Urology Interagency Coordinating Committee (UICC)

Friday, December 12, 2014
10:00 a.m. - 12:30 p.m.
6707 Democracy Blvd. Room 401
Bethesda, MD

Meeting Minutes

Welcome and Introductions
Rob Star, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Dr. Star welcomed participants to the urology interagency coordinating committee. Dr. Star asked participants for any suggestions or recommendations. Any resources that could be leveraged for MAPP would also be welcomed.

The MAPP Research Network: A Novel Study of Urologic Chronic Pelvic Pain Syndromes
Chris Mullins, Ph.D.
National Institute of Diabetes and Digestive and Kidney Disease

Dr. Mullins provided an administrative overview of the MAPP Research Network. During the history of NIDDK's funding for benign urologic disease, the Institute has launched numerous clinical trials and basic science projects over a span of 15 years to address urologic chronic pelvic pain syndromes. After an assessment of study results and programmatic evaluation, NIDDK devTeloped the "Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (MAPP)" in September 2008. The funding announcement was directed to recruit both male and female participants. The primary objectives of MAPP are included below:

Primary Objectives:

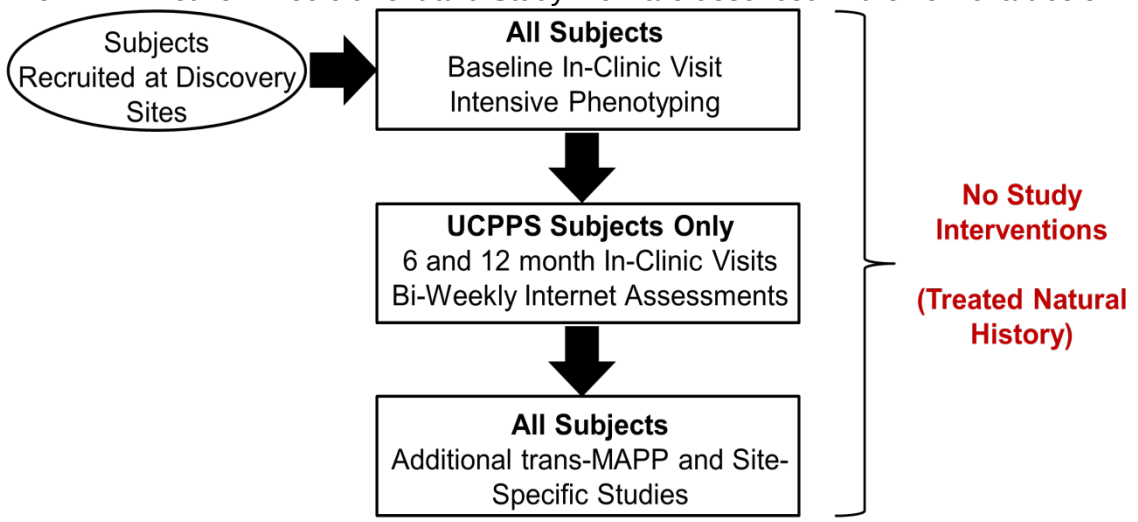
- Develop a multidisciplinary, highly collaborative, and integrated approach to study UCPPS as a "systemic disorder", including associations between urologic and non-urologic pain conditions (e.g., CFS, FM, IBS).
- Address underlying disease pathophysiology and natural history and risk using select cohorts and human study material (e.g. serum, urine, DNA, imaging data, etc).
- Provide a "translational foundation" for improved clinical trials/management (e.g. patient phenotypes, sub-groups, drug targets, diagnostic features, improved outcomes, etc).

Dr. Mullins noted that the original MAPP Network Organization included a Network Chair and two Network co-chairs to assist oversight of the Network. There are 6 discovery sites, one data coordinating core, one tissue analysis and technology core, and a total of

four subcontract sites. The MAPP Network was well represented with broad geographic distribution. Network investigators developed and initiated numerous Trans-MAPP (i.e., collaborative across sites) protocols, as well as some single site and ancillary studies:

- Trans-MAPP Epidemiology/Phenotyping Protocol
- Trans-MAPP Biomarker Validation and Discovery Protocol
- Trans-MAPP Infectious Etiology Protocol
- Trans-MAPP Functional Neurobiology Protocol
- Trans-MAPP Structural Neurobiology Protocol
- Trans-MAPP Pressure-Pain Threshold (PPT) Protocol
- Trans-MAPP Expanded Flare "Focus Group" Protocol
- UCPPS Animal Models Translational Science Studies
- Discovery Site-Specific Studies
- Ancillary Studies

The MAPP Network Recruitment and Study Flow are described in the flow chart below:



MAPP Network Cohort Recruitment was highly successful and exceeded its goals. The integration of network studies required that all studies use common patients/controls and clinical data integrated to provide layers of phenotyping for an individual patient or patient group (DCC). In addition, all studies used common biosamples from the tissue analysis and technology core (TATC) and address common overarching hypothesis designed to address clinical relevant questions. Lastly, neuroimaging parameters and data management were standardized across all sites.

Two papers that described The MAPP Network Study design details were published in BMC Urology: *The MAPP research network: a novel study of urologic chronic pelvic pain syndromes* and *The MAPP research network: design, patient characterization and operations*. Unique from other urology studies, MAPP focused on the multi-layered assessment of phenotype and disease etiology. Factors such as neurobiology/brain structure-function, risk factors/psycho-social measures, infectious agents/microbiome, relationship of co-morbids and epidemiology/symptoms were examined to determine disease etiology, natural history/risk, patient phenotype, develop new "tools" for clinicians, and to lead to hypothesis generating.

The second project period for the MAPP Network includes an expansion from July 2014 through June 2019. Primary objectives in the second project phase:

- Continue analysis of clinical data and biological samples collected in the first project period.
- Develop and implement a second phase of collaborative protocols that build upon insights from the first phase and further address the central goals of the network.
- Expand the expertise and scientific scope through the integration of new Discovery Sites.

The MAPP Network organization for Phase 2 will consist of a Network chair, two Network co-chairs, nine discovery sites (3 new sites), a DCC, and a TATC.

Dr. Mullins closed his presentation by discussing the following future directions for the MAPP Research Network:

- Trans-MAPP Symptom Patterns Study (SPS)
  - Assessment of symptom patterns and corresponding biologic change through longer follow-up
  - Evaluation of promising candidate biomarkers from MAPP I
  - Further assessment of the microbiome
  - Longitudinal neuroimaging and quantitative pain testing
  - In-depth assessment of treatment response
  - Phenotyping before and after the initiation of certain therapies
  - Identification of clinically relevant UCPPS patient sub-groups
- Bi-directional discovery work between animal models and humans

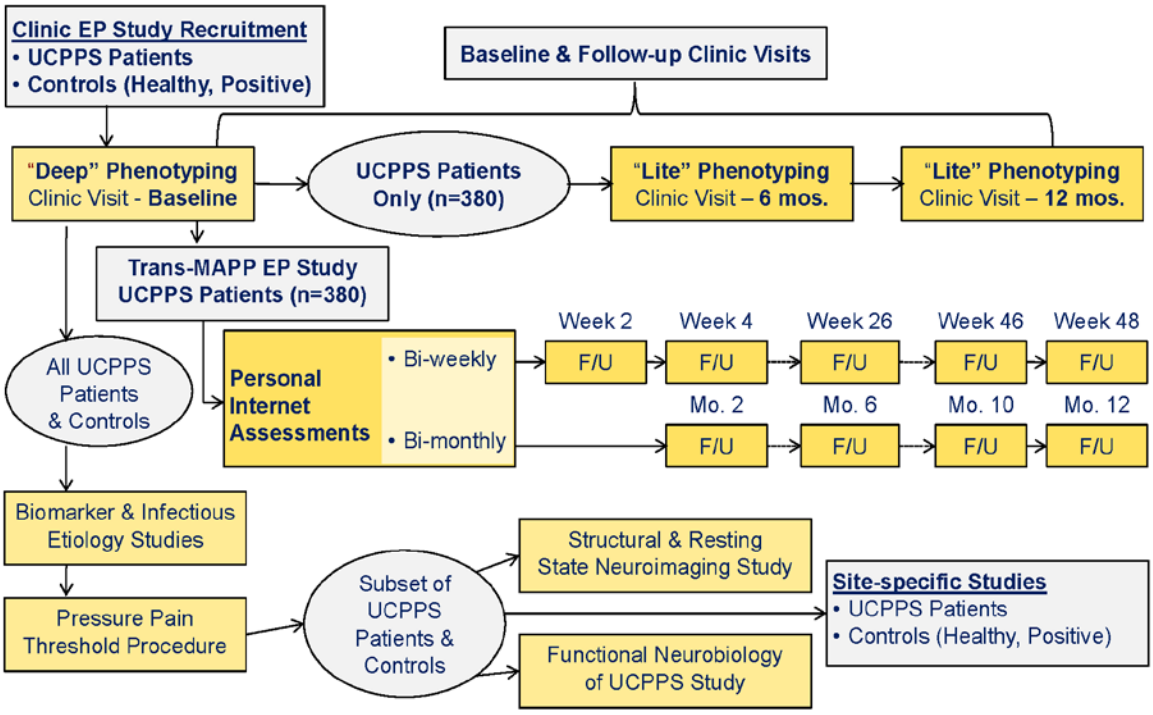
Comments: None

The MAPP Research Network: Design, Implementation, Management, and Support of a Multi-Center Network
Nancy Robinson-Garvin, Ph.D. University of Pennsylvania, Philadelphia, PA

Dr. Mullins introduced Dr. Robinson-Garvin, a senior research investigator within the MAPP Research Network Data Coordinating Center. Dr. Robinson-Garvin began her presentation by detailing the aims for a Trans-MAPP Epidemiology and Phenotyping (EP) Study:

- Aim 1: To estimate cross-sectional prevalence's and evaluate associations among baseline characteristics of subjects with Urologic Chronic Pelvic Pain Syndrome (UCPPS).
- Aim 2: To characterize longitudinal profiles of symptoms and evaluate associations between baseline characteristics and symptom profiles over a one-year period.
- Aim 3: To characterize the pattern of fluctuations in symptoms and evaluate associations between baseline characteristics and variability in symptoms over a one-year period.
- Aim 4: To identify factors that are predictive of more severe illness impact (including healthcare seeking and decreased quality of life) in individuals with UCPPS.
- Aim 5: To identify risk factors for self-reported worsening of symptom (flares) among individuals with UCPPS.

To further detail study design and implementation, Dr. Robinson-Garvin described the process in the flow chart below:

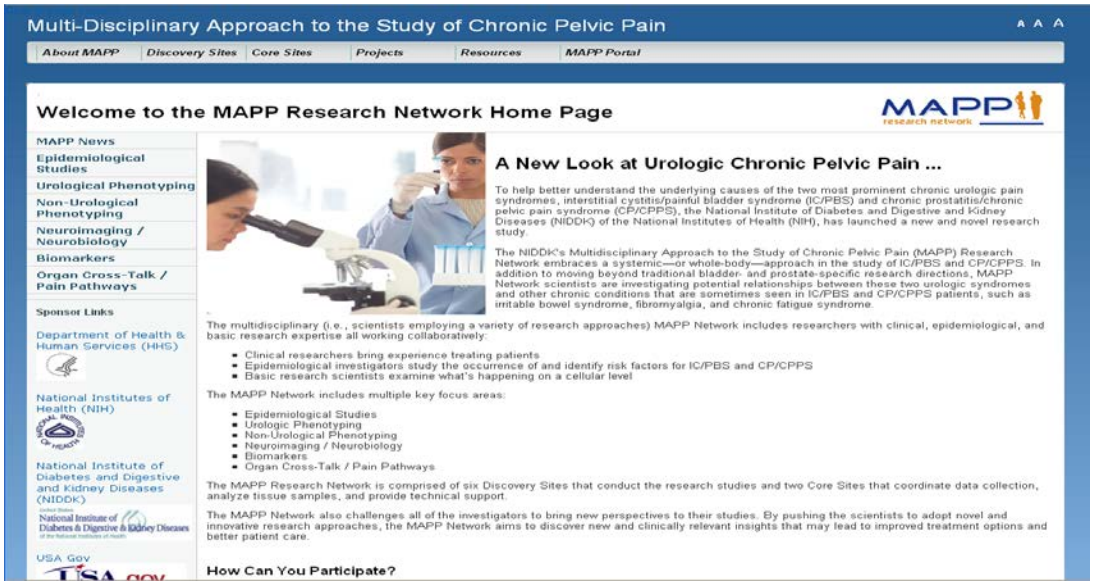


Inclusion criteria for the study included the following:

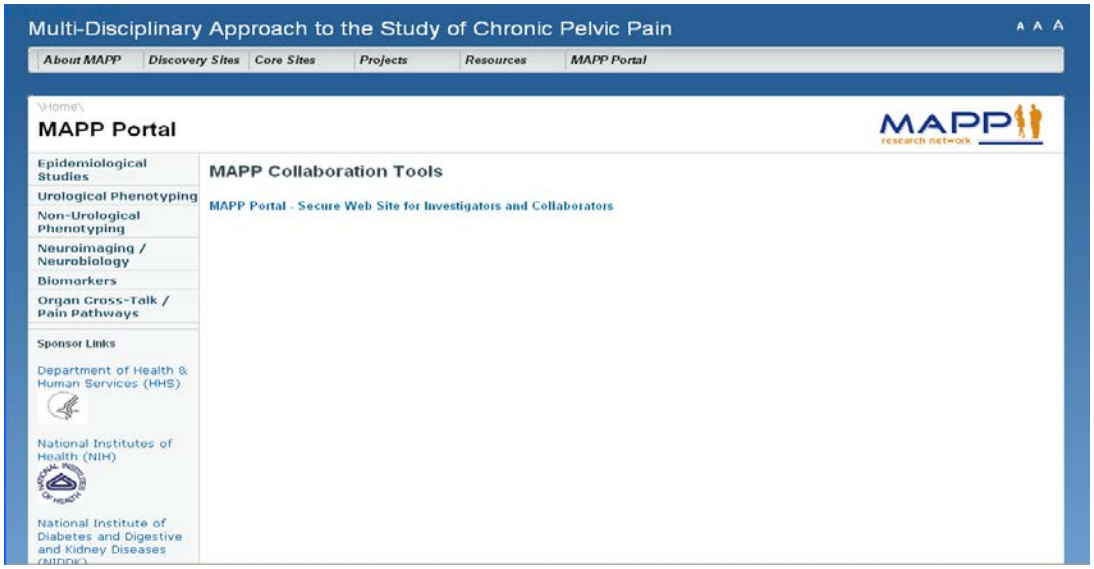
- Broad Inclusion criteria (EP)
  - Diagnosis of IC/BPS or CP/CPPS
  - Age 18+
  - Standard Exclusions (pelvic malignancy, neurologic disorders, etc.)
  - Target was 50% with symptoms < 2 years
- Controls
  - Asymptomatic
  - 'Positive' Controls – with fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome

The Trans-MAPP EP study baseline clinic visit for patients included an eligibility screening as well as phenotyping and biosample collection. Biospecimen collection included samples from patients with "flare" and "non-flare" symptoms. Patients were provided with a home collection kit.

Dr. Robinson-Garvin noted that there were special considerations for managing MAPP network activities. Centralized vs distributed roles / tasks had to be distinguished, common case report forms and standardized visit schedules across protocols had to be established, and an accessible web-based data management system and study tools were needed. Dr. Robinson-Garvin noted that data entered onsite was paired with all tissue analysis and neuroimaging data, as well as technology core data. The MAPP Web Portal (www.MAPPNETWORK.org) was created as a resource for study participants, coordinators, PIs, and individuals interested in learning about MAPP. The web portal consists of public and private sections. Public domain contents included MAPP network & study specific public iinformation, general participant information, recruitment site contacts, and link to participant survey as pictured below:



Private domain contents included a data management system, research coordinator data entry tools, study case report forms, study documents, and a participant web survey module as pictured below:



In the MAPP data management system, the participant completed web survey was designed for ease of use with one question per screen, survey windows automatically applied for correct survey, ability for participant can stop and resume survey, built in logical checks, and built in skip patterns. Additional study reports within the MAPP Network data management system were generated for recruitment and monitoring as well as kit requests and specimen tracking. The specimens shipping and drug dictionary portion of the website was designed to input participant requests. Step by step instructions for collection personnel were provided for participants to ship flare and non-flare urine samples to the TATC. Participants were provided with flare and non-flare kits to ship to TATC. The MAPP biospecimen and sample ID management portion, under

the management of the tissue analysis and technology core, provided a schedule of biologic specimen collection in the Trans-MAPP EP study (below):

Specimen	Approximate Volume	Implementation Schedule
Blood (plasma)	10 ml	Baseline, 6 , and 12 Month Clinic Visits
Spot urine	90 ml	Baseline, 6 , and 12 Month Clinic Visits
VB urine	20 ml (VB1,VB2; females); 30 ml (VB1, VB2, VB3; males)	Baseline, 6 and 12 Month Clinic Visits
Cheek Swab for DNA	Two Swabs	Baseline (or other visit if not collected at baseline) Visit
Flare urine	90 ml (VB2, biomarker) 20 ml (VB2, IE)	Two clean-catch mid-stream collections on same day. Once, at initial report of flare (specimen collected at home; shipped to TATC)
Non-Flare urine	90 ml (VB2, biomarker) 20 ml (VB2, IE)	Two clean-catch mid-stream collections on same day. Once, when randomly selected to complete Flare during report of non-flare (specimen collected at home; shipped to TATC)

The MAPP Biospecimen Collection was summarized as follows:

- **Compliance rate for collection is high ~98%**
- **>96% of participants have matching Plasma/biomarker urine, and VB1/2 specimens at baseline**
- **Specimens available for research projects**
  - Urine specimen aliquots: ~85,000
  - Plasma aliquots: ~16,000
  - DNA: >98% participants
- **Distribution of specimens for research projects**
  - Provided >6000 specimens for six sites
  - Transfer of baseline aliquots of specimens to NIDDK Central Repository
- **Quality control/Analyte analysis**
  - Specimen analysis (creatinine/protein concentration, IL-6) in support of discovery site biomarker and IE studies

Dr. Robinson-Garvin noted that the neuroimaging data curation and transfer model used an overarching identity management module to ensure that separate data elements are unambiguously linked to the correct MAPP participant identity (PID) at all stages of quality control (QC) implementation, derived variable construction and validation, as well as creation of transfer-specific datasets for analysis. The overall goal is to ensure data integrity, preparing integrated (phenotypic, image) data stored in the PAIN-LONI system,

and eventually the NIDDK repository, while also implementing a dynamic monthly update and data integration process. Neuroimaging study parameters are standardized across sites and scan data is centrally managed by the University of California at Los Angeles (UCLA) Center for Neurobiology of Stress (painrepository.org), in close collaboration with UCLA-Laboratory of Neuroimaging (LONI), which has extensive experience in the collection, storage and analysis of large multi-site MRI data sets (loni.usc.edu). In this way diverse findings across protocols may be integrated to allow a detailed characterization of a single UCPPS patient or patient sub-groups. Importantly, these efforts are also generating a unique national resource of highly detailed longitudinal clinical and epidemiological data associated with data from additional, integrated phenotyping studies and linked biological samples, for future use by the wider research community through the NIDDK Data and Sample Repositories.

The MAPP research network ancillary studies program, which was designed to encourage PIs,included the following rationale and general guidelines for ancillary studies:

- To enhance scientific value and productivity of the MAPP Research Network.
- Individual investigators will be encouraged to apply for resources to conduct ancillary studies within the MAPP Research Network.
- An ancillary study is one based on information from MAPP Network study participants in an investigation or analysis which is relevant to, yet not described in, the current MAPP Network Study protocols, and may derive support from non-MAPP Network Study funds.
- To protect the integrity of the MAPP Research Network, ancillary research endeavors must be reviewed and approved by the MAPP Steering Committee before submission of a proposal for funding (either internal or external) consideration.

Approved ancillary studies served to share MAPP forms, clinical data, biospecimens, and neuroimaging data.

Dr. Robinson-Garvin displayed the MAPP Publication activity as of 11/14:

- Published – 17
- In Press – 5
- Submitted to Journals – 3
- In Preparation – 40
- Accepted Abstracts for 2014
    - AAGUS 2014
    - APS 2014 (2 abstracts)
    - AUA 2014 (5 abstracts)
    - CUA 2014
    - IASP 2014
    - SUFU 2014

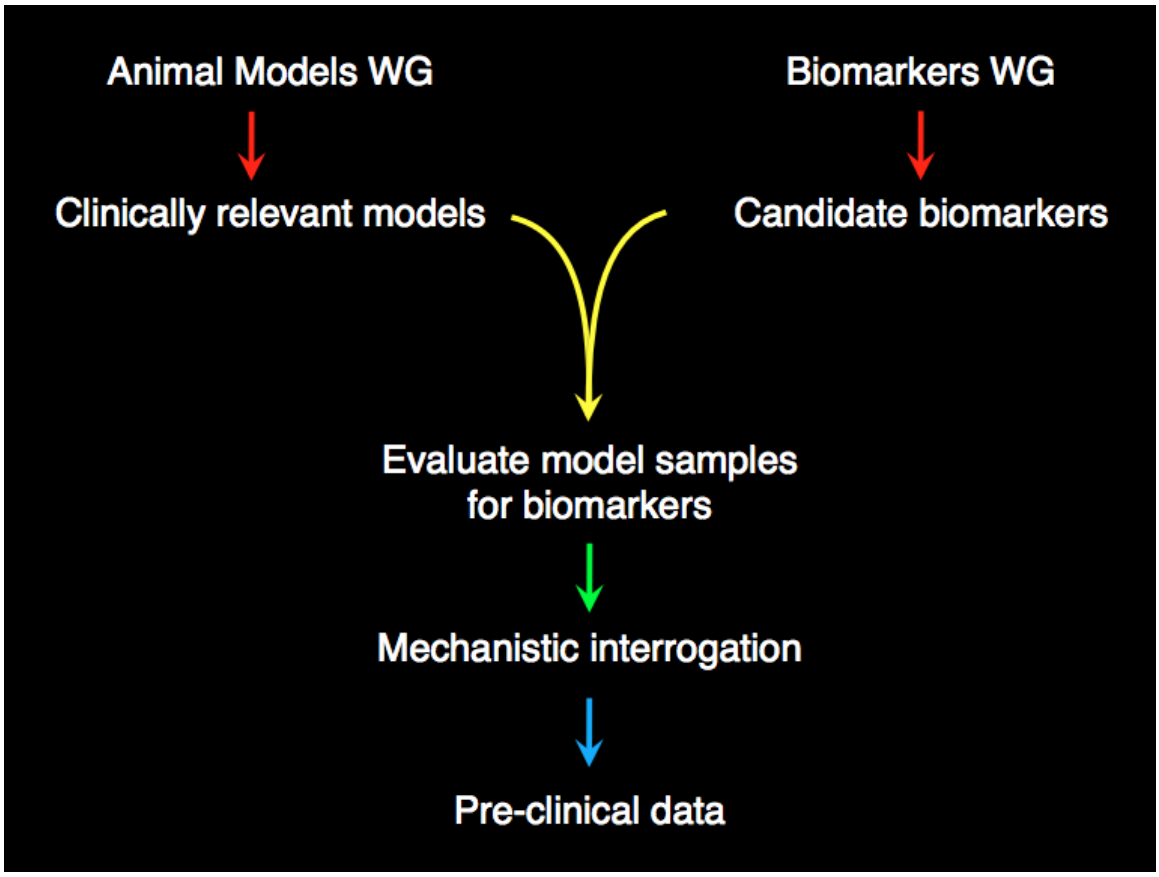
Following on the initial efforts of the MAPP study, the MAPP Network extended the follow-up with Phase I participants for up to 5 year. There are now five participants with a follow up visit at five years. In the second phase of MAPP, MAPP II, focused on symptom patterns study (SPS) design and implementation. MAPP II was built one the following guiding principles:

- Develop a longitudinal Trans-MAPP study to assess symptom change, risk, and associated phenotypic characteristics, with integrated phenotyping efforts.

- Build on insights from MAPP I
- Strive to identify and characterize clinically relevant UCPPS subgroups based on differing underlying phenotype, to inform future clinical studies (e.g., trials).
- Incorporate additional, complementary layers of phenotyping to include: Neurobiology, molecular markers, microbiome, PRO measures, and mechanistic and translational studies using validated animal models.
- Incorporate new and novel methods to address clinically relevant questions

The timeline for MAPP II is longer than MAPP (12 months) I so that longitudinal data of 36 months can be completed. One year is devoted to 1 year phenotyping and follow-up and two additional years are dedicated to follow up. The monthly online data capture for MAPP II included questions to participants about use of medications and non-mediation therapies. All participants received reminders to contact their research coordinator before starting therapy if they received a prescription for one of the targeted therapies: oral opioids, tricyclic antidepressants, pelvic floor physical therapy, elmiron/oral pentosan polysuflate (female only), or alpha-adrenergic blockers (male only). MAPP II data domains continued to collect demographic, urologic, non-urologic, and biopsychosocial information.

The aim of the MAPP II Animal Modelers Work Group was to test whether putative biomarkers identified in patients are mechanistically linked to voiding dysfunction/pain in models (mechanistic validation of putative biomarkers), e.g. XXX (see below). The Group found several biomarkers.



In conclusion, Dr. Robinson-Garvin presented a graphic for the proposed composition of MAPP Phase II symptom patterns study compared to MAPP Phase I UCPPS participants by target recruitment factors (below):

Actual Dist'n: MAPP Phase I

BPI Body Map Location	Sex	UCPPS Subtype				Total
		BPS: No	BPS:Yes			
		Neither	Painful Filling	Painful Urgency	Both	
PP Only	Males	14 (24.56)	2 (3.51)	17 (29.82)	24 (42.11)	57
	Females	7 (13.73)	4 (7,84)	14 (27.45)	26 (50.98)	51
PP and Beyond	Males	33 (24.63)	14 (10.45)	33 (24.63)	54 (40.30)	134
	Females	20 (10.99)	16 (8.79)	34 (18.68)	112 (61.54)	182
Total		74	36	98	216	424

Proposed Dist'n: MAPP Phase II

BPI Body Map Location	Sex	UCPPS Subtype				Total
		BPS: No	BPS:Yes			
		Neither	Painful Filling	Painful Urgency	Both	
PP Only	Males	60	40		60	160
	Females	60	40		60	160
PP and Beyond	Males	60	40		60	160
	Females	60	40		60	160
Total		240	160		240	640

Meeting participant comments:

- To successfully reprogram PIs to work in a clinical network and with uniform standards set by the DCC, PIs wanted a clear justification of where this effort was going.
- To create structure of the network, flexibility from an administrative point was important.
- At the coordinating core, there are many different workgroups and teams that comprise this core.

MAPP Research Network: Analytic Approaches for a Multifaceted Study of UCPPS
Alisa Stephen-Shields, Ph.D. University of Pennsylvania, Philadelphia, PA

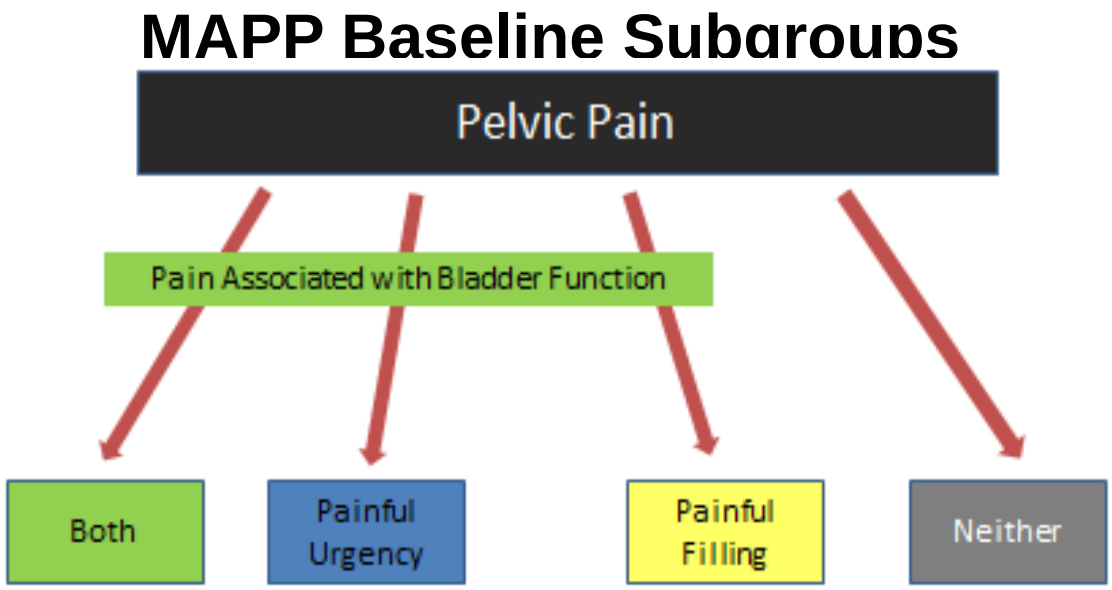
Following Dr. Robinson-Garvin, Dr. Stephen-Shields introduced herself to meeting participants. Dr. Stephen-Shields noted that the Trans-MAPP Epidemiology and phenotyping protocol was the protocol that tied everything together and supplied the clinical data and psychological factor. She presented a graphic that displayed the number of participants (target, enrolled) by cohort, sex, and number of participants with biospecimens by type, MRI scans completed and PPT data collected at baseline visit. A challenge in obtaining the data was developing the methods. Making sense of high dimensional data required defining a bivariate endpoint using principal components and factor analysis to measure pain severity and urinary severity. Different forms such as anxiety and depression were also collected.

The following questions from the RAND Interstitial Cystitis Epidemiology (RICE) Male Study were related to BPS subtypes in MAPP:

- Do you have bladder pain?

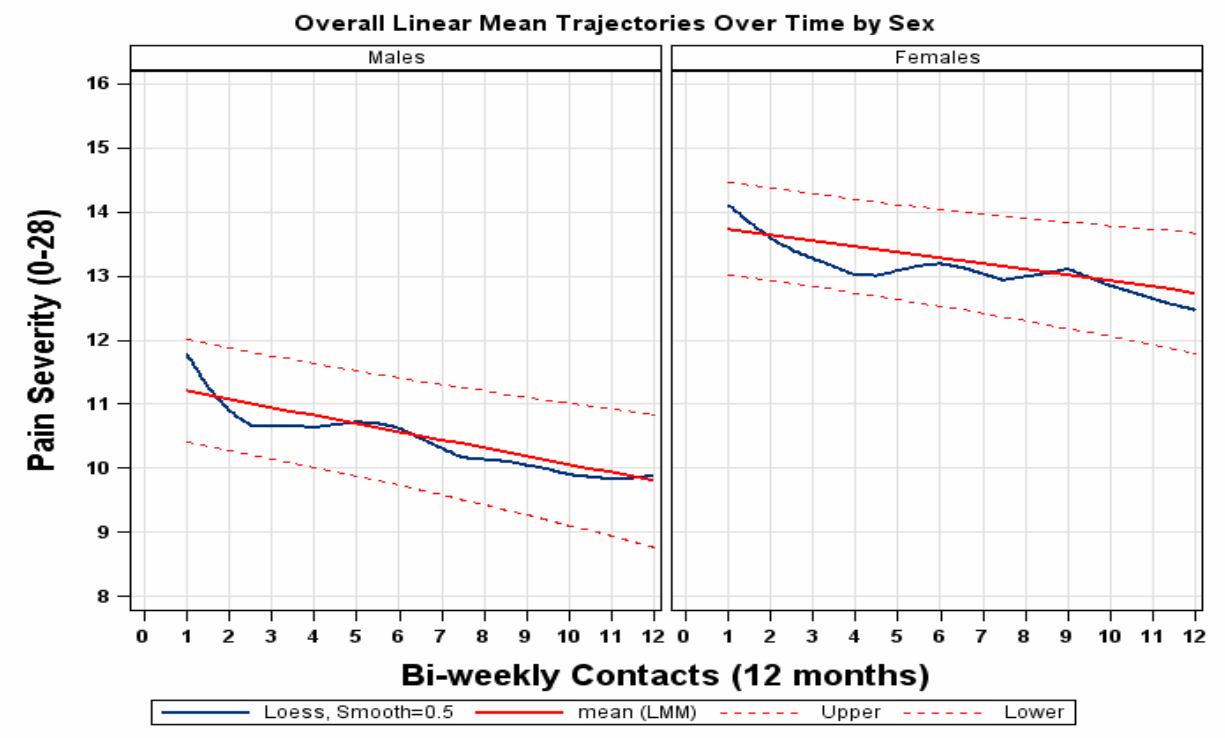
- What is your urgency due to pain, pressure, discomfort?
- Does the pain, pressure, discomfort get worse as the bladder fills?

Dr. Stephen-Shields displayed a graphic of the BPS subtypes derived from RICE Questions:



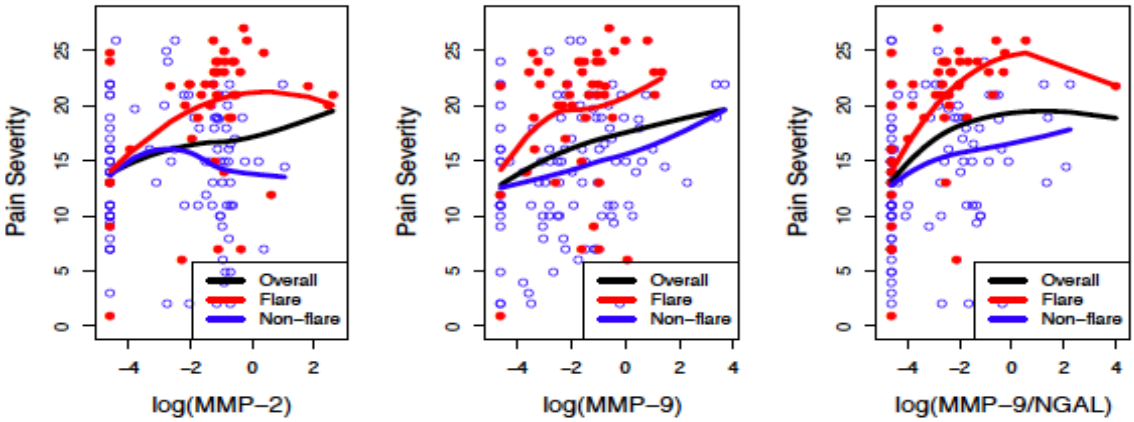
<u>"Painful Filling"</u> **RICE Q4=1** **(Gets Worse)**	**<u>"Painful Urgency"</u>** **RICE Q3=1 (Urgency due to Pain, Pressure, Discomfort)**		
Frequency **Row Pct**	**No**	**Yes**	**Total**
No	74 17.45	98 23.11	172 40.57
Yes	36 8.49	216 50.94	252 59.43
Total	110 25.94	314 74.06	424 100.00

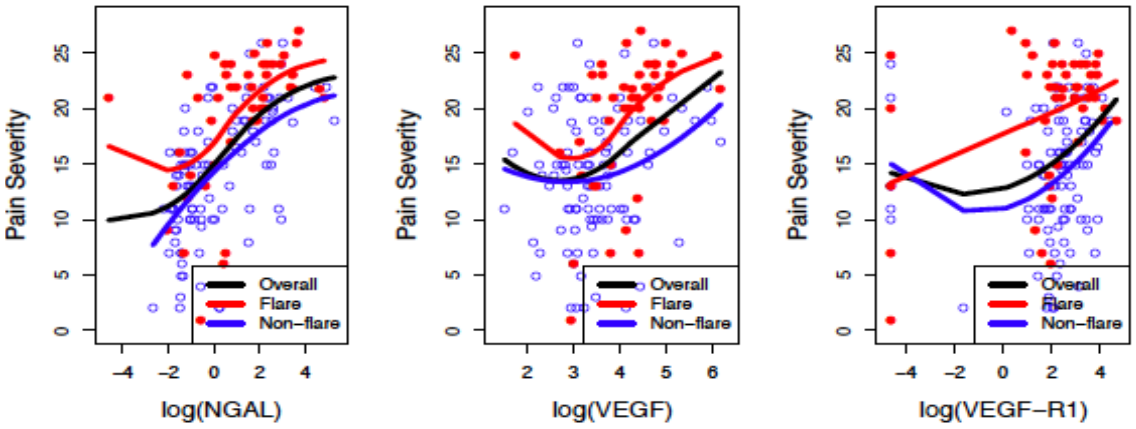
Dr. Stephen-Shields showed an example of UCPPS symptom patterns for two patients and noted that, within the pain severity score there was a linear mean trajectory over time by sex:



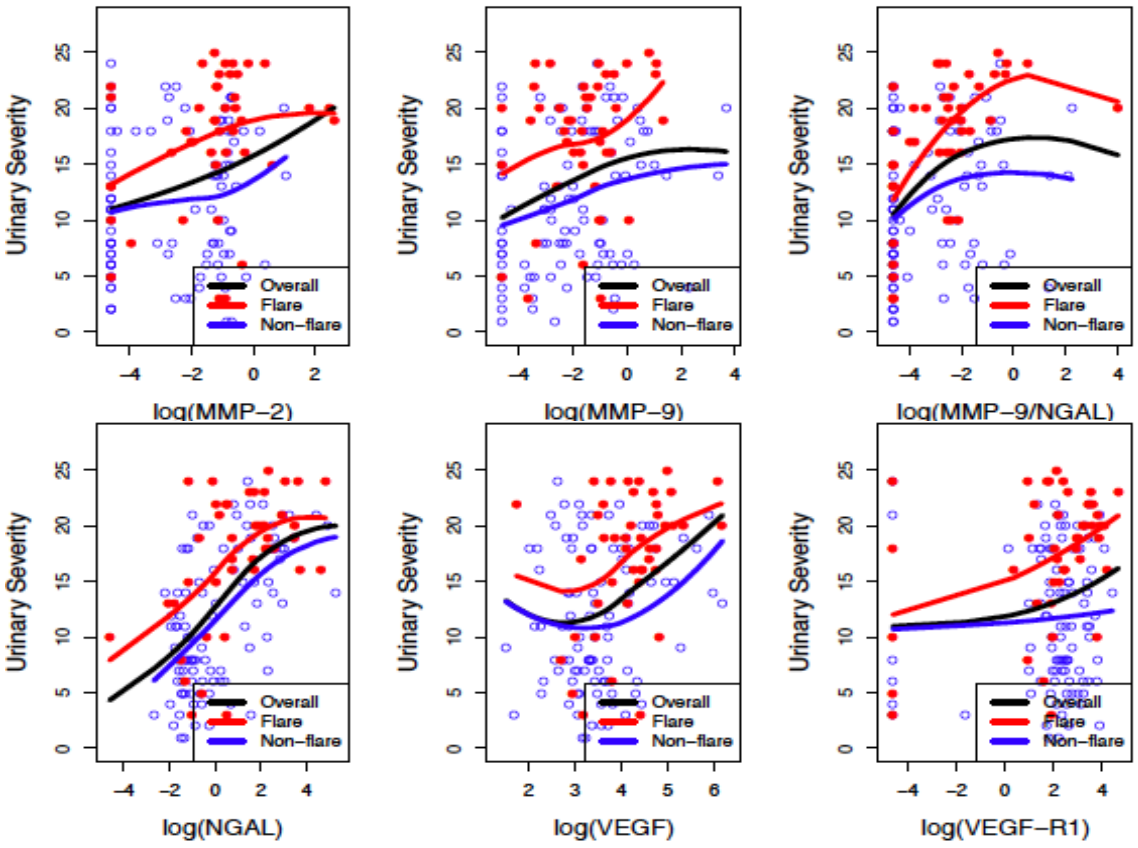
Dr. Stephens-Shield noted that patients were classified into clusters by similar longitudinal pattern and showed either stabilization or improvement according to the pain severity scale. Among other key findings, Dr. Stephens-Shield noted that the VB1 microbiome in male UCPPS subjects versus controls showed significant difference. Also, the flare and fungi relationship in VB2 specimens was not strong. The fungi were more prevalent in the participants who listed "flare" occurrences.

Dr. Stephens-Shield noted key biomarker in pain severity for females:





Key biomarkers in urinary severity for females were used to predict change: The findings suggested that high levels of biomarkers had faster rates of decline in severity:



In conclusion, Dr. Stephens-Shield summarized the following points: 1) The MAPP Research Network is an integrative approach to the study of Urological Chronic Pelvic Pain Syndrome; 2) Analyses to date have used a variety of standard and advanced methods across disciplines to characterize patients' symptoms and progression, and 3) MAPP I emergent findings will be further validated in MAPP II.

Meeting participant comments:

- Pelvic pain and pelvic pain and beyond categories make sense. Longitudinal data will be helpful to communicate future treatment trend for IC patients to patients. Only 20% have a trajectory of worsening symptoms over 1 yea. Most patients do not get worse.
- MAPP II will explore physical therapy options that will be helpful to evaluate treatment options for patients.
- This group has been very successful at recruiting and retaining a population for a condition that is not prevalent.
- Susie Meikle from NICHD noted that they are encouraging applications on vulvodynia.. Also, endometriosis is an area of overlap with pelvic pain. Expanding portfolio on endometriosis. Recently acquired expertise to help the Institute expand this area.
- Dr. Mullins noted the trans-NIH pain consortium. This consortium is becoming more interested in comorbid pain conditions.
- Martha Matocha from NINR noted that they study symptoms rather than conditions. However, irritable bowel syndrome is being researched. There is growing research in this area.
- Susie Meikle from NICHD noted that the conceptual framework for a network such as this is very important. Also, NICHD mentioned two possible opportunities for collaboration with NIDDK.
- Martha Matocha from NINR noted the importance of self reported data. Frequency and timeliness for recall is important. Access for patients to self report data is very important to increase results.
- Mary Worstell from HHS noted that the focus should be on "how does this help patients today". Get message out that only 20% of population with IC condition gets worse. How do we get research results and information out to the provider community so that it might be communicated to patients? Also, how can patients change course of this disease?
- Dr. Star noted the need for multidisciplinary collaboration in large projects. Where do we do these efforts and how far back do we go? It is important to not get too far ahead of the data. Are there other efforts that may complement MAPP?
- Mary Worstell from HHS noted the importance of gathering info across the lifespan. Chronic fatigue syndrome, chronic pelvic pain, fibromaygia are all understudied. Chronic pain is a condition itself. Important to move research results to other areas such as this. Dr. Mullins noted that the MAPP group is looking to reach out to other communities with data.

Discussion – Federal resources – is there more we should do?

Dr. Bavendam noted MAPP and LURN are the two established networks for both genders. These are focused on patients that are in treatment. The Prevention of LUTS (PLUS) in women initiative has been launched and applications are forthcoming. It will consider bladder conditions broadly including urinary incontinence, urinary tract infections and bladder pain syndrome/interstitial cystitis.There is a need to focus this initiative on early stage patients. The NICHD pelvic floor network is doing important work primarily focused on treatment trials. There is a need to communicate cross-institute to develop research needs, conduct research and disseminate the findings.

Susie noted that the pelvic organ prolapse and anal incontinence are related but notinterchangeable.

Dr. Bavendam noted that the next UICC meeting will focus on urinary stone disease.

12:30 p.m. Meeting Adjourned