UPMC LIFE CHANGING MEDICINE

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

Title of Study: Phenotyping Interstitial Cystitis/Bladder Pain Syndrome by ICE-MRI Based Bladder Permeability Assay

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Key Information

You are being asked to participate in a research study. Research studies include only people who CHOOSE to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision.

You are being asked to have a single Magnetic Resonance Imaging (MRI) test, where radio waves and a powerful magnet are linked to a computer to look at organs and structures inside of your body, because we are testing whether MRI can measure bladder permeability, a function of how leaky the bladder is. During the MRI, we will put contrast directly into your bladder using a sterile catheter, a small hollow tube through which fluids pass. This procedure will take up to 90 minutes. Study participation may require up to 3 in person visits, and you are being asked to participate because you may meet the eligibility criteria for the study, and because you either have been diagnosed with interstitial cystitis/bladder syndrome (IC/BPS) or you do not have IC/BPS and you have agreed to be a control. Furthermore, patients with the diagnosis of IC/BPS who have Hunner lesions present or absent also have the following symptoms: 1) Pain (suprapubic, pelvic, urethral, vaginal or perineal) associated with bladder storage symptoms and pain on bladder filling that is relieved upon emptying 2) Urgency or nocturia (average of >1 nighttime urine void over 3 consecutive days on bladder diary). Patients must also score >9 on the O'Leary-Sant Interstitial cystitis symptom index (ICSI) and >8 on the O'Leary Interstitial cystitis problem index (ICPI).

Key study procedure is instilling a mixture of drugs into the bladder followed by MRI, and your risks from participation in these procedures may include the following (which are also explained in greater detail later in the consent form):

Common: A urinary tract infection related to the insertion of a catheter. Headache, nausea, vomiting, dizziness, unpleasant taste in your mouth, feeling hot, numbness or tingly feeling, itching or rash, malaise related to the contrast agent.

Very Less Likely: The strong, MRI magnetic field may attract magnetic objects and may cause you injury if those objects become projectiles. As such, all magnetic items are requested to be removed prior to entering the MRI scanner. The magnetic fields create loud knocking noises which may harm your hearing if ear protection is not used. They may also cause limb (muscle) or nerve stimulation that may feel like a twitching sensation. The radiofrequency energy used during the MRI scan may

increase the temperature of your body. The contrast agent may cause low blood pressure or swelling of your arms or legs.
Very Rare but Serious: Catheter placement may cause injury to your urethra or narrowing due to scar tissue. Rare risks of contrast MRI include drowsiness, confusion, mood changes, increased thirst, loss of appetite, weight gain, shortness of breath, seizures, breathing problems, pounding heartbeats or fluttering in your chest, pain, burning, or irritation around the urethra.

You will receive no direct benefit from this study. However, the goal of this research is to more accurately measure bladder permeability using imaging rather than cystoscopy or surgery reducing the number of times that you need to go through these procedures.

If you decide not to participate in this study, you will still be able to receive your usual care for IC/BPS that you and your doctor have agreed is appropriate.

Why is this research being done?
We are testing the accuracy of a new Magnetic Resonance Imaging (MRI) technique to better understand bladder permeability.

Who is being asked to take part in this research study?
You are being asked to participate in this study because you have been diagnosed with either interstitial cystitis/bladder syndrome (IC/BPS), or you do not have IC/BPS and you have agreed to be a control. We are asking 30 people with or without IC/BPS to participate in this research at UPMC/ University of Pittsburgh.

What procedures will be performed for research purposes?
If you choose to participate in the study, the study team will check your study records. The study will involve 2 or 3 visits depending on whether you need a current cystoscopy performed. Cystoscopy is a procedure to look inside the bladder using a thin camera called a cystoscope. A cystoscope is inserted into the urethra (the tube that carries pee out of the body), and it is passed into the bladder to allow a doctor or nurse to see inside. Informed consent will be obtained during the first visit. Also, during this first visit you will provide a voided urine sample to screen your urine for urinary tract infection (UTI) and urine pregnancy test. If the information about any cystoscopy performed in the past 6 months is not available from your study records, then a second visit for cystoscopy will be scheduled and performed within 2-4 weeks of the first visit. The second visit for cystoscopy will be performed for research purposes. Also, during this visit you will provide a voided urine sample to screen your urine for UTI. Prior to the cystoscopy procedure, your urethra will be prepped with antiseptic and viscous lidocaine gel will be inserted into your urethra and bladder to provide local anesthesia for the procedure.

Th MRI procedure, the last visit, will be scheduled by Dr. Chermansky's research coordinator. This last visit may take up to 90 minutes. You will not receive a confirmation call from the MRI Research Center. On the day of the procedure, you will not be able to drink any liquids for 4 hours prior to the procedure. You will be allowed to drink enough water to take any medications that you normally take. Upon arriving at the MRI Research Center on the 8th floor of UPMC Presbyterian Hospital at 200 Lothrop Street in Pittsburgh, you will be asked if you suffer from claustrophobia or have any history of allergy to contrast agent. Also, you will be asked if you have any implanted devices, prostheses or pacemakers that may not be permitted in an MRI due to the strong magnetic field. Then, you will be instructed to change from your street clothes into a provided gown, and to remove any jewelry or metal objects from your person. You will then provide a voided urine sample to screen your urine for UTI, and if you are a woman of childbearing age, you will be asked to take a urine pregnancy test to ensure that you are not pregnant. Also, a sample of this urine will be collected and stored for analysis at a later date of urine molecules that stimulate cell movement towards sites of inflammation .

You will then be brought into the MRI scanner, and you will lay down on the table and be asked to stay as still as possible during the scans. We will capture images of your bladder before we give you the contrast dye. After these initial images, your urethra will be prepped with antiseptic using sterile technique, and a lubricated catheter will be placed into your bladder to empty the bladder of all urine. Then, a 50 ml (3.5 tablespoons) mixture of gadolinium-based contrast agent (GBCA) and iron-based Fermoxytol contrast agent will be placed through the catheter, and the catheter will be plugged to keep the contrast within the bladder. The contrast will be held in your bladder for 15-30 minutes. Though commonly given through the vein, these contrast agents are not presently FDA approved for instillation into the bladder. The contrast solution will make it easier for the doctors to see the penetration of Gadobutrol into the bladder wall to assess permeability. We will take a second series of MRI images of your bladder with the contrast dye. After the MRI images are obtained, the contrast is removed using a syringe and the catheter is removed. Following the procedure, you will be allowed to urinate as needed with no special precautions. The contrast dye will be gone from your system in about 24 hours. You will be contacted by the study team 3-5 days after your MRI to make sure you are not having symptoms of a possible urinary tract infection. If you do, you will be tested and treated if needed by the study team.

What are the possible risks, side effects, and discomforts of this research study?

Risks of cystoscopy:
The most common risks of cystoscopy include urinary tract infection (UTI), bleeding, bladder or urethral pain during the procedure, and pain with urination after the procedure. To minimize the risk of UTI, you will receive an oral antibiotic and an antiseptic solution will be applied to your urethral opening prior to the cystoscopy procedure. To minimize the risk of pain during the cystoscopy and pain with urination after the procedure, viscous lidocaine gel will be inserted into your urethra and bladder to provide local anesthesia

Risks of catheterization:
The most common risks of catheterization include urinary tract infection (UTI), bleeding, bladder or urethral pain during the procedure, and pain with urination after the procedure. To minimize the risk of UTI, you will receive an oral antibiotic and an antiseptic solution will be applied to your urethral opening prior to the catheterization procedure. Rare Risks of catheterization include 1) injury to the urethra (the tube that carries urine out of the body) when the catheter is inserted incorrectly or 2) narrowing of the urethra from a urethral stricture that may develop after injuring the urethra during catheterization

Risks of Magnetic Resonance Imaging (MRI)
MR images are made without using any ionizing radiation, energy that comes from radioactivity, so you are not exposed to the harmful effects of ionizing radiation as in X-ray or CT scan. But while there are no known health hazards from temporary exposure to the MR environment, the MR environment involves a strong, static magnetic field that changes with time (pulsed gradient field), and radiofrequency energy, each of which carry specific safety concerns:

The strong, static magnetic field will attract magnetic objects (from small items such as keys and cell phones, to large, heavy items such as oxygen tanks and floor buffers) and these magnetic objects may cause damage to the scanner or injury to the patient or medical professionals if those objects become projectiles. Careful screening of people and removal of all magnetic objects prior to entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile.

The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause muscle or nerve stimulation in the arms or legs that may feel like a twitching sensation. Participants may be provided ear protection to reduce

noise exposure.

The radiofrequency energy used during the MRI scan could lead to temporary heating of the body. The potential for heating is greater during long MRI examinations.

Some patients find the inside of the MRI scanner to be uncomfortably small, and some may become claustrophobic (highly fearful of the small space) while in the machine. If you experience such a sensation, the staff will quickly stop the procedure and remove you from the scanner. You are in voice contact with the staff at all times during the MRI."

Risks of gadolinium-based contrast agents (GBCAs):
Side Effects are uncommon but may include:
headache
nausea
vomiting
feeling unwell (malaise)
dizziness
abnormal or unpleasant taste in your mouth
feeling hot
numbness or tingly feeling
itching or rash
skin redness
injection site reactions (cold feeling, warmth, pain, or burning).

Tell your doctor if you have serious side effects of gadolinium-based contrast agents which include:
urinating less than usual or not at all;
drowsiness, confusion, mood changes, increased thirst, loss of appetite;
swelling, weight gain, shortness of breath;
seizures (convulsions);
breathing problems;
pounding heartbeats or fluttering in your chest;
or severe pain, burning, or irritation around urethra.

Risks of iron-based Fermoxytol :
Side Effects are uncommon but may include:
Low Blood Pressure,
Diarrhea,
Headache,
Nausea
Dizziness
Constipation
Swelling in your hands or feet

Risk of breach of confidentiality
While we will take every precaution to protect your privacy it is possible that someone outside of the research team may learn your identity and your participation in this study.

Unknown Risks
"*As with any experimental procedure, there may be adverse events or side effects that are currently unknown and some of these unknown risks could be permanent, severe or life-threatening.*"

What are possible benefits from taking part in this study?

You will receive no direct benefit from this study; however, the goal of this research is to more accurately measure bladder permeability by imaging, thereby better characterizing your IC/BPS subtype and directing you to targeted treatment based on your subtype.

If I agree to take part in this research study, will I be told of any new risks that may be found during the study?
You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., cystoscopy, catheterization, the MRI with contrast). You will be charged, in the standard manner, for any procedures performed for your routine medical care .

Will I be paid if I take part in this research study?
You will be compensated a total of $300 for your participation in this study. Each subject will receive a payment of $50 upon completing screening and cystoscopy. Then, each subject will receive $250 upon completion of both MRIs. This will cover your time off work, travel, and parking costs. UPMC utilizes an electronic payment card as a secure payment method to disburse research study compensation. The study staff will discuss the use of this electronic payment card with you and answer any questions you may have about the reimbursements. All compensation is taxable income to the participant regardless of the amount.

If a participant receives $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 26% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 74% of the expected payment.

Your data or specimens used in this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights, nor will you share in any money that the investigators, the University of Pittsburgh, or outside agencies may receive.

Who will pay if I am injured as a result of taking part in this study?
If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. Currently, there is no plan for any additional financial compensation and "*You do not waive any rights by signing this form."*

Who will know about my participation in this research study?
All records related to your involvement in this research study will be stored in a locked environment and all electronic records will be stored in password-protected locations. Your identity on these records will be limited to the research team members. You will not be identified by name in any publication of the research results unless you sign a separate consent form

giving your permission (release). If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state, or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Will this research study involve the use or disclosure of my identifiable medical information?
This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other health care provider (for example, your physician's office) records; this authorization is valid for an indefinite period of time. This information that will be recorded will be limited to information concerning care received here for treating your condition. This information will be used to determine your eligibility for this study.

This research study will result in identifiable information that will be placed into your medical records held at UPMC. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes diagnostic MRI scan and urinalysis (UA) and urine pregnancy testing results.

Who will have access to identifiable information related to my participation in this research study?
In addition to the investigators and their research staff listed on the first page of this informed consent form, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

- Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.
- In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.
- Authorized representatives of National Institutes of Health (NIH), who sponsored the funding for this research, and the main awardee institution of Lipella Pharmaceuticals may review the

research findings of this study, but not your identifiable medical information, for the purpose of monitoring the appropriate conduct and progress of this research study

- Authorized representatives of the U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data. While the U.S. Food and Drug Administration understands the importance of maintaining the confidentiality of your identifiable research and medical information, the University of Pittsburgh and UPMC cannot guarantee the confidentiality of this information after it has been obtained by the U.S. Food and Drug Administration.
- Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

In addition, de-identified data may be shared in the future with other researchers who share the same interest. *We will store your urine sample, data, and MRI images indefinitely. Information will be shared with other researchers in the future, but those researchers will not be able to identify you. Your urine sample and data (including MRI images and test results) may be used in any type of research. Your data may be shared with others, including federal repositories, and will be shared without identifiers*.

We will protect your privacy and the confidentiality of your records, as described in this document, but cannot guarantee the confidentiality of your research records, including information obtained from your medical records, once your personal information is disclosed to others outside UPMC or the University.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of seven years after final reporting or publication of a project.

May I have access to my medical information that results from my participation in this research study?
Yes. In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider. To ensure the scientific integrity of the study, you may not be able to review some of your records related to the study until after the study has been completed.

Is my participation in this research study voluntary?
Yes. Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the

purposes described above; you will not be allowed to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?
Yes. You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

It is possible that you may be removed from the research study by the researchers if the study investigators on further review of your information determines that your study participation may not in the interest of study goals and your safety.

Clinically Relevant Research Results
You will be notified of any results that might affect your personal health or decisions.

VOLUNTARY CONSENT

The above information has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns, or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation.

By signing this form, I agree to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____	_____
Participant's Signature	Date / Time
_____	
Printed Name of Participant	

CERTIFICATION OF INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Study Investigator	Role in Research Study
_____	_____
Signature of Study Investigator	Date / Time