Study title: A NOVEL MULTIPLEX IMMUNOASSAY FOR THE EARLY DETECTION OF BLADDER CANCER

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CONSENT FORM FOR RESEARCH

Study title: A NOVEL MULTIPLEX IMMUNOASSAY FOR THE EARLY DETECTION OF BLADDER CANCER

Sponsor: Cedars Sinai Medical Center
National Cancer Institute (NCI)

Cedars-Sinai Principal Investigator: Charles J. Rosser, MD

Study contact phone number at Cedars-Sinai: 310-423-4700

1. Key Information

We are asking for your consent to take part in this research study. This section provides key information about the study. The rest of this form has more detailed information.

- **Voluntary:** Taking part in this research study is your choice. You can also stop taking part at any time. You will not lose any services, benefits or rights you would normally have if you choose not to take part or stop taking part.

- **Purpose:** The purpose of this study is to see if an investigational test can assist doctors in evaluating patients at risk of developing bladder cancer with the express purpose of detecting these cancers early, when they are more curable.

- **Procedures:** The main things that will happen in this study include the following. If you agree to join this study, you will be asked some questions to confirm your eligibility, as well as additional questions for research purposes including race, height, weight and tobacco exposure. Your medical records may be accessed to obtain some of the study data. You will be asked to give a urine sample (1/2 –3/4 cup). The urine sample will be used to do the investigational test as well as your standard medical tests. We will schedule you to be seen by our team every 12 months for the collection of a voided urine sample.

  You will also be asked permission so this investigational test can be done on any bladder tumor that you may subsequently develop, using only left-over portion of any tumor that is removed from your bladder during your normal medical care.

  The research test results will not be given to you or used to make decisions about your care.

- **Duration:** Taking part in this study will last about 15 minutes on each visit, 1 visit per year for a total of 4 years.

- **Risks:** All research studies involve some risks. Risks or discomforts from this study may be: There is the risk of loss of privacy if you join this or other research studies. In order to protect you as best possible, your personal information will be kept in a password-protected database by the research team at Cedars Sinai Medical Center. Data that is collected for the study will contain personally identifiable information. However, all identifiable information will be removed from the rest of the data and only linked with a unique study code. All subjects will be assigned a coded subject ID, which will be used on forms and the samples to help protect your identity.

- **Benefits:** The possible benefits of taking part in this study include the potential of detecting bladder cancer at an early stage.

- **Alternatives:** You can choose not to take part. There may be other choices for you.

Please take time to read this entire form. You should ask questions before deciding whether to take part in this study. You can talk with family, friends and/or healthcare providers before you decide.

During the study, we may find out new information about this research study. We will tell you about any important changes or new findings that may impact whether you want to continue taking part in the study.

2. Purpose of the Study

Bladder cancer occurs both in men and women with a higher frequency in men (4 to 1 ratio). Bladder cancer is more common in the elderly, with an average age of a typical bladder cancer patient of approximately 68 years. Environmental exposures, specifically tobacco smoke, increases the risk of many cancers, including bladder cancer. It was estimated that current cigarette smokers have an approximately 3X higher risk of bladder cancer than non-smokers. Thus, a simple, non-invasive test to screen these high risk individuals would be important in the care of disease. We believe that our urine-based test has the potential to accurately detect bladder cancer before symptoms arise. In order to determine the effectiveness of this test, we would have to do a large clinical study. However, prior to starting such a large study, a smaller study should be conducted to determine the ability to identify these high risk individuals, enroll these high risk individuals into a study, follow these high risk individuals over a period of 4 years and test the urine samples for the presence of bladder cancer in these high risk individuals. The collection of samples and information will take place throughout the time you are on the study. Patients 50 years of age and older presenting with an extensive tobacco history may join the study.

This research study is designed to a) determine the likelihood of conducting a larger trial in this setting and b) learn if a biomarker test is helpful to decide if it can detect bladder cancer. A

biomarker is a biological molecule found in blood, other body fluids or tissues. Biomarkers may be a sign of a condition or disease and can be used to predict someone's response to a specific treatment. This test will hopefully allow researchers to determine if the early detection of bladder cancer is possible. This test has not been approved by the U.S. Food and Drug Administration (FDA).

This research is being done to see if an investigational test can assist doctors in evaluating patients at risk of developing bladder cancer with the express purpose of detecting these cancers early, when they are more curable.

The study will include up to 200 people in total.

3. Study Procedures

This section talks about what will happen in this study.

When you read this section, also read the flowchart of procedures. The flowchart is given with this consent form. The flowchart of procedures shows a timeline of the study. It shows which study procedures are research-related and which are standard of care (routine).

Research-related procedures are procedures done only for the research study. They would not be performed for your routine care outside of the study. **Standard of care (routine) procedures** would be performed as part of your routine care even if you did not take part in this study.

The procedures in this study are often part of routine care for a person with your condition. They are not experimental procedures. The procedures and their risks are research-related. This means they are being done only for research purposes. These common procedures and their risks should be the same as when performed outside this study.

Description of research procedures:
If you agree to join this study, you will be asked some questions to confirm your eligibility, as well as additional questions for research purposes including race, height, weight and tobacco exposure. Your medical records may be accessed to obtain some of the study data. You will be asked to give a urine sample (1/2 –3/4 cup). The urine sample will be used to do the investigational test as well as your standard medical tests. We will schedule you to be seen by our team every 12 months for the collection of a voided urine sample.

You will also be asked permission so this investigational test can be done on any bladder tumor that you may subsequently develop, using only left-over portion of any tumor that is removed from your bladder during your normal medical care.

The research test results will not be given to you or used to make decisions about your care.

For patients with noted blood in the urine, follow-up will be recommended. Such follow-up usually involves an exam of the interior bladder with a special telescope in addition to urinary cytology, CT scan, MRI or ultrasound.

- **Questionnaires:** You will be asked to complete a questionnaire. We will ask you questions to find out your exposure to tobacco and other environmental carcinogens. We think it should take about 10 minutes to complete the questionnaire. Questionnaires will ask you to respond to sensitive questions about past and current tobacco use.

- **Demographic Information:** We will ask you about demographics, which may include your age, gender identity, sexual orientation, race and ethnicity.

- **Medical History Review:** We will ask you about your medical and surgical history.

- **Urine Collection:** You will be asked to provide a urine sample in a collection cup for biomarker test. Biomarker test results will not be provided to you or your physician, thus it will not affect your clinical management.

Long-term banking of specimens for unspecified future research:
Cedars-Sinai Medical Center has a wealth of clinical experience and has an internationally recognized leadership role in the management of conditions, both cancer and benign. In this position, we have an obligation to learn from our experience, and to apply this knowledge to improve the care of our patients. To do this, we store specimens collected on studies for future potential research to answer key questions. The urine and tissue collected on this study will not have any of your identifiers and may be used for such a future research project. Prior to its use, the proposed research project must be reviewed and approved by the ethics committee at Cedars.

How long will you be in the study?
Participation in this study will last for 48 months (4 years). Each study visit will take about 10-15 minutes. The eligibility research questions will take about 10 minutes and will be performed only at your initial visit. The urine sample, which is collected prior to any procedure, will take only a few minutes. If you are unable to provide enough urine, you may be asked to drink fluids and wait at the clinic until enough urine can be voided. If you decide not to participate or withdraw from the study, it will not affect your medical care.

Cedars Sinai Medical Center is dedicated to finding the causes and cures of disease. The data, urine samples and tissue collected during this study are important to this study and to future research.

Data will be securely stored and maintained at Cedars Sinai Medical Center. At the end of the study the National Cancer Institute (NCI) will own the data. Dr. Charles J. Rosser, a co-investigator on this study, and Nonagen Bioscience Corp, the company who developed the investigational test, will be allowed unlimited access to the data in order to obtain FDA approval of the test.

Urine and tissue will be stored at Cedars Sinai Medical Center.

4. Possible Risks and Discomforts of the Research Procedures

This section talks about the possible risks and/or discomforts of the study procedures.

- **Questionnaires:** Some questions may make you feel uncomfortable or embarrassed. The questionnaire will be labeled with a unique study number. This will link your identity so that only the research team can recognize you.

- **Demographic Information:** This does not have any physical risks.

- **Medical History Review:** This does not have any physical risks.

- **Urine Collection:** This does not have any physical risks.

Genetic studies may place research subjects at risk for discrimination based on genetics. The federal Genetic Information Nondiscrimination Act (GINA) was passed to address this concern. GINA makes it illegal for medical insurance companies and most employers to discriminate based on genetic information. The protections of GINA do not apply to life, disability or long-term care insurance. We follow federal and state privacy laws to protect against unauthorized disclosure of your protected health information that could lead to discrimination or the misuse of your genetic information.

5. Benefits From Taking Part in the Study

Taking part in this research study may or may not have direct medical benefit to you. The possible benefits of taking part in the research study are evaluation and the early detection of bladder cancer in a high risk population. No benefit is guaranteed. It is possible that your condition may stay the same or even get worse.

We hope the information learned from this research study will be used to design and launch a larger similar study that if proven to be effective, can bring to the clinic a new tool to assist in screening at risk individuals for bladder cancer.

6. Whether Research Results Will Be Shared

Some of the research tests done in this study follow standard clinical procedures. These are performed in certified clinical labs. These test results may be shared with you. They may be placed in your Cedars-Sinai medical record.

Other research tests done in this study are for research purposes only. They are performed in a research only lab where the results are not for clinical use. These research-only results will not be shared with you. They will not be put in your Cedars-Sinai medical record.

<u>Unanticipated Incidental Findings</u>
We will contact you using the last contact information you gave if, unexpectedly, we find results that suggest potentially clinically relevant medical information. We may suggest you talk with your treating physician about possible additional clinical testing to further evaluate the research finding. You and/or your insurance would pay for any additional testing and any related treatment.

7. Reasons Participation May Be Stopped

Your participation in this study may be stopped at any time. The researcher or the sponsor can stop your participation without your consent for any reason. Some reasons for stopping your participation include:

- The study is stopped or suspended.
- Funding for the study is reduced, stopped or withdrawn.
- It is in your best interest.
- You do not follow the study procedures.

8. Choosing to Take Part and Other Options

Taking part in research is voluntary. You have the right to choose not to take part. You can stop taking part in this research study at any time. You can do this without any penalty or loss of benefits to which you would be entitled outside of the study. Your choice not to take part or to stop taking part will not affect the care you get at Cedars-Sinai.

If you decide to stop taking part, we will keep any data collected on you up to the time you choose to stop. Also, if you stop taking part, the study team may ask you whether you want to give further data from your routine medical care.

9. Confidentiality Protections

We will do our best to keep your personal information collected as part of this study private. But we cannot guarantee total privacy. We may put a copy of your research consent and authorization forms in your electronic medical record at Cedars-Sinai. Your personal information may be given out if required by law. Publications or presentations about this study at scientific meetings will not use your name and other identifiable personal information.

Organizations that may look at and/or copy your medical records for research oversight, quality assurance and data analysis include:

- Accrediting agencies (agencies that grant official certifications to educational institutions)
- Government and regulatory groups, such as the Food and Drug Administration (FDA) and Office for Human Research Protections (OHRP)
- The Institutional Review Board (IRB), which reviews research to protect people taking part in studies
- Safety monitors, which monitor the safety of individual participants and the overall safety of the study
- Companies that sponsor the study and authorized representatives of the sponsor

Attached to this consent form is an Authorization Form. It outlines with whom your information may be shared for this research and under what circumstances.

We might share your information and/or research samples collected in this study. It might be shared with other researchers at Cedars-Sinai, other academic institutions or third-party commercial entities for future research without additional informed consent from you. Information that identifies you will be removed and will not be shared with other researchers or anyone outside of Cedars-Sinai.

Protections From Forced Disclosures (Subpoenas) – Certificates of Confidentiality

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.

10. Research-Related Illness or Injury

We do not expect you will have any illness or injury from this research study. If you believe that you are ill or have been injured from this study, please contact the study team at the phone number listed on page 1 of this consent form.

11. Financial Considerations

Costs of Participation
The attached flowchart lists items, drugs and services that will be billed to you and/or your insurance and those that will be covered by the Study Sponsor. Review the flowchart for details.

For items billed to your insurance, you remain responsible for all deductibles, copays and balances under your health benefit plan. If your insurance company does not pay, you will be billed for those charges. If you have questions or concerns about your insurance coverage, you should ask your health benefit plan.

Payment
You will be paid for being a part of this study with a gift card. The total amount for completing the whole study is $100. You will be paid a portion at each study visit. You will only be paid for those visits and procedures you complete.

The payment breakdown for this study is below:
• $20 after you complete each clinic visit at baseline, 1, 2, 3 and 4 years (Total a 5 clinic visits. $20 each visit for a total of $100).

You may have to fill out a W-9 form to get paid. Our accounting department at Cedars-Sinai will keep the W-9 form. Any amount of payment may be reportable to the IRS. If you receive $600 or more from Cedars-Sinai in a calendar year, a 1099 form will be filed with the IRS in accordance with federal tax law. Check with a tax professional if you have questions.

If you are a Cedars-Sinai employee, you should provide your employee identification number to the research team. This allows your payment to be processed through Payroll. For your own protection and to comply with tax laws, your payment for taking part will be reported to the IRS together with other payment you get from Cedars-Sinai.

You will not be paid for giving biological samples (e.g., urine, tissue) for this study. Once you give the samples for the research, you no longer have access to them. The Study Sponsor will

own your donated samples. Researchers might use your samples to develop new products, tests or discoveries. These inventions may result in commercial profit for the researchers, Cedars-Sinai and other organizations. If this happens, you will not receive any financial benefits.

Financial Interest in the Research
A significant financial interest is a situation in which financial considerations could influence a person's professional judgment. This study has been designed to minimize the impact of the investigator's financial interest. You can ask the investigator to explain how the financial interest disclosed below will be managed.

A member of the research team, Dr. Charles Rosser, a co-investigator has a personal interest in the investigational test that is being used in this study, as he holds intellectual property rights for the investigational test.

12. Contact for Questions or Problems

Please contact the investigator for questions, problems or concerns about the research. Their contact information is on page 1 of this form.

You might have feedback, questions, problems, concerns or want to obtain more information about this study. If so, you can talk with someone who is not part of this study by contacting:

Cedars-Sinai Human Research Protection Program (HRPP)
Phone: 310-423-3783
Email: ResearchConcerns@cshs.org
Website: cedars-sinai.org/research/administration/office-of-research-compliance/review-board.html

The Cedars-Sinai HRPP protects the rights and welfare of research participants.

Experimental Subject's Bill of Rights

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

AUTHORIZATION FOR USE AND DISCLOSURE OF IDENTIFIABLE HEALTH INFORMATION FOR RESEARCH

1. USE AND DISCLOSURE OF HEALTH INFORMATION

If you agree to this Authorization, you give permission to the Sponsor, Principal Investigator, other investigators and their research team described in the Consent Form for Research ("Research Team") to use or disclose your identifiable health information ("private information") for the research study titled "Novel multiplex immunoassay for the early detection of bladder cancer" which is described in the Consent Form for Research ("Consent Form") to which this Authorization is attached. In particular, you authorize the research team acting under the direction of the Principal Investigator to review your medical records and collect your private information from the following sources:

- ☒ Laboratory tests
- ☒ Pathology reports
- ☒ Imaging reports (e.g., x-rays or scans)
- ☐ Photographs or videos of your image
- ☒ Doctor/clinic records
- ☒ Hospital/medical records
- ☐ Mental health records
- ☐ Billing records
- ☒ Demographics, which may include age, gender identity, race, ethnicity, and/or sexual orientation
- ☐ Other tests or other types of medical information:

2. WHO WILL HAVE ACCESS TO YOUR PRIVATE INFORMATION?

Your private information will be used by and/or shared with the Research Team.

In addition to the research team, if applicable, the following parties may receive your private information and inspect your records:

- The reviewing Institutional Review Boards and Cedars-Sinai offices with authority to oversee research compliance.
- U.S. government agencies, such as the Food and Drug Administration and the Department of Health and Human Services.
- Researchers at other organizations who are participating in this research study.
- The Study Sponsor, its business partners, and Cedars-Sinai's business partners for matters related to research study oversight, conduct of the research, data analysis, use of research results in product development, and payment or reimbursement.

- Representatives from regulatory agencies in other countries may join in the review of your research records, including research-related medical reports and information, with the Sponsor and/or the FDA.

Cedars-Sinai takes steps to protect your private information when sharing it with the recipients described above. Though these steps and applicable law are meant to protect your private information, there is a risk that a recipient could share your private information without your permission.

3. WHEN WILL MY AUTHORIZATION EXPIRE?

By signing this document, you authorize the use and sharing of your private information until the end of the research study and any related optional sub-study you choose to participate in.

4. REVOKING AUTHORIZATION

You may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, the research team may still use or disclose private information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To revoke this Authorization, you must write to the Principal Investigator of the research study by writing to the Office of Research Compliance and Quality Improvement, 6500 Wilshire Blvd, Suite 1800, Los Angeles, Calif. 90048 and/or emailing to ResearchConcerns@cshs.org.

5. NOTICE OF RIGHTS AND OTHER INFORMATION

You do not have to agree to this Authorization, but if you do not agree, you may not participate in the research study. Cedars-Sinai may not condition (withhold or refuse) the provision of standard of care treatment for you on whether you agree to this Authorization.

If you agree to this Authorization, please sign on the appropriate signature line on the Signature Page. You will receive a copy of this Authorization.

Flowchart of Visits, Tests and Procedures

-	Baseline	Follow-up			
		Month 12	Month 24	Month 36	Month 48
Informed Consent	R				
Medical history/Questionnaire	R				
Disease / Survival Follow-up [1]		R	R	R	R
Dipstick Urinalysis [2]	R	R	R	R	R
Complete Urinalysis [3]		S	S	S	S
Urine culture [3]		S	S	S	S
Multiplex immunoassay [4]	R	R	R	R	R
Urine cytology [3]		S	S	S	S
Cystoscopy [3]		S	S	S	S
Upper tract imaging [3]		S	S	S	S
TURBT and/or bladder biopsies [3]		S	S	S	S
Urine collection	R	R	R	R	R
FFPE tumor collection [4]		R	R	R	R
Handling and/or conveyance of specimen - Biomarker assays (urine)	R	R	R	R	R

LEGEND

R = Research item/procedure done only for research purposes and covered by the study

S = Standard of care item/procedure that is part of regular care and billed to the patient/insurance

Footnotes:

1 Information about disease response assessments & other therapies received after completion of study treatment will be collected if available.

2 Voided urines will be analyzed by urinary dipstick.

3 As medical needed if urinary dipstick shows blood

4 If tumor is note, then collect 10 unstained FFPE and 1 H&E slide.

Signature Page

Consent Form for Research and Authorization
for Use and Disclosure of Identifiable Health Information (Research)

If you agree to take part in this study, you should sign and date on the signature lines below. You will be given a signed and dated copy of this form. This includes the "Experimental Subject's Bill of Rights," "Authorization for Use and Disclosure of Identifiable Health Information (Research)" and any optional sub-study descriptions, when applicable.

Signature by the Participant
Main Research Study: *I agree to take part in the research study described to me during the informed consent process and described in this informed consent form. My questions have been answered to my satisfaction.*

You will be given a signed and dated copy of this form.

Participant name (please print)	Signature	Date

Authorization for Use and Disclosure of Identifiable Health Information (Research): *I hereby agree that my identifiable health information may be used and/or disclosed in accordance with the "Authorization for Use and Disclosure of Identifiable Health Information (Research)."*

Participant name (please print)	Signature	Date

Signature by the Investigator
I attest that all the elements of informed consent described in this form have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.

Investigator name (please print)	Signature	Date

Signature by the Interpreter/Witness

(Signature of an interpreter is only required when enrolling a non-English-speaking subject with the assistance of an interpreter and IRB-approved "short form" consent processes. The witness may be any person who is conversant in both English and the language of the non-English-speaking subject, such as a certified hospital interpreter, study staff, a family member or other person. The witness signs the consent forms to confirm that the oral interpretation occurred.

Signature of a witness is required when an English-speaking subject who has been determined to have capacity to consent is unable to read or physically sign the consent form but chooses to indicate via a "mark" or verbally that he/she agrees to participate. The witness signs the consent form to confirm that an oral consent process occurred and that the individual verbally consented to participate in the research.)

_____

Interpreter/Witness name (please print) Signature Date of signature

To be marked at time of signature:

Consent obtained:

☐ *From non-English speaking individual with assistance of interpreter*

☐ *From English-speaking individual who is not physically able to sign the consent document*