

AWARD NUMBER: W81XWH-19-1-0288

TITLE: Deployable Interstitial Cystitis Urine Diagnostic Technology Development

PRINCIPAL INVESTIGATOR: Dr. Bernadette Zwaans

CONTRACTING ORGANIZATION: William Beaumont Hospital Research Institute

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14. ABSTRACT This proposal directly focuses on the PRMRP Topic Area of Interstitial Cystitis (IC), including the Area of Encouragement for the identification of biological markers for making a definitive diagnosis of IC. This is not a clinical trial as there is no intervention. The <i>objective</i> of this grant is to develop a new diagnostic tool, the Interstitial Cystitis Risk Score (IC-RS), to identify and classify IC patients. In year 3, we continued online and clinical collection with all sites; we currently have 1817 samples collected. In addition, 3 manuscripts related to this study were published, and our work was presented at the 2022 annual meeting of the American Urological Association. During year 3, this grant got transitioned to a new PI, Dr. Bernadette Zwaans, as Dr. Lamb pursued other career opportunities. Dr. Zwaans is dedicated to completing the aims of this grant. Although we encountered delays in our research due to the COVID-19 pandemic, we are on track to complete all the aims of this grant. A request for NCE was approved in spring of 2022.					
15. SUBJECT TERMS Interstitial Cystitis; Bladder Pain Syndrome; Diagnostic Test; Machine Learning; Cystitis, Interstitial; Pelvic pain; Lower Urinary Tract Symptoms; Pelvic Floor Disorders; Biomarkers					
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1. INTRODUCTION:

The subject of this research is to improve diagnosis of Interstitial Cystitis (IC), a devastating disease of pain and altered urinary function that is challenging to diagnose. The purpose of this research is to develop a simple test for diagnosing IC based on urine and symptom scores called the Interstitial Cystitis Risk Score (IC-RS). Our scope of this research includes: 1) Refining and evaluating IC-RS in a large, crowdsourced collection of urine samples from IC patients and normal controls; 2) Comparing patient collected IC-RS from similar collected urine samples and demographic from three academic urology practices that will test civilian and military patients with and without IC and also cohorts of patients with UTI, bladder cancer, and overactive bladder with incontinence to assess specificity of the IC-RS; and 3) Urine kit optimization.

2. KEYWORDS:

Interstitial Cystitis; Bladder Pain Syndrome; Diagnostic Test; Machine Learning; Cystitis, Interstitial; Pelvic pain; Lower Urinary Tract Symptoms; Pelvic Floor Disorders; Biomarkers

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: Refine and evaluate IC-RS in a large, crowdsourced collection of urine samples from IC patients and normal controls.

Major Task 1: Study Start Up

- Target Date: 6 months
- Milestones Achieved: Local IRB and HRPO Approval; Trained research team; Study logistics determined; Online tools and urine collection kits ready
- Completed, all milestones achieved by 11 months

Major Task 2: Strategy for Participant recruitment, shipping & returning of collection kits

- Target Date: 28 months
- Milestones: Study begins; 1000 IC, 1000 non-IC human urine samples recruited and processed; Evaluation of shipping kits and recruitment strategies
- Year 4 actual: We have shipped 1192 IC and 2384 non-IC human urine sample collection kits 565 IC and 701 non-IC human urine samples have been collected and processed. Manuscript on description of crowdsource methodology has been published.
- Completed

Aim 1b. Refine and evaluate IC-RS in urine samples from men and women with IC and from normal controls within the military.

Major Task 3: Participant recruitment, shipping & returning of collection kits targeting military personnel.

- Target Date: 28 months
- Milestones: Study begins; 100 urine samples recruited and evaluated; Evaluation and adjustment of shipping kits and recruitment strategies for military personnel (including veterans).
- Year 4 actual: No change from prior year. Milestone had been completed.
- Completed, all milestones completed by 28 months

Major Task 4: Data Acquisition and Analysis

- Target Date: 34 months
- Milestone: Report and review results from data analyses
- Year 4 Actual: Data acquisition is completed on 100% of collected samples; data analysis is completed; finalizing manuscript
- 90% completed

Specific Aim 2: Compare patient collected IC-RS from similar collected urine samples and demographic from three academic urology practices that will test civilian and military patients with and without IC to assess specificity of the IC-RS.

Major Task 1: Study start-up

- Target Date: 6 months
- Milestones: Local IRBs and HRPO Approvals; Trained research teams; Study logistics determined.
- Completed, all milestones achieved by 10 months

Major Task 2: Recruitment and Collection

- Target Date: 28 months
- Milestones: Study begins; Completed urine sample and corresponding survey collection; 75 IC and 150 non-IC human urine samples recruited and evaluated per site (total: 225 IC and 450 non-IC)
- Year 4 actual: 79 IC and 139 non-IC urine samples collected at Baylor. 44 IC and 192 non-IC urine samples have been collected at Einstein. 15 non-IC urine samples have been collected at Beaumont. Total 123 IC and 346 non-IC samples are collected.
- 80% completed. This is expected due to COVID-19 restrictions.

Major Task 3: Data Acquisition and Analysis

- Target Date: 36 months
- Milestones: Report and review results from data analyses; manuscript and abstracts submissions
- Year 4 actual: Data analysis under way. An abstract describing the machine learning based symptom score for IC was presented at the 2023 AUA annual meeting. The manuscript for this study is expected to be finalized in the fall of 2023. Two additional manuscripts are in preparation: 1. Comparing online crowdsourcing with clinic patient enrollment, and 2. Describing characteristics of our IC patient population. The poster presented at the 2023 AUA is included in the appendix.
- 70% completed

Specific Aim 3: Urine kit optimization

Major Task 1: Evaluation of kits and online support tools (e.g. videos, documents, etc.)

- Target Date: 28 months
- Milestones: Optimized urine collection kit ready-for market
- Year 4 actual: No change from prior year. Milestone had been completed.
- Completed, all milestones achieved at 24 months

Major Task 2: As needed, redesign kits to reflect suggested improvements from Task 1 above

- Target Date: 28 months
- Milestones: Optimized urine collection kit ready-for market
- Year 4 actual: Redesign of kit completed; kit manufacturing delays due to COVID-19; need to finish additional analysis for survey design.
- 60% completed

Aim 3b: Advance the technology to perform IC-RS in a small table-top system that can be run in any basic clinical laboratories regardless of location and without specialized expertise.

Major Task 1: Develop and optimize assay on new platform

- Target Date: 28 months
- Milestones: IC-RS work-flow includes a small table-top system; verified to work at three different sites; manuscript and abstract submission
- Year 4 actual: We have obtained and setup the ELLA system (Protein Simple) and begin validation testing for initial Quality Controls, a critical step to ensure robust and meaningful results. We are actively working with Bio-Techne to develop the GRO/CXCL1 cartridge for human urine samples. This development is anticipated to be completed by December 2023, allowing the remainder of the time to finalize the data collection, analysis and dissemination.
- 40% completed

Major Task 2: Verify results across platforms at two other geographical locations

- Target Date: 36 months
- Milestones: IC-RS work-flow includes a small table-top system; verified to work at three different sites; manuscript and abstract submission.
- Year 4 actual: the completion of this task is dependent on the completion of Major Task 1.
- 0% completed

Major Task 3: Translation of final product for commercialization with Beaumont Technology Transfer Mi-KickStart

- Target Date: 36 months
- Milestones: Patent issued.
- Year 4 actual: no change from prior year.
- 20% completed

What was accomplished under these goals?

To date, we have completed our online participant recruitment and are finalizing clinic sample collection. Data acquisition using the Luminex system has been completed. And to date several manuscripts have been published describing study methodology and the success of using crowdsourcing to collect urine samples. We maintained regular research study communication through virtual, online meetings in addition to email and phone calls. Full data analysis using computer learning is completed and the manuscript describing these results in progress. Feedback on the urine at-home collection kit and online support tools was completed and optimization is

completed. Despite significant work, we have so far been unsuccessful in transferring the IC-RS to work on a smaller platform due to issues around quality controls and specificity which we will continue to work on addressing. We have also presented our work at the 2023 annual meeting of the American Urological Association in Chicago, IL.

What opportunities for training and professional development has the project provided?

Study training for all study investigators was done at a meeting in person in Washington DC in September 2019. Due to COVID-19 and travel restrictions, additional study training for study staff has occurred by video conferencing (Microsoft Teams). Webinars that covered laboratory techniques related to this grant were shared with laboratory staff and attended by Sarah Bartolone and Elijah Ward. Dr. Lamb attended several Rapid Acceleration of Diagnostics (RADx) seminars and met with staff regarding the development and commercialization of innovative technologies for diagnostic testing. This project was not intended to provide training and professional development opportunities outside of what was necessary for the research study. However, we have provided an opportunity for Prasad Sharma, a promising medical student who is a veteran, to gain research experience. Prasad has published 1 manuscript, co-authored another manuscript, and has presented his work at an international conference. He is now applying for urology residency programs.

How were the results disseminated to communities of interest?

Nothing to Report.

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

Our main focus will be finalizing the main manuscript on the IC score developed using machine learning, optimization of the technology to perform IC-RS in a small table-top system, and translation of final product for commercialization. We are currently working with Bio-Techne to develop a GRO/CXCL1 cartridge, one of the 4 analytes that form the IC-RS score, to be able to run the IC-RS as a small table-top system. We are doing this in partnership with the vendor. Lastly, we will work with Beaumont's Commercialization Center to develop a final product package ready for commercialization in partnership with a vendor who has extensive expertise in this area.

4. IMPACT:

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

We have published and presented our crowdsourcing methodology allowing for other research groups to apply our methods to other research projects. In addition, we have analyzed and published the cost effectiveness of online sample collection to clinical sample collection and have found that online sample collection is more cost effective. Three additional manuscripts on crowdsourcing, characterizing our IC population and on the IC-RS score are being finalized.

What was the impact on other disciplines?

Because of our work on this DoD project, we have an intimate knowledge of how to design good, clinically meaningful diagnostic tests including how to ensure they are sensitive, specific, reliable, and validated. We are also knowledgeable as to the regulatory requirements for FDA approval.

Because of our work on this DoD, we were well positioned to be the first globally to observe that some COVID-19 patients suffer from severe bladder dysfunction, including inflammation in their urine.

What was the impact on technology transfer?

We were issued the following patent.

Chancellor MB, Lamb LE, Janicki JJ. Methods for Detecting, Diagnosing, and Treating Ulcerative Interstitial Cystitis. United States Patent US 10,859,579 (filed March 31, 2016, and issued December 18, 2020).

What was the impact on society beyond science and technology?

Given the extensive disruption of COVID-19 on society, and the letters we get from patients and doctors from across the globe, we know there has been an incredible impact on global public health.

5. CHANGES/PROBLEMS:

Due to an initial delay to obtain HRPO approval and then COVID-19, we experienced delays to study start in year 1. However, we have overcome this and are now on track to accomplish our aims without changes required to our approach or SOW. In addition, there was a change in PI at the beginning of year. Dr. Zwaans has taken over as PI of this grant and is dedicated to successfully complete the aims of this study.

Actual or anticipated problems or delays and actions or plans to resolve them

1. COVID-19 pandemic completely closed some clinics for a while and has reduced some clinical staff to only 1 day per week. Like any current research study, it is difficult to fully anticipate how the COVID-19 pandemic will continue to impact this study. *If anything, this validates that there is a strong need for research studies that can be completed outside the clinic and instead use alternative strategies like online crowdsourcing and at-home sample collection, as will be done in Aim 1 of this grant.* As such, we have been very successful so far with our crowdsourcing and online recruitment of patients. We will ensure that as our crowdsourcing collection progresses, that we will pay special attention to both effective and ineffective online recruitment strategies, and make sure to disseminate these findings with the larger scientific and medical research communities. We have already shared with the larger urology community our plans for effective crowdsourcing strategies at the annual American Urological Association meeting and a prepared manuscript submitted to PLoS Digital Health (see section 6).
2. We have obtained and setup the ELLA system (Protein Simple) and began validation testing for initial Quality Controls, a critical step to ensure robust and meaningful results. We have determined that there was cross-reactivity for one of the analytes, GRO/CXCL1, in human urine samples and we are working to resolving this issue in cooperation with the vendor's tech support team.
3. Change in PI took place in fall of 2021. Dr. Zwaans now serves as PI of the study. Dr. Lamb still contributes 5% of her time to the study as consultant.

Changes that had a significant impact on expenditures

As stated previously, enrollment was initially limited by the COVID-19 pandemic. Subsequently, the rate of enrollment was slower than anticipated, resulting in cost saving in salary, travel, subcontract and other miscellaneous costs. Budgeted funds will be needed to achieve the aims of the study.

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

None

Significant changes in use or care of human subjects

None

Significant changes in use or care of vertebrate animals

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

Publications, conference papers, and presentations

Lamb LE. 2020. Translational Research in Benign Bladder Disorders. 17th Annual Inside Urology, Great Lakes SUNA Chapter 2020 Conference. Livonia, MI, March 13, 2020. (canceled due to COVID-19)

Lamb LE, Bartolone SN, Janicki JJ, Peters KM, ICA, Abraham N, Laudano M, Smith CP, Chancellor MB. 2020. National Collaborative Crowdsourcing Method of Diagnostic Biomarker Development for Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS). American Urological Association’s 2020 Annual Meeting, Washington DC, May 15. (virtual due to COVID-19; published in AUA journal)

Lamb LE. 2020. Developing a Point-of-Risk Molecular Test for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). European Society for Translational Medicine (EUSTM), Vienna, Austria, September 25, 2020. (virtual due to COVID-19)

Lamb LE. 2020. Developing a Point-of-Risk Test for novel Coronavirus 2019. Frontiers in Bioengineering Research, Rice University. Houston, TX, April 30, 2020. (virtual due to COVID-19)

Lamb LE. 2021. Improving Diagnostic Testing for Interstitial Cystitis, Radiation Cystitis, and COVID-19. Oakland University William Beaumont School of Medicine Medical Education Week. Rochester, MI, May 20, 2021. (virtual due to COVID-19)

Lamb LE. 2021. Interstitial Cystitis Diagnostic Score Development using Crowdsourcing and Machine Learning Algorithm. American Urological Association Annual Meeting/Society of Basic Urological Science Breakout Session. Las Vegas, NV, September 11, 2021. (published in AUA journal)

Lamb LE and Chancellor MB. 2021. Improving Patient Outcomes through Research in Benign Urology. Neurourology & Pelvic Reconstructive Surgery (NPR) Joint Urogyn Conference. University of Michigan, Ann Arbor, MI. February 15, 2021. (virtual due to COVID-19)

Lamb LE. 2020. Developing a Point-of-Risk Test for COVID-19 and Interstitial Cystitis. University College Cork's Translational Medicine Conference, University College Cork. Cork, Ireland, January 28, 2020. (virtual due to COVID-19)

Ward E, Bartolone S, Carabulea A, Sharma P, Janicki J, Laudano M, Abraham N, Smith C, Zwaans B, *Chancellor M, Lamb L. Comparing Concentration of Inflammatory Cytokines in IC, OAB, UTI, and Bladder Cancer Urine Samples. 2022 American Urological Association annual meeting, New Orleans, LA, USA. May 13-16, 2022. *Presenting author

*Sharma P, Bartolone S, Ward E, Carabulea A, Peters K, Janicki J, Abraham N, Laudano M, Smith C, Zwaans B, Chancellor M, Lamb L. Conducting Urology Research during COVID-19: Social Media-Based Crowdsourcing of Urine Samples for Biomarker Development. 2022 American Urological Association annual meeting, New Orleans, LA, USA. May 13-16, 2022. *Presenting author

Sharma P*, Bartolone S, Ward E, Carabulea A, Peters K, Janicki J, Abraham N, Laudano M, Smith C, Zwaans B, Chancellor M, Lamb L. A Cost and Time Analysis of Participant Recruitment and Urine Sample Collection through Social Media Optimization. 2022 American Urological Association annual meeting, New Orleans, LA, USA. May 13-16, 2022. *Presenting author

Laura E. Lamb, Joseph J. Janicki, Nitya Abraham, Melissa Laudano, Christopher P. Smith, Sarah N. Bartolone, Elijah P. Ward, Kenneth M. Peters, Bernadette Zwaans, *Chancellor MB. Classification of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) Using a Machine Learning Based Symptom Score Constructed on Inflammatory Urine Cytokines and Patient Reported Outcomes Improves Diagnosis. 2023 American Urological Association annual meeting, Chicago, IL, USA. April 29 – May 1, 2023. *Presenting author

Journal publications

Lamb LE, Dhar N, Timar R, Wills M, Dhar S, Chancellor MB. COVID-19 inflammation results in urine cytokine elevation and causes COVID-19 associated cystitis (CAC). *Med Hypotheses*. 2020 Nov 5:110375. doi: 10.1016/j.mehy.2020.110375. Epub ahead of print. PMID: 33213997; PMCID: PMC7644255.

Dhar N, Dhar S, Timar R, Lucas S, Lamb LE, Chancellor MB. De Novo Urinary Symptoms Associated With COVID-19: COVID-19-Associated Cystitis. *J Clin Med Res*. 2020

Oct;12(10):681-682. doi: 10.14740/jocmr4294. Epub 2020 Sep 21. PMID: 33029276; PMCID: PMC7524562.

Ward EP, Bartolone SN, Chancellor MB, Peters KM, Lamb LE. Proteomic analysis of bladder biopsies from interstitial cystitis/bladder pain syndrome patients with and without Hunner's lesions reveals differences in expression of inflammatory and structural proteins. *BMC Urol.* 2020 Nov 7;20(1):180. doi: 10.1186/s12894-020-00751-x. PMID: 33160333; PMCID: PMC7648270.

Lamb LE, Bartolone SN, Ward E, Chancellor MB. Rapid detection of novel coronavirus/Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by reverse transcription-loop-mediated isothermal amplification. *PLoS One.* 2020;15(6):e0234682. doi: 10.1371/journal.pone.0234682. eCollection 2020. PubMed PMID: 32530929; PubMed Central PMCID: PMC7292379.

Preprints on medRxiv:2020.2002.2019.20025155. doi:10.1101/2020.02.19.20025155 and on SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3539654

Appeared in Top Ten of All Time Lancet Papers on SSRN

Appeared in Top Ten of All Time MedRN: Respiratory Tract Infections on SSRN

Top 10% SSRN Authors by total new downloads for 2020 and 2021

Top Article Downloaded from Institution according to ResearchGate in 2020

Ward EP, Bartolone SN, Carabulea AL, Sharma P, Chancellor MB, Lamb LE. Using Social Media to Crowdsource Collection of Urine Samples during a National Pandemic. *Int Urol Nephrol.* 2022 Mar;54(3):493-498. doi: 10.1007/s11255-022-03108-5. Epub 2022 Jan 26. PMID: 35080680

Sharma P, Lamb LE, Bartolone SN, Ward EP, Janicki JJ, Peters KM, Abraham N, Laudano M, Smith CP, Zwaans BMM, Chancellor MB. A Cost, Time, and Demographic Analysis of Participant Recruitment and Urine Sample Collection through Social Media Optimization. *Urology Practice*, doi: 10.1097/UPJ.0000000000000339

Chancellor MB, Lamb LE, Ward EP, Bartolone SN, Sharma P, Janicki JJ, Smith CP, Laudano M, Abraham N, Zwaans BMM. Comparing Concentration of Urinary Inflammatory Cytokines in Interstitial Cystitis, Overactive Bladder, Urinary Tract Infection and Bladder Cancer. *Urological Science*, Mar 2022. doi: 10.4103/UROS.UROS_26_22

Books or other non-periodical, one-time publications

Nothing to Report

Other publications, conference papers and presentations.

Nothing to Report

Website(s) or other Internet site(s)

The website that was dedicated to the study and that contained all study information, study questions and answers, videos on the study, contact information etc. was taken down as the study has completed the collection of urine samples through crowdsourcing.

<https://www.Beaumont.org/urology-research>

Website focused on our translational research lab at Beaumont. This includes a description of our research studies including a link to the above study website, publications, funding sources including DoD, study personnel, and contact information.

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Chancellor MB, Lamb LE, Janicki JJ. Methods for Detecting, Diagnosing, and Treating Ulcerative Interstitial Cystitis. United States Patent US 10,859,579 (filed March 31, 2016; issued December 18, 2020).

Other Products

Dr. Lamb was awarded the 2021 COVID Pandemic-related Outstanding Research Accomplishment (Individual) at the Military Health System Research Symposium. This award “recognizes outstanding research contributions by an individual research scientist with the focus on significant accomplishment(s) of high impact related to the COVID-19 pandemic. This individual has demonstrated outstanding leadership in pursuit of excellence for their country and service.”

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Bernadette Zwaans
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0002-4717-5751
Nearest person month worked:	2
Contribution to Project:	No Change
Funding Support:	No Change

Name:	Michael Chancellor
Project Role:	co-I
Researcher Identifier (e.g. ORCID ID):	ORCID ID 0000-0001-9480-8972
Nearest person month worked:	1
Contribution to Project:	No Change
Funding Support:	No Change

Name: Sarah Bartolone
Project Role: Assistant Manager, Research (promoted from Research Coordinator)
Researcher Identifier (e.g. ORCID ID): ORCID ID 0000-0001-9040-7055
Nearest person month worked: 9
Contribution to Project: No Change
Funding Support: No Change

Name: Elijah Ward
Project Role: Research Coordinator I (promoted from Research Assistant II)
Researcher Identifier (e.g. ORCID ID): ORCID ID 0000-0002-9405-6763
Nearest person month worked: 10
Contribution to Project: No Change
Funding Support: No Change

Name: Nitya Abraham, MD
Project Role: Investigator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: No Change
Funding Support: No Change

Name: Melissa Laudano, MD
Project Role: Sub-I
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: No Change
Funding Support: No Change

Name: Rutul Patel
Project Role: Research Coordinator
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: Coordinated regulatory and study processes
Funding Support: No Change

Name: Christopher Smith MD
Project Role: PI
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 1
Contribution to Project: No Change
Funding Support: No Change

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 for: Nitya Abraham, Melissa Laudano, Christopher Smith

Dr. Zwaans obtained funding from the NIH/NIDDK for an R01 research grant entitled “The role of amphiregulin in mediating radiation cystitis in cancer survivors” in April 2023. Dr. Chancellor is co-investigator on this study. Dr. Zwaans dedicates 3.6 calendar months and Dr. Chancellor dedicates 0.6 calendar months to this study. There is no overlap or conflict between the R01 funding and this award.

Title: The role of amphiregulin in mediating radiation cystitis in cancer survivors

Major Goals: To understand the effect of changes in mechanical characteristics of urinary bladder tissue, due to fibrosis, on the development of bladder dysfunction.

Status of Support: Awarded

Name of PD/PI: Dr. Bernadette Zwaans

Role: PI

Source of Support: National Institutes of Health/NIDDK

Primary Place of Performance: Beaumont Hospital, Royal Oak

Project/Proposal Start and End Date: 4/01/2023 – 3/31/2028

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	B. Zwaans	M. Chancellor
1. 2023	3.6 Calendar months	0.6 Calendar months
2. 2024	4.8 Calendar months	0.6 Calendar months
3. 2025	4.8 Calendar months	0.6 Calendar months
4. 2026	4.8 Calendar months	0.6 Calendar months
5. 2027	4.8 Calendar months	0.6 Calendar months

What other organizations were involved as partners?

Baylor College of Medicine and Michael E. DeBakey VA Medical Center
Houston, Texas

Contribution: Dr. Smith has actively participated in all online meetings and email/phone correspondence along with other key study personnel. He assisted in protocol review and the contributed to the development of the patient recruitment plan. Dr. Smith actively recruited study participants. Dr. Smith also helped to design strategies to troubleshoot anticipated and unanticipated issues as the study progresses. Finally, he was engaged with military and Veteran’s Affair communities in anticipation of eventual transition of study findings to their IC/BPS patient populations. Dr. Smith and his team have collected all urine samples as agreed upon.

Einstein College of Medicine
Bronx, New York

Contribution: Drs. Abraham and Laudano continue to actively participate in all online meetings and email/phone correspondence along with other key study personnel. They assist in protocol review

and the contributes to the development of the patient recruitment plan. They are actively recruiting study participants. They also helped to design strategies to troubleshoot anticipated and unanticipated issues as the study progresses. Drs Abraham and Laudano will be collected several more urine samples for us in the first couple of months of year 5 of this study.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Not Applicable

QUAD CHARTS:

Not Applicable

9. APPENDICES:

Appendix 1_AUA 2023 poster

Classification of Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) Using a Machine Learning Based Symptom Score Leveraging Inflammatory Urine Cytokines and Patient Reported Outcomes



Laura E. Lamb, Joseph J. Janicki, Nitya Abraham, Melissa Laudano, Christopher P. Smith, Sarah N. Bartolone, Elijah P. Ward, Kenneth M. Peters, Bernadette Zwaans, Michael B Chancellor, Corewell Health Beaumont University Hospital; Oakland University William Beaumont School of Medicine Baylor College of Medicine, Michael E. DeBakey VA Medical Center; Montefiore Medical Center, Albert Einstein College of Medicine

Abstract

INTRODUCTION: Diagnosis of IC/BPS currently utilizes patient-reported outcomes (PRO) instruments to assess symptoms, however overlapping symptoms with other diseases can delay proper diagnosis. The objective of this study is to develop an improved IC/BPS risk classification, using machine learning algorithm to leverage both urine inflammatory cytokines and PROs.

METHODS: A national crowdsourcing resulted in 442 urine samples consisting of 153 IC patients (146 female, 7 male), and 289 asymptomatic age-matched controls (155 female, 134 male) with corresponding PRO pain and symptom scores. This included 53 patients with a bladder-centric dysfunction with Hunner's lesions. An independent validation cohort was also collected. Urinary cytokine levels were determined using Luminex assay. A predictive classification model, termed the Interstitial Cystitis Personalized Inflammation Symptom (IC-PIS) Score, was generated from this data into three classification: 1) normal/low IC risk; 2) moderate to high risk for IC with bladder centric dysfunction; and 3) moderate to high risk of IC without bladder centric dysfunction.

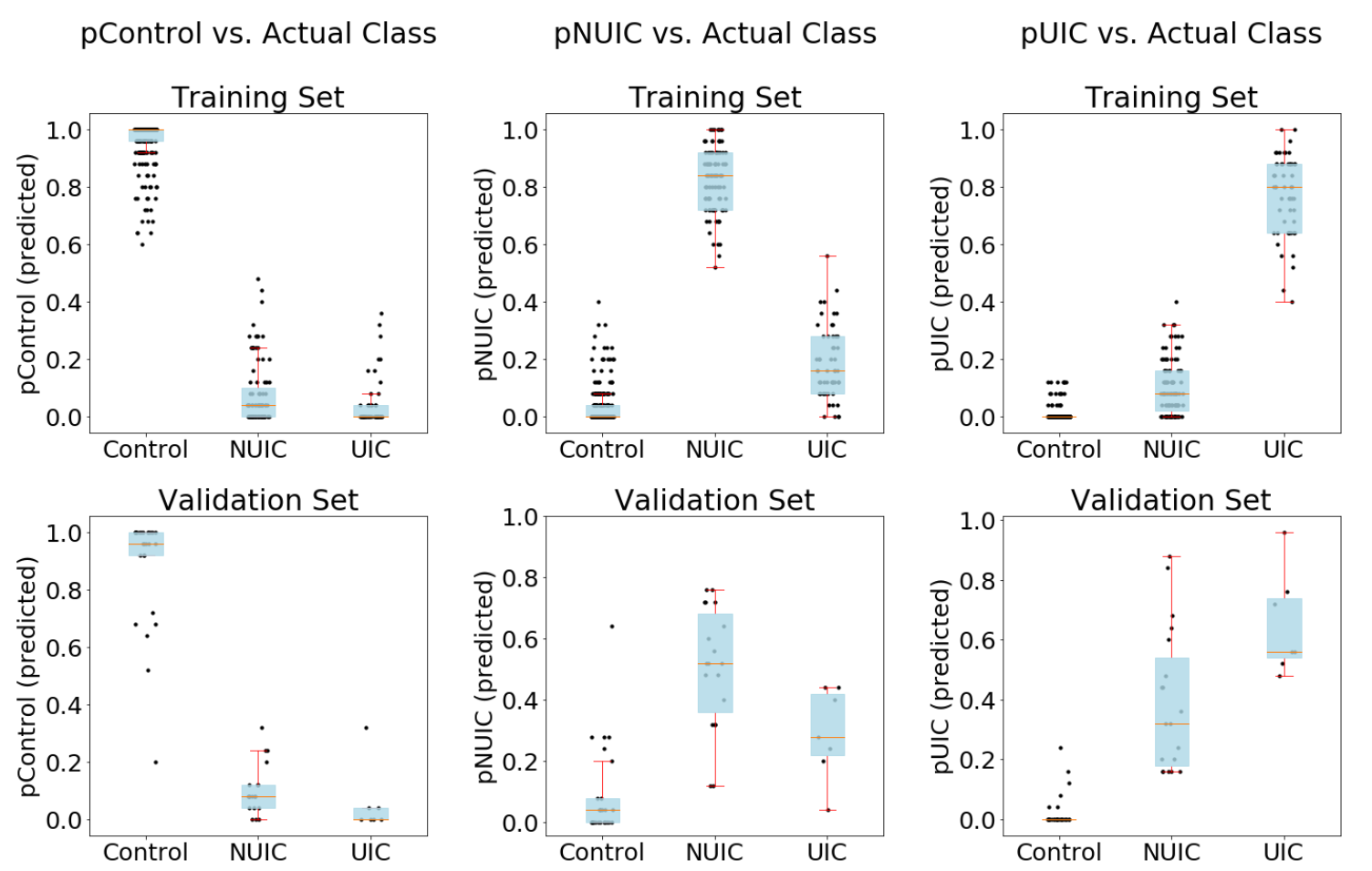
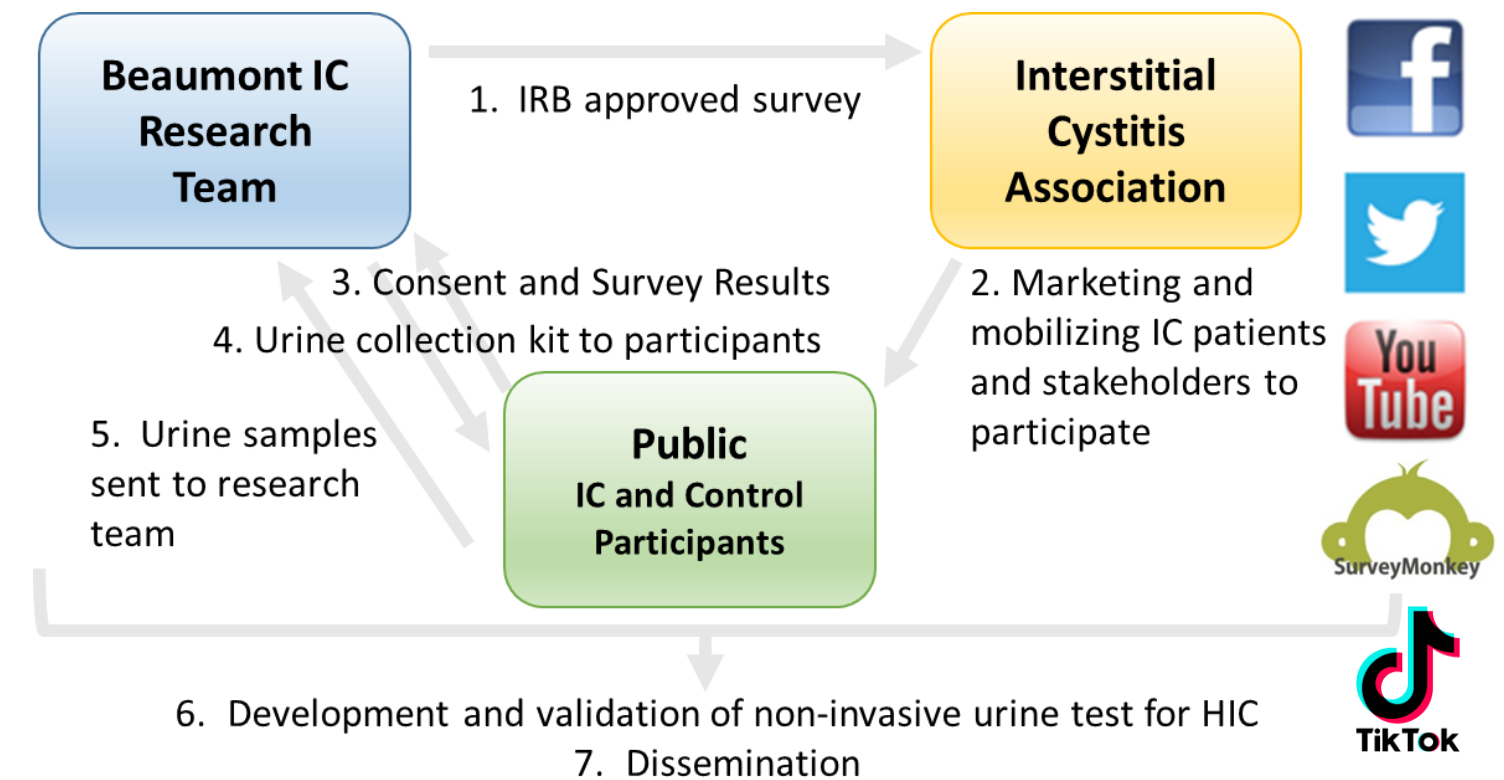
RESULTS: In the training set, the IC-PIS Score correctly classified all controls, all IC patients without Hunner's lesions, and 98% (52/53) IC patients with Hunner's lesions. In the independent validation set, the IC-PIS Score correctly classified 26 of 27 (96%) controls, 14 of 19 (73.7%) IC without Hunner's lesions, and all IC patient's with Hunner's lesions.

CONCLUSIONS: In one of the largest collection of urine samples of IC/BPS patients from across all 50 states of the US, two key findings emerged: 1) A standardized laboratory urine assay IC-Risk Score is comparable to symptoms in accuracy of diagnosis; 2) IC-PIS, using laboratory-based data in combination with PROs, improves the AUC and accuracy of IC/BPS diagnosis. An objective laboratory test for IC/BPS, like tests that have been developed to improve cancer diagnosis, may help expand access, accelerate proper diagnosis, and improve care for IC/BPS, a disease with great unmet needs.

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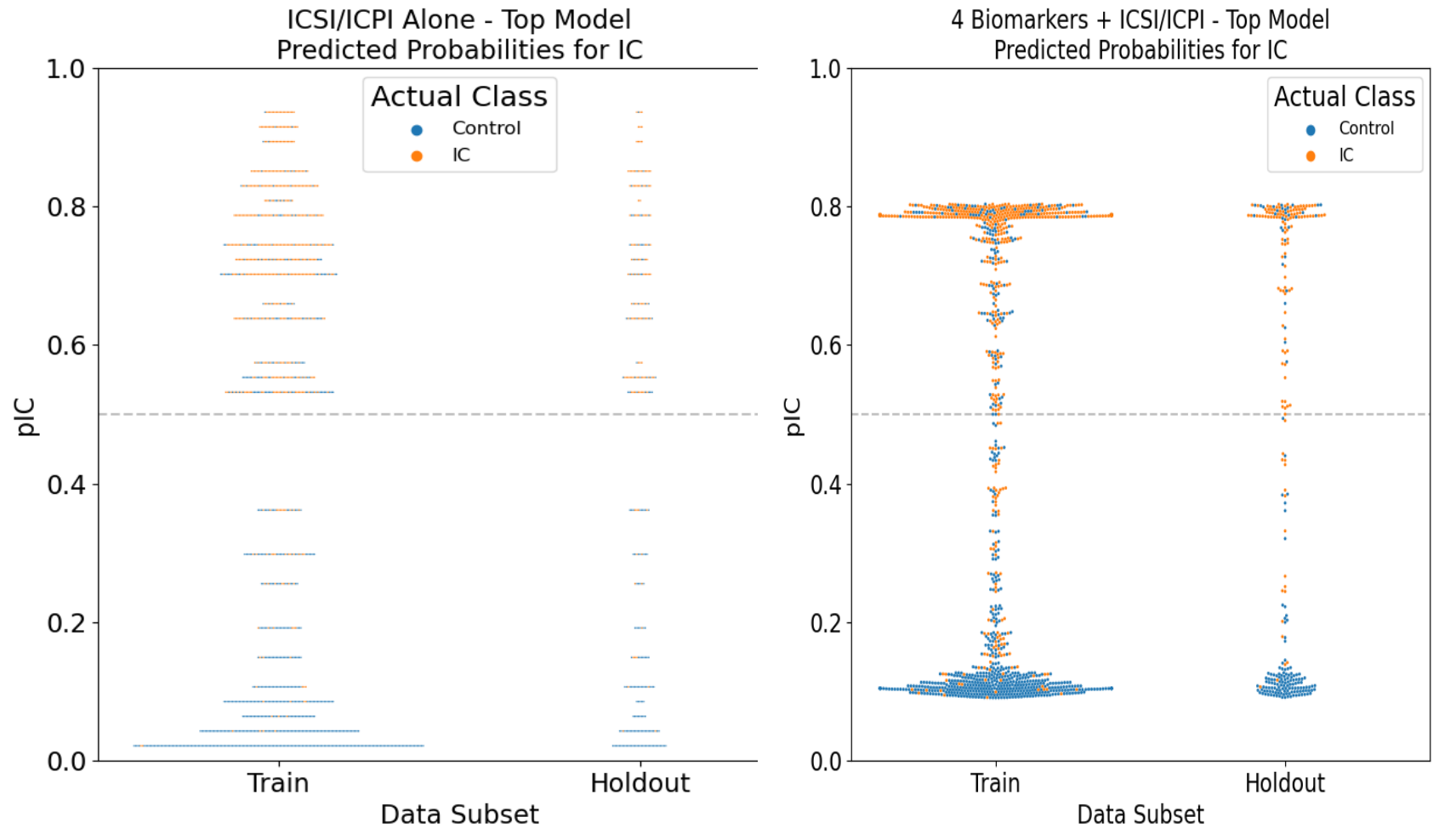


Crowdsourcing



Training set: Score correctly classified all controls, all IC without Hunner's lesions, and 52/53 IC with Hunner's lesions (98%). External validation set: Score correctly classified 26/27 (96%), 14/19 (73.7%) IC without Hunner's and all IC patient's with Hunner's.

Results: Probability of IC Swarm Plot



Conclusions

- A standardized LUMINEX laboratory urine assay-based IC-Risk Score is comparable to ICSI/ICPI in accuracy of diagnosis
- IC-PIS, using laboratory-based objective data in combination with PROs, improves the AUC and accuracy of IC/BPS diagnosis
- This study was one of the first to use machine learning to develop, optimize and validate a clinical predictor based on biologic samples. Using machine learning we were able to optimize the IC-PIS with large sample sets we collected
- This novel method used in our study can potentially be broad in application including overactive bladder, BPH, prostate cancer and bladder cancer