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Urologic chronic pelvic pain syndrome: insights from the MAPP Research Network

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Abstract | Urologic chronic pelvic pain syndrome (UCPPS), which encompasses interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome, is characterized by chronic pain in the pelvic region or genitalia that is often accompanied by urinary frequency and urgency. Despite considerable research, no definitive etiological factors or effective treatments have been identified. The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network uses a novel integrated strategy to characterize UCPPS as a systemic disorder that potentially involves multiple etiologies. The first phase, MAPP I, included >1,000 participants who completed an intensive baseline assessment followed by a 12-month observational follow-up period. MAPP I studies showed that UCPPS pain and urinary symptoms co-vary, with only moderate correlation, and should be evaluated separately and that symptom scores are common and can differ considerably in intensity, duration and influence on quality of life. Longitudinal clinical changes in UCPPS correlated with structural and functional brain changes, and many patients experienced global multisensory hypersensitivity. Additionally, UCPPS symptom profiles were distinguishable by biological correlates, such as immune factors. These findings indicate that patients with UCPPS have objective phenotypic abnormalities and distinct biological characteristics, providing a new foundation for the study and clinical management of UCPPS.

Urologic chronic pelvic pain syndrome (UCPPS): the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network agreed upon the definition of this disorder (discussed in detail) encompasses two highly prevalent chronic pelvic pain disorders: — interstitial cystitis/bladder pain syndrome (IC/BPS) in men and women and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) in men. IC/BPS is a debilitating bladder disorder characterized by urinary urgency, frequency and pelvic pain. Male patients with CP/CPPS report pain in the perineum, penis, testicles or suprapubic region, which often worsens on ejaculation. The presentation of symptoms can be quite variable among patients with UCPPS, which has led to the proposal of multiple etiologies, some of which might be interrelated. UCPPS, like many chronic pain disorders, is poorly understood, and treatment is mostly empirical, with unsatisfactory patient outcomes. Estimates of the prevalence of IC/BPS and CP/CPPS vary widely. Early studies in the 1980s suggested that IC/BPS affected as many as 500,000 US citizens, but prevalence estimates in the past decade (using contemporary definitions of IC/BPS) now exceed 10 million (3–7% in women and 2–4% in men). Quality of life for patients with IC/BPS can be worse than that of patients with end-stage renal disease. Similar to IC/BPS, estimates of the prevalence of CP/CPPS also vary; community-based surveys have reported a prevalence of 8%, but estimates can be as high as 11.5% in men younger than age 30 years.

The MAPP Research Network was established by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the NIH to study the etiology and treated natural history of UCPPS. The aim of the MAPP Research Network is to inform the treatment and management of UCPPS symptoms by improving clinical trial...
Key points
- In urologic chronic pelvic pain syndrome (UCPPS), urological pain and urinary symptoms co-vary, with only moderate correlation, and should be evaluated separately rather than as part of a common symptom cluster.
- Participants with UCPPS who report pain beyond the pelvis have more severe UCPPS symptoms and more symptom flares than those with pelvic pain only.
- Participants with UCPPS reported more psychosocial difficulties than pain-free healthy controls, and individual poor psychosocial functioning in participants with UCPPS was associated with a low likelihood of symptom improvement over time.
- UCPPS involves disturbances in brain-level sensorimotor systems regulating urge storage; these disturbances are powerful enough to produce differences not only in brain function but also in brain structure.
- Different UCPPS symptom profiles are distinguishable by their biological correlates (for example, immune factors).
- Quantitative sensory testing has revealed markedly higher pressure pain sensitivity in participants with UCPPS than in healthy control individuals; high sensitivity was associated with a low likelihood of UCPPS symptom improvement.

Overview
Cronych overlapping pain conditions [I](CPPC) are common to co-occur in similar patients (for example, urogenital chronic pelvic pain syndrome, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, myofascial, fibromyofascial and temporomandibular joint disorder). The design and to identify clinical and biological factors and research measurements that can define clinically relevant subgroups of patients. The MAPP Network includes investigators with diverse clinical and research expertise, including urologists, gynecologists, gastroenterologists, rheumatologists, epidemiologists, biostatisticians, molecular and cellular biologists, neurobiologists, psychologists and psychometricians, and microbiologists, among others, and it incorporates preclinical animal models of UCPPS. The group uses its diverse expertise to promote an interdisciplinary characterization of UCPPS that extends beyond a sole focus on the urological system to encompass a broad spectrum of potential physiological contributing factors.

In the first phase of the MAPP Research Network (MAPP 1), MAPP Network investigators launched a wide range of innovative scientific discovery efforts, moving beyond previous traditional bladder-focused and prostate-focused studies. These efforts included investigations of possible relationships between UCPPS and other nonurological chronic overlapping pain conditions (COPCs), including fibromyalgia, chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS). MAPP Network efforts included the development of an innovative cohort study, an intensive search for clinically important biomarkers and contributing molecular mechanisms; investigation of bacterial, viral and other infectious causative and/or exacerbating agents; multimodal brain imaging studies; and studies of clinically relevant animal models, among others, to better understand the underlying pathophysiology and clinical characteristics of UCPPS.

In this review, we summarize the key insights gained from data from the major research domains of MAPP 1. We discuss these findings in the context of understanding the underlying pathophysiology and diverse symptomatology of UCPPS and how they might inform clinical study design (for example, identification of new clinically relevant patient subgroups and novel targets) to improve outcomes. Finally, we highlight the potential future implications of these findings for the clinical evaluation and management of UCPPS.

MAPP Network design and goals
The current organizational structure of the MAPP Research Network includes six recruiting Discovery Sites, several specialized project-specific Discovery Sites, supporting Cores and a number of integrated subcontracts and ancillary studies, which are all based in North America. Network Discovery Sites evaluate study participants through highly collaborative clinical and basic science studies across sites (referred to as Trans-MAPP studies). To support these efforts, the MAPP Network established two Cores. The Data Coordinating Core (DCC) serves as the central site for data acquisition and storage, provides biostatistical analyses for all network wide studies and promotes network wide quality assurance. The DCC also provides administrative support, including the development and maintenance of a public website. The Tissue Analysis and Technology Core (TATC) monitors biological sample collection and provides technical expertise on a wide range of laboratory assays and/or procedures, as well as sample banking, annotation and distribution services (for a list of MAPP Research Network Discovery and Core sites and affiliated personnel, see Supplementary Box 1).

During its first phase (MAPP 1: 2009-2014), the MAPP Network characterized 424 participants with UCPPS (233 women and 191 men) with a clinical diagnosis of IC/BOFS or CP/CPPS in a 27-month prospective epidemiological protocol — the Trans-MAPP Epidemiology and Phenotyping (Trans-MAPP EP) Study. The Trans-MAPP EP study design was observational (treated natural history), and the participant’s physician managed clinical care, including treatment. Participants were initially assessed at baseline in a ‘deep phenotyping’ session that included numerous urological
Nonpelvic pain and UCPPS symptom severity.

To characterize the treated natural history of UCPPS with respect to differences between localized or regional pain (pelvic pain only) and systemic pain (pelvic pain plus pain in other areas of the body) over time, a body map with a checklist of 45 body site locations was administered to each participant with UCPPS at baseline and at bimonthly assessments. Approximately 25% (106 of 444) of the participants with UCPPS reported localized abdominal-pelvic pain only at baseline, whereas the majority (~75%) reported pain at other sites beyond...
the pelvis, with 33% reporting pain at 13 nonpelvic regions (that is, widespread pain in addition to pelvic pain)\(^1\). Findings were similar in men and women.

In addition, participants with widespread pain had more severe UCPS symptoms than those with pelvic pain only. These data suggest the presence of a central pain phenotype in many patients with UCPS, potentially characterized by CNS alterations or systemic pathologies. In addition, participants with pelvic pain plus widespread pain reported more psychosocial difficulties than participants with pelvic pain alone\(^1\).

Whether or not other symptoms related to the central pain phenotype (such as somatic symptoms and sensory sensitivity) could be used to further phenotype patients is an important question for future studies.

These findings were instrumental in designing MAPP II studies, in which targeted enrollment will be performed to enrich the UCPS cohort (50%) with participants who report pelvic pain only at baseline. This enrichment will facilitate more detailed future comparisons with the widespread pain subgroup that was possible in MAPP I. In addition, a standardized physical examination assessing the extent and severity of pelvic floor muscle tenderness will be performed in MAPP II participants to examine whether this metric provides insight into the ‘pelvic pain only’ phenotype.

Nonurological COPCs and UCPS symptom severity. Using validated symptom-based diagnostic criteria, over one-third (38%) of the MAPP I participants with
UCPPS were found to have least one of the three common neuroological COPCs (that were evaluated — IBS (32%), dyspareunia (4%), CPP (3%) or multiple COPCs (10%))

The prevalence of an additional pain syndrome was higher among women (44%) than men (31%), which might be due to the higher rate of these COPCs in the female population in general. Participants with UCPS who had additional syndromes reported more severe UCPS symptoms and more frequent depression and anxiety than those with UCPS alone. These data suggest that the presence of COPCs should be considered as a risk factor with potential clinical significance in studies evaluating pathophysiologi cal mechanisms and treatment of UCPS. Further studies investigating the influence of COPCs — including the development of new COPC symptoms and their resolution — on UCPS symptoms will be performed in MAP II.

Bladder-focused symptoms and UCPS symptom severity. Two RAND interstitial cystitis epidemiology (RICE) survey items were used to investigate bladder-focused symptoms (bladder-focused phenotype) in the 424 MAP II participants with UCPS. The RICE items queried male and female participants as to whether they had ‘painful bladder filling’ and/or ‘painful urinary urgency’. As expected, the majority of female MAP II participants with UCPS (~94%) reported painful bladder filling and/or painful urinary urgency, given that the RICE items were developed to survey women for symptoms that are consistent with IC/BPS. Interestingly, 12% of these women did not endorse either RICE item; this UCPS symptom group will be further characterized in MAP II to better understand this unique and understudied phenotype. Of note, 75% of male participants with UCPS reported painful bladder filling and/or painful urinary urgency. These bladder associated symptoms are usually observed with IC/BPS; however, most of the male participants with UCPS in MAP II were originally diagnosed with CP/PPS, suggesting that bladder-focused symptoms are more common in CP/PPS than previously recognized.

These findings suggest a previously underestimated overlap in symptomatology between CP/PPS (men) and IC/BPS (predominantly women). Men and women with a bladder-focused phenotype characterized by painful bladder filling and/or painful urinary urgency had more severe UCPS symptoms (pelvic pain, urinary urgency and urinary frequency), more generalized neurosurgical symptoms and syndromes and a poorer quality of life than those who did not endorse either of the RICE items. Thus, bladder-focused hypersensitivity profiles are potentially important for the identification of clinically important subsets of patients with UCPS.

These MAP II clinical findings heavily informed the design of the MAP II study. Important questions that will be addressed in this longer-term prospective observational cohort study include the reliability of the bladder focused phenotype and whether these phenotypes predict improvement (or worsening) of symptoms over time in the setting of usual care. In addition, patients with UCPS in the MAP II study will be characterized on the basis of the presence or absence of bladder’s lesions (which was not done in MAP I) to examine the influence of these lesions on clinical phenotyping.

During a follow-up period of 12 months in MAP I, 69% of participants with UCPS had stable symptoms, whereas 20% demonstrated UCPS symptom improvement and 20% exhibited symptom deterioration (worsening). The extent of widespread pain, number of neurosurgical symptoms and poor overall health status were predictive of poor outcomes. Importantly, these observations were made while participants were receiving usual care for their symptoms, and medications and/or treatments were recorded only every 2 months. Thus, it was not possible to determine the impact of individual treatments on symptom trajectories. In MAP II studies, participants with UCPS will be followed for a longer period of time (16 months) than in MAP I, and UCPS treatments will be prospectively recorded to determine whether specific phenotypic characteristics correlate with treatment response to specific agents. We hope that the findings from these studies will lead to focused clinical trials in which specific agents can be targeted to specific patient phenotypes.

Assessment of urological pain and urinary symptoms. Using questionnaire responses from participants with UCPS, principal component and exploratory factor analyses were performed to determine a simple yet comprehensive set of symptom indices to characterize and quantify UCPS symptoms. Two factors — pelvic pain severity and urinary symptom severity — provided the best psychometric description of items from the multiple symptom questionnaires that were administered. Latent factors were used to create two separate symptom indices, one for UCPS pain and another for urinary symptoms. UCPS pain, but not urinary symptoms, was associated with symptoms of depression, suggesting that urological pain and urinary symptoms vary in their influence on a patient’s quality of life. On the basis of these findings, UCPS pain and urinary symptoms should be measured separately using the Genitourinary Pain Index (GUPI) and Interstitial Cystitis Symptom Index (ICSI) symptom subscales, which provide a brief but discriminating UCPS symptom severity assessment based on well accepted instruments. Future MAP Network studies will investigate how these symptom indices change over time, their relationship to other important physiological factors (for example, catastrophizing and anxiety) and whether they can predict disease outcomes.

Collectively, these insights suggest that at least three critical factors should be prioritized in the clinical phenotyping of patients with UCPS — pain localization (pelvic pain only versus pelvic pain plus widespread pain), the presence or absence of the full range of COPCs and bladder-focused symptoms (Table 1). Another major implication of this week is that clinicians should consider abandoning the use of comprehensive symptom indices that report total scores for UCPS and instead evaluate urological pain and urinary symptoms separately.
UCPPS symptom flares

Patients with UCPPS frequently report ‘symptom flares’ (acute worsening of symptoms). However, no previous studies have systematically examined the characteristics of UCPPS symptom flares or the influence that flares have on the patient experience. To develop an improved, patient-centric understanding of symptom flares, the MAPP Network conducted a multi-site, in-person group study with patients with UCPPS and two smaller site-specific studies. These studies revealed the presence of multiple types of UCPPS symptom flares, which vary in symptom presentation, severity and duration (from minutes to days or longer). Furthermore, increased flare frequency was an important component of overall symptom severity and morbidity. Focus group participants also indicated that flare predictability is a major concern for patients: flares that arise without any warning or explanation lead to increased distress and have a negative influence on a patient’s daily function. A resultant and clinically significant effect of frequent flares is social avoidance and social isolation.

Another important focus of the MAPP Network studies is to explore flare triggers. Although several previous studies have asked patients what they believe triggers their flares, few studies have examined these possible triggers empirically. Thus, as part of the Trans-MAPP EP Study, we performed a case–crossover study that compared participants’ experiences before and after three flare events with their experiences between three random biweekly visits during which they reported not having flares; this design enabled each participant to serve as his or her own control. At each of the case–crossover study assessments, participants completed a ‘flare risk factor’ questionnaire that assessed factors that could potentially trigger flares (for example, foods and drinks, physical activity, sexual activity and infections). Of the factors examined, recent sexual activity was the only factor associated with flare onset in the full study population.

However, in subpopulations that were thought to be highly susceptible to certain triggers, additional associations were observed for several foods and drinks, as well as for abdominal exercises. For example, in the subset of participants who identified dietary factors as a cause of UCPPS symptom flares, consumption of tomatoes, yogurt, spicy foods, alcohol, caffeinated beverages and carbonated beverages was associated with flare onset. These findings suggest that flare triggers are specific to certain patients and, therefore, that adoption of global flare prevention strategies would be too restrictive for many patients.

Finally, data from the case–crossover study also enabled assessment of the incidence of UCPPS symptom flares over the entire study period. Almost 80% of all participants with UCPPS reported at least one symptom flare during the 12-month study period. Specifically, 24% reported no flares during the follow-up period, 23% reported one flare, 36% reported two to three flares and 24% reported four or more flares. Flares were more frequently reported in women (mean 2.8 flares) than in men (mean 1.9 flares). Furthermore, flares were more common in participants who endorsed body map pain sites beyond the pelvic region than those in the subgroup with pelvic pain only and in participants with the most severe bladder symptoms. Questions related to flares and their influence, including the use of mobile technology applications and ecological momentary assessments to examine short-term (hourly) flare patterns and their associated risk factors, will be further addressed in ongoing MAPP Network studies.

Psychosocial factors

Psychosocial factors have a major influence on quality of life and other outcomes related to chronic pain. The MAPP Network study is the first to directly assess a large cohort of male and female patients with UCPPS using a broad range of psychosocial variables. Participants with UCPPS reported more psychosocial difficulties, including higher levels of current and lifetime stress, poorer coping and more self-reported cognitive deficits, than healthy control individuals matched for age and sex who did not have pain. In addition, both sexes showed similar levels of psychosocial problems, although women had higher levels of childhood adversity and widespread discomfort than men.

Interestingly, the level of psychosocial problems was not solely attributed to the severity of UCPPS symptoms, suggesting that a reduction in the symptoms associated with UCPPS alone would be insufficient to produce clinically significant improvements in quality of life for some patients. Perhaps unsurprisingly, the presence of neurocognitive COPCs (fibromyalgia, IBS and/or CPS) in the UCPPS cohort was associated with higher rates of depression and anxiety, as well as greater UCPPS symptom severity. Finally, several psychological variables—such as catastrophizing, a lowered sense of mental and physical well-being, and the presence of life stressors—were associated with a low probability...
of symptom improvement over a 12-month period. MAPP II studies will help to determine the stability of these patterns by assessing psychosocial variables in participants with UCPS over a 36-month period.

Neuroimaging

Before the MAPP Network, few published studies had assessed alterations in brain structure or function in patients with UCPS. These early studies primarily aimed to demonstrate the feasibility of neuroimaging to study chronic urological pain disorders and were limited by their small sample sizes, restriction to male patients only, and lack of convergent findings of altered brain structure and function. Concurrently, research in other chronic pain conditions had started to demonstrate that brain structure and function are important factors to be considered in persistent pain, as specific brain phenotypes can perhaps promote or inhibit recovery from pain.

The MAPP Network, when established, recognized the crucial importance of assessing the involvement of brain-level changes as part of the central Trans-MAPP EP Study to enable a comprehensive characterization of UCPS beyond the bladder or prostate.

To substantially increase the sample size for studies assessing the contributions of brain structure and/or function to UCPS, the MAPP Network developed an innovative protocol that standardized MRI data acquisition across sites. This approach has yielded a common neuroimaging data set integrated with clinical data and other phenotyping domains that is unprecedented in the field. Importantly, the MAPP Network treated sex as a crucial biological variable by focusing neuroimaging data analyses exclusively on either women or men or by stratifying participants by sex. The MAPP Network neuroimaging study was also the first to use multiple neuroimaging modalities in a common protocol for assessing brain correlates of UCPS in urological and pain symptoms.

Convergent findings of altered brain structure and function (in the context of a comparison between participants with UCPS and controls) were reported in MAPP I neuroimaging studies. Differences between participants with UCPS and healthy control individuals were particularly apparent in medial areas of the motor and sensory cortices, the right posterior insula and the perisplenial grey (PAG) area of the brainstem. These motor and sensory areas are consistent with the somatosensory representation of the pelvic area. The right posterior insula consistently activates during intravesical infusion of fluid and is thought to be a primary visceral sensory region associated with the bladder. The PAG has a crucial role in both the control of urination and the descending modulation of nociceptive signals. Findings of altered grey matter structure, white matter structure and resting-state function are particularly congruent in the supplementary motor area (SMA), a region that has a key role in providing centripetal input to active pelvic floor muscles. These findings collectively enable us to make the preliminary conclusion that UCPS involves disturbances in brain-level sensorimotor systems regulating urination storage and that these disturbances are powerful enough to produce differences not only in brain function but also in brain structure. Thus, it seems that dysfunction associated with UCPS is not confined to either the end-organ (bladder or prostate) or spinal-level neural systems in many patients but involves measurable brain-level changes. MAPP II studies will determine whether these findings can be reproduced in a separate cohort of patients with UCPS.

Comparison of participants with UCPS with healthy control individuals provides an important first-level understanding of the neural contributions to the syndrome. However, MAPP Network neuroimaging data also provide a novel means of identifying underlying neurobiological factors for patients with UCPS who display different clinical features. One such clinical consideration is the longitudinal progression of symptoms; symptoms were relatively constant for some patients with UCPS, whereas symptoms improved and/or were worsened over time for others. In 2017, the MAPP Network published the first study showing that rs-fMRI data are predictive of trends in UCPS pain symptom severity in the 3 months following the scan. Importantly, the neuroimaging readings were conducted in a blinded manner in these studies. Participants with UCPS whose pain symptoms improved had stronger functional connectivity in the left frontoparietal brain network than those whose pain symptoms remained constant or worsened. These differences in brain function might reflect neural systems that allow the regulation of a patient’s attention to their symptoms. Furthermore, neuroimaging findings from other MAPP Network studies have revealed that UCPS involves structural, chemical and functional brain changes consistent with other chronic pain conditions, such as fibromyalgia.

Network studies addressing the possible contributions of a centralized pain phenotype in UCPS have also shown changes in functional connectivity patterns associated with the presence of widespread pain versus pain localized to the pelvis, providing a neurobiological correlate to a potential subgroup of patients with UCPS. Ongoing studies, including longitudinal neuroimaging and a natural bladder-filling paradigm (via diuresis), are underway in MAPP II to extend these observations.

Quantitative sensory testing

Another characteristic of patients with centralized chronic pain is a generalized or global abnormality of sensory processing. In the MAPP Network, sensory processing abnormality was assessed using quantitative sensory testing (QST) (Table 1), which refers to experimental procedures that assess evoked perceptual responses to quantifiable physical stimuli delivered to the body (for example, blunt thresh table pressure combined with graphical touch screen interface to measure pain level). Data from QST studies suggest a normal distribution of
pain sensitivity across the general population, with the majority of individuals with centralized pain exhibiting marked hypersensitivity (falling on the right side of the normal distribution curve)\(^\text{17-19}\). Importantly, hypersensitivity can be present in both symptomatic and non-symptomatic body sites, the latter of which is strongly suggestive of CNS-related pathophysiological mechanisms and occurs in many chronic pain conditions, such as fibromyalgia\(^\text{20-22}\), IBS\(^\text{23}\), temporomandibular joint (TMJ) disorder\(^\text{24-26}\) and lower-back pain\(^\text{27}\).

Previous research suggests that some patients with UCPPS also exhibit QST findings that are consistent with a centralized pain phenotype, including generalized pain hypersensitivity and deficient endogenous pain inhibition\(^\text{28-30}\). However, these studies mostly had small sample sizes and were limited to women, making it difficult to explore potential sex and subgroup differences in UCPPS sensory processing. MAPPI included the largest examination of generalized pain sensitivity in UCPPS to date. In MAPPI, an automated QST system\(^\text{31}\) delivered computer-controlled pressure stimuli to the thumb nail as a validated model of centralized pain\(^\text{32-34}\). Analyses revealed a significant (P < 0.05) increase in pressure pain sensitivity in participants with UCPPS (n = 153; 51% female) compared with healthy control individuals (n = 108; 59% female) (S.E.H., H.H.L., S.S., B.D.N. and J.R.L., unpublished observations). However, participants with UCPPS were generally less sensitive to pressure pain than a mixed pain comparison group that included participants with fibromyalgia, CFS and IBS (n = 35; 77% female). Additional network studies examining auditory sensitivity and endogenous analgesia in UCPPS were also conducted. Participants with UCPPS showed increased sensitivity to unpleasant auditory stimuli compared with healthy control individuals, and an association between deficient endogenous pain inhibition and self-reported nonurological pain was observed (S.E.H., H.H.L., S.S., B.D.N. and J.R.L., unpublished observations). These data indicate the presence of a global multisensory hypersensitivity for unpleasant or painful stimuli in UCPPS, providing further evidence for a centralized pain phenotype. QST findings were also examined as a predictor of longitudinal symptom change in participants with UCPPS. Exploratory analyses indicated that low pressure pain sensitivity at baseline was associated with a high probability of improvement in urogenital pain severity over a 12-month period (S.E.H., H.H.L., S.S., B.D.N. and J.R.L., unpublished observations).

A broadened arsenal of QST methods — including analyses of endogenous analgesia and temporal summation of pain — is being used in MAPPI II to enable a more comprehensive evaluation of sensory processing in UCPPS than was attainable in MAPPI I. In addition, a considerably larger group of participants with UCPPS will undergo assessments with both QST and neuroimaging in MAPPI II. Together, these data will
provide greater insight into the neurobiological mechanisms underpinning UCPS symptoms and the prediction of longitudinal symptom patterns.

**Molecular phenotyping**

Within the MAPF Network, molecular phenotyping refers to the investigation of molecular and pathological correlates of UCPS. Several approaches have been used to study biomarkers in the MAPF Network using a variety of collected biological samples (Table 1). MAPF studies were initiated with a comprehensive literature review that identified a panel of candidate biomarkers for UCPS, including matrix metalloproteinase 2 (MMP2), MMP9, neutrophil gelatinase-associated lipocalin (NGAL), the MMP9-NGAL complex, vascular endothelial growth factor (VEGF) and VEGF receptor 1 (VEGFR1). These factors were measured in the urines of participants with UCPS, positive control individuals (i.e., participants with one or more COPD) and healthy control individuals in the TRANS-MAPF study. Normalized urine concentrations of VEGF (P = 0.001), VEGFR1 (P = 0.004) and MMP9 (P = 0.001) in men and VEGF (P = 0.0078) in women were significantly higher in participants with UCPS than in healthy control individuals. Differences in the urine levels of MMP9, MMP9-NGAL and VEGFR1 in men and all assayed biomarkers in women were associated with the severity of clinical symptoms. These findings might have importance in understanding the varied bladder pain phenotypes (pain with bladder filling or pain relief by bladder emptying observed in UCPS), as well as potential sex differences in the underlying pathophysiological mechanisms. One proposed mechanism in UCPS is alteration of bladder blood flow, given that VEGF is involved in the development and regulation of blood vessels. VEGF and MMP9 have a role in neuropathic pain, suggesting a possible neuropathic aetiology for UCPS in some participants. MMP9-NGAL is considered a marker of infection or inflammation; thus, the observed elevations in UCPS also suggest an inflammatory aetiology.

To discover novel urinary biomarkers of UCPS, a comparative quantitative mass spectrometry (MS)-based analysis is underway and has identified a number of new candidates that are differentially expressed in the urines of patients with UCPS and healthy control individuals. MAPF Network studies have also found that female participants with UCPS exhibit an exaggerated inflammatory response compared to healthy control individuals, as evidenced by a greater inflammatory response to stimulation of Toll-like receptor 2 (TLR2) and TLR4 in patient-derived peripheral blood mononuclear cells (PBMCs) and TLR2 and TLR4, which recognize specific molecular components of microorganisms (such as bacteria) to activate the innate immune system, have an important non-canonical role in pain sensitization at the level of the spinal cord. Response to TLR4 stimulation also positively correlated with urethral pain severity and distinguished participants with UCPS who had consulted COPD2 and widespread pain from those with pain confined to the pelvic region and/or bladder. The TLR4 response was also associated with low pressure pain thresholds measured at the thumb base. These findings represent novel insights into pathophysiological mechanisms underpinning UCPS and that previous studies have not used such a stimulated biological response method to examine immune system correlates. In addition, these analyses also revealed abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis in participants with UCPS and showed that a combination of HPA dysregulation and inflammatory responsiveness was a strong predictor of pelvic pain. This finding is similar to that reported in other systemic chronic pain conditions and lends further support to the hypothesis that UCPS has systemic contributors beyond urological organs or tissues in some patients. Furthermore, increased TLR2 and TLR4 responsiveness was associated with decreased improvement in pelvic pain over time, whereas TLR4 responsiveness alone was associated only with decreased improvement in urinary symptoms. This association between response and specific phenotypes will be studied further in MAPF II.

The MAPF Network also conducted metabolomic studies of urine specimens using MS-based global metabolite profiling approaches—multivariate analysis of liquid chromatography (LC)-MS and LC-MS with tandem MS (LC-MS/MS) data—to discern small-molecule correlates of UCPS (compared with controls) and symptoms profiles. These studies found that the tetrahydroisoquinoline methylated etiocholan-3a,17α-dione sulphate (EtoS) distinguished female participants with UCPS who have a high symptom burden from those with a low symptom burden at follow-up periods of 6 and 12 months. In previous studies, EtoS has been associated with inflammatory response following administration in humans. Further investigation of this novel finding might lead to previously unconsidered mechanisms that contribute to UCPS symptoms.

**Contributions of the microbiome**

The expansion of pathogenic bacteria in the bladder and urinary tract is well known to lead to common urological disorders, including cystitis, pyelonephritis and prostatitis. However, past investigations in IC/BPS and UC/PFPS, including published studies of antibiotic use as a medical intervention, have been inconclusive and even contradictory in demonstrating the contribution of microbial infection to symptoms. Over the past decade, paradigm-shifting analyses using culture-independent next-generation sequencing (NGS) and modified, sensitive culture techniques have identified a putative bladder microbiome and have subsequently linked decreases in bacterial diversity in the bladder to multiple urological conditions, including IC/BPS and UC/PFPS. These insights and the evolution of new and increasingly powerful high-throughput methodologies have renewed interest in addressing long-standing questions of the role of the microbiome in urological disorders, including UCPS.

To overcome previous methodological limitations in studies of UCPS, the MAPF Network used a novel
Burkholderia cenocepacia
Lactobacillus gasseri
Candida
Saccharomyces
Escherichia coli
E. coli

On the basis of these validation criteria, cyclophosphamide-induced (chemical cystitis), urinary tract infection (UTI) (acute infection and post-UTI pain), chronic stress-water avoidance (stress-induced pain), transgenic URO-OVA mouse (autoimmune cystitis in the bladder; induced in animals expressing self-ovalbumin under a bladder urothelial cell-specific promoter by introduction of activated OVA-specific T cells), transgenic URO-MCP1 mouse (monocyt chemoattractant protein 1 (MCP1, also known as CCL2) expression in the urothelium producing bladder hypersensitivity) and pseudomonas aeruginosa (PRV; neurogenic cystitis) models were selected. Importantly, these models are founded on leading hypotheses of underlying pathophysiological mechanisms in human UCPSs. All models examined demonstrated pelvic nociception (referred mechanical allodynia) with von Frey filament testing. Nociception to bladder distention, pelvic nociception, and urinary frequency were recapitulated in the cyclophosphamide and chronic stress-water avoidance models. Pelvic nociception and urinary frequency were present in the URO-OVA and URO-MCP1 models, and the UTI and PRV models demonstrated bladder hypersensitivity.

Following validation, additional mechanistic studies using these UCPS models were performed. Results from these studies highlighted the importance of central sensitization, inflammation-associated bladder dysfunction and pelvic visceral organ cross-sensitization in the pathogenesis of pelvic pain. For example, MAPP Network investigators showed that chronic pelvic allodynia could develop after the resolution of UTI caused by a strain of Escherichia coli lacking O-antigen expression (post-UTI chronic pain). Moreover, treatment of the bladder with probenecid sulfate was found to be analgesic and tissue protective and suppressed the expression of inflammatory cytokines that are normally associated with nociception after an E. coli UTI. The importance of metabotropic glutamate receptor 5 (mGluR5)-extracellular signal-regulated kinase (ERK) signalling pathway activation at the levels of the spinal cord and the central nucleus of the amygdala in the development of central sensitization was also revealed.

In MAPP II, investigators are building on the observations of the first-phase studies to enable further analysis of new clinical insights in validated UCPS models. Areas of special interest will include assessing the in vivo contribution of biological factors (supported by evidence from biomarker studies) to nociception and urinary dysfunction, rodent neurotransmission studies to examine the effects of stress on functional brain reorganization, nociception and bladder function, and comparison with insights from the human neuroimaging studies.

Implications of MAPP Network findings
A major objective of MAPP Network studies is to improve the clinical evaluation of patients with UCPSs and to provide supporting information to guide future studies, including clinical trials. To advance this goal, we designed studies to elaborate on symptom profilers and reveal discrete patient subgroups (clinical phenotypes) within the broad cohort under study. In addition, this
Future clinical trial design. MAPP Network findings indicate that specific clinical factors that are easily measurable — including the presence of pain beyond the pelvis, the presence of COPCs and the severity of bladder-focused symptoms (particularly pain with bladder filling) — have a clear influence on symptom trajectories over time. These findings suggest that future clinical trials should consider stratifying patients according to these factors, as they might influence treatment efficacy. Furthermore, the correlations between widespread pain and neuromodulation and/or QST findings suggest that a subset of patients with UCPS have a centralized pain phenotype and that they might respond to centrally acting treatments. This possible relationship between osteopathic characteristics (central versus peripheral pain mechanisms) and response to treatment (centrally acting versus peripherally acting therapies) is a major focus of MAPP II studies.

In addition, MAPP Network studies have revealed the importance of measuring urological pain and urinary symptoms separately, rather than with a composite score. Specific therapies could possibly lead to improved outcomes for patients with one type of symptom but not necessarily both; such relationships might have been missed in previous clinical trials in which the primary outcome measure was assessed using composite scores.

Multimodal management. MAPP Network studies have provided novel insights into symptom severity in UCPS. Indeed, patients with neuromuscular COPCs (such as IBS, CFS and fibromyalgia) or those presenting with widespread pain in addition to pelvic pain frequently endorsed the highest measure of UCPS pain severity in clinician-administered questionnaires and, perhaps unexpectedly, have a higher risk of depression and anxiety and a poorer quality of life than those with UCPS alone and pelvic pain alone, respectively. The high percentage of participants with UCPS who had accompanying neuromuscular COPCs and psychosocial comorbidities suggests an important role for multimodal management and the frequent need for therapies that extend beyond the pelvic visceras. This information is critically important for clinicians from the perspective of identifying other therapeutic targets and patient counselling. This finding also raises the question as to whether a patient’s symptoms would be best managed in medical environments that can address these varied needs using holistic approaches that take into account psychosocial comorbidities, COPCs and patient experiences with symptom flares. Interventions that aim to improve a patient’s ability to cope with and self-manage symptoms and their effects, such as cognitive-behavioural therapy, have shown promise in treating chronic pain conditions and deserve further study in UCPS.

The attainment of highly reliable information about the prognosis of UCPS symptoms over time (for example, the likelihood of worsening or improving) is one of the major clinical goals of the MAPP Network and is being further addressed in the extended observational period of the MAPP II study.

Aetiological crossover. In standard urological practice, men tend to present with pelvic pain of unknown aetiology and are, therefore, classified with the general diagnosis of prostatectomy (prostate Type III, CP/ID). This condition has a limited number of effective therapies. Data generated within the MAPP Network have revealed a strikingly high prevalence of painful bladder filling and/or painful urinary urgency in male participants with UCPS, suggesting the existence of a clinical and perhaps aetiological crossover between IC/BPS (predominantly women) and CP/ID (men). This finding illustrates the importance for clinicians of querying male patients with chronic pelvic pain about bladder symptoms, as an affirmative response might lead to a change in diagnosis and subsequent therapy assignment.

Bladder-focused pain and urinary urgency frequency outcomes. To date, the combination of pelvic pain, urinary symptoms and other measures (such as quality of life) to derive a composite score has been a common practice: these composite scores are used to assess outcome measures in clinical trials and to monitor clinical progress. One of the most important findings of MAPP I is that this approach might not be appropriate. The MAPP Network has shown that UCPS pain and urinary symptoms (urgency and/or frequency) have a different quality of life influence and severity pattern over time and, therefore, should be assessed separately in patients with UCPS in research and, potentially, clinical settings. This finding has major implications for the design of research studies and patient follow-up procedures in standard practice. In addition, new instruments developed on the basis of these findings might influence how outcomes (symptom improvement) are assessed and how patient cohorts are screened in future clinical trials.

Symptom flares. Once a diagnosis of UCPS has been made, clinicians typically begin therapy to treat pain that is known to be chronic but is often assumed to be stable in its severity and characteristics. MAPP Network symptom flare data have dispelled this traditional notion by demonstrating that flares occurred in almost all participants with widely different frequencies, severities, durations, symptoms, influences on quality of life and, possibly, triggers. The finding that symptom flares are common and can have a profound psychosocial influence strongly suggests that their assessment needs to be a priority in clinical evaluation and management. An understanding of flare characteristics can be helpful for the selection of appropriate therapies that aim to mitigate flare-specific symptoms. For example, factors that trigger symptom flares (for example, foods, beverages and physical activity) might need to be modulated in a patient-centric manner and as part of a personalized approach to management.
strategies for addressing these (a 'care plan') need to be developed on the basis of understanding of the patient experience rather than preconceived management approaches. These approaches might range from simple strategies, such as taking a warm bath, controlling constipation with diet or medications or carrying medications at all times, to more aggressive interventions, such as intrathecal baclofen installations.

Physiological factors. One of the primary clinical goals for patients with UCPS is to improve their quality of life. Many clinicians (and patients) assume that once symptoms improve, quality of life will similarly improve. MAPP Network findings have demonstrated that this assumption might not be the case of the patient has substantial coexisting psychosocial comorbidities or severe nonurological pain.

Furthermore, psychological dysfunction (that is, depression, anxiety or catastrophizing) was more commonly identified and was associated with more severe UCPS symptoms and poorer outcomes in patients with comorbid nonurological symptoms than in those without such comorbidities. Thus, greater emphasis should be placed on early identification and treatment of nonurological symptoms and psychological dysfunction as separate and exacerbating clinical factors in UCPS.

Pain and centrally acting therapies. MAPP Network studies of structural and functional brain changes in UCPS have revealed similarities to other chronic pain syndromes and confirmed that the pain experienced by some patients is more complex than simply neuropathy localized to the pelvis. Importantly, these observations might explain the favourable responses to some patients with UCPS have to centrally acting therapies (amitriptyline, pregabalin and sacral nerve stimulation), which is under further investigation in ongoing MAPP II studies, and might provide potential new targets for future medical or even surgical interventions. In MAPP I studies, QST revealed global pain processing abnormalities in participants with UCPS, particularly those with concomitant pain beyond the pelvis (S. H., H. L., S. S., R. D. N. and J. R., unpublished observations). The potential utility of neuroimaging approaches in clinical management (as opposed to research studies) will need to be further evaluated, but QST is a relatively simple method to apply and might ultimately have clinical utility for patient phenotyping and stratification in personalized therapies (that is, centrally acting therapies for those with centralized pain or peripherally acting therapies for those with non-centralized pain).

Molecular biomarkers for diagnostic algorithms. The development of molecular biomarkers of UCPS, although not yet validated for clinical use, has shown promise. Initial MAPP Network studies revealed correlations between molecular biomarkers and distinct clinical features, including a relationship between TLR8 responses and unexplained pain profiles. The identification of patient subgroups that overexpress or underexpress specific biomarkers (or a panel of biomarkers) might improve our understanding of the underlying pathophysiological mechanisms, identify new molecular targets, predict response to therapies and add predictive value to UCPS diagnostic algorithms in the future.

Antibiotic stewardship. In our clinical experience, the majority of patients with UCPS have had multiple unsuccessful empirical courses of antibiotics throughout their clinical history without improvement in symptoms.

Thus, the routine use of antibiotics in the absence of an identified infection is discouraged. New molecular techniques (for example, culture-independent NGS or ribosomal RNA (rRNA) gene sequencing and expanded quantitative urine culture) used in MAPP Network studies have the potential to uncover previously unidentified microorganisms involved in UCPS that would be otherwise missed using standard culture methods. The identification of novel microbial pathogens, as well as changes in microbial diversity between urine samples from patients with UCPS and healthy individuals or between patients with distinct symptom profiles, holds great promise in the characterization of novel host-microbial relationships in UCPS. These insights might promote new approaches to antibiotic treatment or prophylaxis in some patient subgroups.

Conclusions

The coordinated multisite efforts of the MAPP Research Network have resulted in the extensive characterisation of a number of symptom, as well as biological, domains in a sizeable cohort of patients with UCPS and control individuals. This large longitudinal database has identified subsets of patients with UCPS who have specific phenotypic profiles, suggesting the existence of different mechanisms underlying the pathogenesis of UCPS symptoms. This heterogeneity might explain the failures of previous clinical trials. MAPP Network studies also indicate that patients with UCPS who have neuroendocrine COPCs or widespread pain have a more systemic condition with a different natural history and are more likely to exhibit symptom progression and decreased quality of life than those with isolated UCPS symptoms. No consistent sex differences in the aforementioned relationships were reported, suggesting that UCPS (in women and men) and CP-UCPS (in men) are similar conditions. In addition, individuals with UCPS have a lower overall pain threshold and different brain patterns on fMRI compared with healthy control individuals, suggesting that differences in CNS pain processing have a fundamental role in this disorder. These translational studies and findings will rationalize the next generation of clinical trials for UCPS. Finally, by revealing these new insights into UCPS, the MAPP Network has demonstrated the feasibility and benefit of a research approach focused on highly collaborative and integrated studies by investigators with diverse and complementary expertise. Such an approach could serve as a model for the study of other syndromic disorders that have proved difficult to characterize using traditional research strategies.