<0.001	0.740
PFDI20 17	0.97 (0.92)	1.55 (1.27)	1.48 (1.31)	1.29 (1.04)	<0.001	0.290
PFDI20 18	0.68 (0.78)	2.01 (1.39)	1.50 (1.36)	1.04 (0.94)	<0.001	0.651
PFDI20 19	1.02 (1.16)	1.51 (1.31)	0.67 (0.95)	0.44 (0.54)	<0.001	0.578
PFDI20 20	1.95 (1.33)	2.32 (1.19)	0.65 (0.96)	0.33 (0.39)	<0.001	1.214
fGUPI1a	0.47 (0.48)	0.50 (0.46)	0.14 (0.32)	0.06 (0.22)	<0.001	0.730
fGUPI1b	0.52 (0.48)	0.51 (0.47)	0.12 (0.28)	0.03 (0.13)	<0.001	0.874
fGUPI1c	0.57 (0.47)	0.44 (0.44)	0.09 (0.23)	0.03 (0.13)	<0.001	0.960
fGUPI1d	0.77 (0.40)	0.85 (0.31)	0.23 (0.39)	0.06 (0.21)	<0.001	1.505
fGUPI2a	0.55 (0.48)	0.72 (0.42)	0.16 (0.35)	0.02 (0.10)	<0.001	1.189
fGUPI2b	0.52 (0.46)	0.43 (0.41)	0.12 (0.29)	0.09 (0.27)	<0.001	0.717
fGUPI2c	0.55 (0.48)	0.67 (0.44)	0.13 (0.32)	0.02 (0.12)	<0.001	1.109
fGUPI2d	0.51 (0.47)	0.68 (0.44)	0.16 (0.34)	0.06 (0.22)	<0.001	0.984
fGUPI3	3.13 (1.27)	3.94 (1.14)	1.25 (1.32)	0.44 (0.70)	<0.001	1.904
fGUPI4	5.08 (2.38)	6.57 (1.97)	2.18 (2.50)	0.56 (1.14)	<0.001	1.802

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fGUPI5	2.34 (1.72)	3.59 (1.70)	1.90 (1.50)	0.55 (0.81)	<0.001	1.134
fGUPI6	2.88 (1.48)	4.11 (1.03)	2.85 (1.43)	1.22 (1.14)	<0.001	1.197
fGUPI7	1.30 (1.08)	2.26 (0.80)	1.18 (1.14)	0.18 (0.49)	<0.001	1.305
fGUPI8	2.41 (0.75)	2.67 (0.55)	2.05 (0.98)	0.55 (0.77)	<0.001	1.486
fGUPI9	4.69 (1.21)	5.34 (0.90)	4.33 (1.25)	2.01 (1.58)	<0.001	1.327

Table 1. *Patient survey scores for subjects seeking care in a urogynecology clinic by* 4-cluster machine learning diagnostic groups. Means and standard deviations are reported for each group. *LUTS*: lower urinary tract symptoms; *PFD*: pelvic floor disorders; *Pain*: pelvic pain complaints; *Mild symptoms/controls*: patients with mild or minimal complaints. *SMD*: standard mean difference.

Mean (SD)	MUI n = 100	SUI/Control n = 143	IC/BPS n = 91	POP n = 6	NUPP n = 60	MPP n = 40	FI/MUI n = 7	UUI n = 45	MFS n = 22	*p*	SMD
Age	65.8 (15.1)	57.5 (15.7)	50.1 (15.5)	55.8 (15.8)	59.2 (16.1)	57.3 (15.1)	57.9 (11.4)	65.5 (13.9)	59.0 (17.0)	<0.001	0.361
ICSI1	1.77 (1.30)	0.49 (0.69)	1.97 (1.48)	3.18 (0.74)	1.05 (1.17)	4.16 (1.29)	1.43 (1.90)	3.38 (1.72)	2.21 (1.42)	<0.001	1.152
ICSI2	2.65 (1.34)	1.50 (1.34)	3.50 (1.28)	4.00 (0.89)	1.95 (1.37)	4.50 (0.96)	2.22 (0.91)	4.21 (0.99)	3.99 (0.99)	<0.001	1.163
ICSI3	1.76 (1.26)	1.32 (1.19)	1.96 (1.23)	2.75 (0.42)	0.91 (0.76)	3.41 (1.24)	2.29 (1.11)	2.66 (1.40)	2.02 (1.18)	<0.001	0.864
ICSI4	0.48 (0.86)	0.27 (0.61)	2.52 (1.76)	0.89 (0.45)	1.64 (1.18)	2.80 (1.64)	0.43 (0.79)	0.33 (0.60)	1.14 (1.34)	<0.001	0.961
ICPI1	2.07 (1.14)	0.75 (0.99)	2.57 (1.01)	3.05 (0.83)	1.45 (1.29)	3.85 (0.36)	1.47 (1.39)	3.40 (0.72)	3.05 (0.90)	<0.001	1.307
ICPI2	1.86 (1.39)	0.88 (1.02)	2.18 (1.12)	3.02 (0.87)	0.88 (0.84)	3.52 (0.93)	3.00 (1.15)	2.92 (1.19)	2.59 (1.30)	<0.001	1.053
ICPI3	1.74 (1.16)	0.38 (0.69)	1.48 (1.15)	2.96 (0.95)	0.69 (0.87)	3.45 (0.64)	1.97 (1.32)	3.18 (1.15)	1.71 (1.20)	<0.001	1.338
ICPI4	0.77 (1.04)	0.28 (0.65)	3.15 (1.13)	2.44 (0.89)	2.11 (1.28)	3.55 (0.88)	1.81 (1.51)	1.05 (1.24)	2.23 (1.68)	<0.001	1.218
OABq2	2.91 (1.45)	1.54 (0.87)	3.87 (1.27)	5.00 (0.89)	2.74 (1.45)	5.40 (0.94)	2.14 (1.57)	4.58 (1.21)	4.15 (1.23)	<0.001	1.373
OABq3	2.96 (1.48)	1.35 (0.66)	2.44 (1.40)	4.33 (1.63)	1.99 (1.07)	5.22 (0.97)	3.00 (1.91)	4.44 (1.44)	3.09 (1.41)	<0.001	1.198
OABq4	2.85 (1.46)	1.81 (1.12)	1.91 (1.30)	3.83 (2.14)	1.75 (1.00)	3.98 (1.93)	4.00 (1.83)	4.08 (1.61)	1.84 (1.27)	<0.001	0.798
OABq5	3.25 (1.68)	1.91 (1.15)	3.08 (1.50)	4.33 (1.86)	1.99 (1.13)	4.94 (1.25)	4.71 (1.25)	4.25 (1.50)	4.23 (1.38)	<0.001	0.972
OABq6	3.48 (1.73)	2.06 (1.31)	3.44 (1.41)	4.33 (1.37)	2.14 (1.12)	4.99 (1.37)	3.57 (1.81)	4.71 (1.24)	4.36 (1.43)	<0.001	0.892
OABq8	2.70 (1.54)	1.31 (0.65)	1.88 (1.33)	3.33 (2.25)	1.43 (0.66)	4.38 (1.76)	2.68 (1.48)	4.26 (1.49)	1.96 (1.35)	<0.001	0.967
PFDI20 1	0.94 (1.04)	0.45 (0.54)	2.31 (1.03)	2.50 (1.64)	1.42 (1.13)	2.33 (1.21)	1.14 (1.57)	1.00 (1.19)	1.73 (1.45)	<0.001	0.741
PFDI20 2	0.82 (0.97)	0.38 (0.47)	2.01 (1.13)	1.67 (1.97)	0.85 (1.05)	1.93 (1.21)	1.57 (1.62)	0.71 (1.15)	1.05 (1.25)	<0.001	0.602
PFDI20 3	0.68 (1.20)	0.30 (0.37)	0.34 (0.55)	1.92 (1.63)	0.16 (0.26)	0.43 (0.62)	0.71 (0.95)	0.29 (0.58)	0.02 (0.10)	<0.001	0.652
PFDI20 4	0.66 (0.99)	0.52 (0.70)	0.57 (0.85)	2.17 (1.83)	0.23 (0.41)	0.62 (0.66)	1.43 (1.51)	0.65 (1.04)	0.18 (0.66)	<0.001	0.579
PFDI20 5	1.35 (1.07)	0.70 (0.69)	1.32 (0.99)	2.83 (0.98)	0.72 (0.84)	2.09 (1.37)	2.14 (1.21)	1.53 (1.34)	3.29 (0.84)	<0.001	1.070
PFDI20 6	0.07 (0.20)	0.07 (0.17)	0.06 (0.12)	3.33 (0.82)	0.05 (0.14)	0.17 (0.44)	0.14 (0.38)	0.12 (0.36)	0.00 (0.00)	<0.001	1.410
PFDI20 7	0.96 (1.11)	0.50 (0.61)	0.87 (0.92)	1.86 (1.71)	0.49 (0.73)	1.19 (1.01)	2.00 (1.73)	0.96 (1.13)	0.82 (1.33)	<0.001	0.498
PFDI20 8	0.91 (1.04)	0.72 (0.70)	1.33 (1.01)	1.67 (1.63)	0.71 (0.82)	1.40 (1.17)	1.19 (1.68)	1.09 (0.99)	0.91 (1.38)	<0.001	0.333
PFDI20 9	0.05 (0.20)	0.20 (0.28)	0.14 (0.39)	0.73 (1.61)	0.06 (0.11)	0.12 (0.18)	3.57 (0.79)	0.35 (0.68)	0.00 (0.00)	<0.001	1.560
PFDI20 10	0.25 (0.59)	0.30 (0.45)	0.37 (0.57)	1.25 (1.94)	0.28 (0.54)	0.46 (0.63)	3.71 (0.76)	1.10 (1.16)	0.11 (0.43)	<0.001	1.366
PFDI20 11	0.80 (1.09)	0.53 (0.55)	0.49 (0.73)	1.00 (1.67)	0.46 (0.72)	0.85 (0.90)	2.38 (1.57)	1.07 (1.21)	0.38 (0.97)	<0.001	0.532
PFDI20 12	0.34 (0.78)	0.13 (0.22)	0.56 (0.89)	0.77 (1.60)	0.17 (0.37)	0.47 (0.74)	0.14 (0.38)	0.18 (0.44)	0.00 (0.00)	<0.001	0.427
PFDI20 13	0.75 (1.00)	0.49 (0.57)	0.80 (0.90)	1.42 (1.86)	0.37 (0.62)	1.04 (0.96)	2.57 (1.81)	0.83 (0.98)	0.50 (1.10)	<0.001	0.569
PFDI20 14	0.14 (0.39)	0.24 (0.47)	0.16 (0.34)	0.97 (1.07)	0.12 (0.28)	0.79 (1.79)	1.43 (1.62)	0.26 (0.58)	0.36 (1.18)	<0.001	0.492
PFDI20 15	2.01 (1.22)	1.27 (0.95)	2.21 (0.84)	3.25 (0.88)	1.15 (1.05)	2.81 (0.95)	1.43 (1.81)	3.16 (0.97)	2.86 (1.32)	<0.001	0.906
PFDI20 16	1.52 (1.16)	0.73 (0.68)	0.91 (0.91)	1.58 (1.86)	0.57 (0.66)	2.08 (1.37)	1.74 (1.37)	2.58 (1.27)	0.70 (1.26)	<0.001	0.711

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PFDI20 17	1.30 (1.28)	1.29 (1.04)	1.21 (0.93)	0.42 (1.02)	0.72 (0.79)	1.72 (1.23)	2.00 (1.91)	1.80 (1.21)	0.64 (0.95)	<0.001	0.567
PFDI20 18	1.20 (1.15)	1.04 (0.94)	0.79 (0.77)	2.25 (0.99)	0.61 (0.74)	1.97 (1.45)	2.89 (1.64)	1.95 (1.51)	0.45 (0.86)	<0.001	0.870
PFDI20 19	0.65 (0.90)	0.44 (0.54)	0.95 (0.92)	2.75 (0.76)	0.42 (0.62)	1.33 (1.28)	1.00 (1.41)	0.68 (1.00)	2.95 (1.17)	<0.001	1.106
PFDI20 20	0.69 (0.96)	0.33 (0.39)	2.34 (1.13)	1.92 (1.56)	1.40 (1.27)	2.38 (1.13)	1.00 (1.53)	0.50 (0.85)	1.84 (1.70)	<0.001	0.836
fGUPI1a	0.21 (0.37)	0.06 (0.22)	0.52 (0.48)	0.61 (0.44)	0.51 (0.48)	0.48 (0.47)	0.03 (0.07)	0.01 (0.06)	0.16 (0.35)	<0.001	0.810
fGUPI1b	0.15 (0.31)	0.03 (0.13)	0.58 (0.47)	0.61 (0.44)	0.55 (0.48)	0.49 (0.48)	0.17 (0.37)	0.04 (0.16)	0.16 (0.35)	<0.001	0.774
fGUPI1c	0.11 (0.26)	0.03 (0.13)	0.72 (0.43)	0.44 (0.46)	0.50 (0.47)	0.44 (0.45)	0.07 (0.11)	0.04 (0.16)	0.14 (0.30)	<0.001	0.857
fGUPI1d	0.28 (0.42)	0.06 (0.21)	0.92 (0.25)	0.66 (0.41)	0.70 (0.42)	0.87 (0.29)	0.14 (0.38)	0.12 (0.30)	0.30 (0.45)	<0.001	1.207
fGUPI2a	0.18 (0.36)	0.02 (0.10)	0.71 (0.44)	0.57 (0.50)	0.43 (0.48)	0.75 (0.41)	0.29 (0.49)	0.10 (0.29)	0.18 (0.35)	<0.001	0.842
fGUPI2b	0.15 (0.31)	0.09 (0.27)	0.65 (0.44)	0.32 (0.40)	0.43 (0.46)	0.45 (0.41)	0.14 (0.38)	0.06 (0.21)	0.24 (0.38)	<0.001	0.619
fGUPI2c	0.08 (0.24)	0.02 (0.12)	0.76 (0.42)	0.55 (0.50)	0.25 (0.41)	0.68 (0.43)	0.14 (0.38)	0.23 (0.42)	0.52 (0.49)	<0.001	0.854
fGUPI2d	0.14 (0.31)	0.06 (0.22)	0.64 (0.46)	0.73 (0.44)	0.37 (0.45)	0.67 (0.44)	0.43 (0.53)	0.17 (0.37)	0.37 (0.45)	<0.001	0.731
fGUPI3	1.34 (1.33)	0.44 (0.70)	3.39 (1.16)	2.79 (0.98)	2.91 (1.25)	4.11 (1.07)	1.49 (1.80)	1.01 (1.21)	2.69 (1.53)	<0.001	1.250
fGUPI4	2.47 (2.67)	0.56 (1.14)	5.80 (1.93)	4.52 (2.07)	4.56 (2.54)	6.88 (1.79)	2.14 (2.85)	1.55 (1.93)	3.48 (2.55)	<0.001	1.220
fGUPI5	1.95 (1.46)	0.55 (0.81)	2.64 (1.66)	3.41 (1.57)	1.33 (1.36)	3.62 (1.74)	2.00 (1.63)	1.77 (1.59)	3.82 (1.26)	<0.001	0.950
fGUPI6	2.40 (1.25)	1.22 (1.14)	3.48 (1.18)	3.01 (1.21)	1.62 (1.23)	4.28 (0.91)	1.71 (1.38)	4.04 (1.04)	3.79 (0.94)	<0.001	1.208
fGUPI7	0.83 (0.91)	0.18 (0.49)	1.45 (1.05)	2.02 (1.25)	1.11 (1.13)	2.29 (0.72)	2.14 (1.46)	1.82 (1.19)	1.24 (0.97)	<0.001	0.860
fGUPI8	1.88 (0.94)	0.55 (0.77)	2.49 (0.67)	2.55 (0.50)	2.25 (0.84)	2.69 (0.56)	2.43 (1.13)	2.35 (0.98)	2.47 (0.77)	<0.001	0.793
fGUPI9	3.99 (1.20)	2.01 (1.58)	4.91 (1.07)	4.93 (1.11)	4.35 (1.43)	5.40 (0.86)	4.43 (1.62)	5.06 (0.96)	4.68 (0.88)	<0.001	0.812

Table 2. ***Group symptom means and differences for 9 symptom subclusters of subjects seeking care in a urogynecology clinic***. Groups means and standard deviations are reported for each group. MUI: mixes urinary incontinence; Control/SUI: Asymptomatic subject/stress urinary incontinence; IC/BPS: interstitial cystitis/bladder pain syndrome; POP: pelvic organ prolapse; NUPP: non-urologic pelvic pain; MPP: myofascial pelvic pain; FI/MUI: fecal incontinence/mixed urinary incontinence; UUI: urgency urinary incontinence; MFS: myofascial frequency syndrome. SMD: Standard mean difference.

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