Study title: A NOVEL MULTIPLEX ELISA ASSAY FOR EVALUATING PATIENTS WITH GROSS HEMATURIA FOR BLADDER CANCER

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CEDARS-SINAI MEDICAL CENTER

CONSENT FORM FOR RESEARCH

Title: A NOVEL MULTIPLEX ELISA ASSAY FOR EVALUATING PATIENTS WITH GROSS HEMATURIA FOR BLADDER CANCER

STUDY SUPPORT PROVIDED BY: CEDARS-SINAI MEDICAL CENTER
NATIONAL CANCER INSTITUTE (NCI)
NONAGEN. BIOSCIENCE CORP

PRINCIPAL INVESTIGATOR: HIDEKI FURUYA, PHD

STUDY CONTACT PHONE NUMBER AT CSMC: 310-423-4700

AFTER HOURS CONTACT (24 HOURS): 310-423-4700 (24-HOUR NUMBER)

This research study is sponsored by National Cancer Institute (NCI), Cedars Sinai Medical Center and Nonagen Bioscience Corp. Nonagen is providing access to testing kits, National Cancer Institute provides funds for the conduct of the study including compensation to staff at Cedars Sinai Medical Center and the Principal Investigator for their participation in the study.

KEY INFORMATION ABOUT THIS RESEARCH STUDY

We are seeking your consent to take part in this research study. Your participation in this research is voluntary. If you choose to participate, you can stop at any time. Please consider the following summary, along with the more detailed information provided throughout this consent form.

- This research is being done to see if an investigational test can detect bladder cancer in urine.
- The main procedures of this study include collection of urine and tissue samples. If you choose to take part in this study, it will last about 12 months.
- All research studies involve some risks. Risks or discomforts from this study may include a risk of loss of privacy.
- You are not expected to benefit from taking part in this research study, but the information learned from this study may help others in the future.
- Participation in this study is voluntary. You will not lose any services, benefits or rights you would normally have if you choose not to participate. Please discuss your choices with the researchers.

Please take time to read this entire form and ask questions before deciding whether to participate in this study. You are encouraged to talk with family members, close friends, trusted advisors and/or healthcare providers before you make your decision.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

You are being asked to take part in this research study because you have gross (visible) blood in your urine, which may be an early sign of bladder cancer. This research is being done to see if an investigational test can detect bladder cancer in urine. Bladder cancer occurs both in men and women. Early diagnosis of cancer is important in the treatment and care of the disease. In order to determine the effectiveness of this new test, we will collect a sample of your urine, bladder tissue collected during a routine procedure (if available), and information about your condition from your medical record. People who are 18 years of age or older, who do not have cancer and who are having a cystoscopy to evaluate the blood in their urine may join the study. We expect to enroll 450 people to the study, 175 at Cedars Sinai Medical Center.

This research study is designed to test the investigational use of a urine-based laboratory test designed to test your urine for 10 proteins previously found to be associated with bladder cancer. This test will allow researchers to determine the risk one has of having a bladder tumor. This test has not been approved by the U.S. Food and Drug Administration (FDA).

2. WHAT WILL HAPPEN DURING THE STUDY?

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as Appendix A.

The flowchart shows a timeline for research-related or standard of care procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study. **Standard of care (routine)** procedures would be performed both as part of this study and if you do not participate in this study.

Overview of study:
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 age, race and history of tobacco exposure. Your medical record will be accessed to obtain some of the study data. At the time of your cystoscopy, which is standard of care for your condition, you will be asked to give a urine sample (1/2 to 3/4 cup). The urine will be used to do the investigational test as well as your standard of care medical tests. Also, if at any time new cancer cells or tumor are found at routine follow-up during your normal medical care, a portion of the tissue will be collected for future investigational testing. The research test results will not be given to you or to your physician, thus the research test results cannot be used to make decisions about your care. Your doctors will determine what treatment you may or may not need. Any remaining urine from these investigational tests will be stored at the Cedars Sinai Medical Center.

How long will you be in the study?
Participation in this study will last for 12 months. The study visit will take about 30 minutes to 1 hour. The eligibility research questions will take about 10 minutes. The urine sample 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. About one year after the urine sample is collected and tested, the researchers will look at your medical records to gather information about your condition and to

see if any tissue is available for collection, after which your participation in the study will be completed. If you do decide not to participate or decide to withdraw from the study, it will not affect your medical care.

What happens to data, urine samples and tissue samples that are collected in the study?
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.

Testing of your specimens may go on for a long period of time. Therefore, while your direct participation in this study will be done once you have completed the procedures/visits described above, your specimen(s) may be studied for many years.

Data will be securely stored and maintained at the Fred Hutchinson Cancer Research Center (Fred Hutch) in Seattle, Washington and Cedars-Sinai Medical Center (CSMC) in Los Angeles, California. At the end of the study the National Cancer Institute (NCI) will own the data. Dr. Charles J. Rosser and Nonagen bioscience Corp. 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 for future research related to developing better lab tests. We do not yet know exactly what testing will be done in the future, but it may involve genetic testing. If genetic testing occurs and you agree, we may put your information into genetic databases, which are available to help other researchers study different diseases.

Genetic studies have raised concern as to whether the studies would 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. Although there are substantial protections against the risk of discrimination, you should be aware of this general concern.

We try to protect all research subjects from placing them in a position where sensitive information could be disclosed that could lead to discrimination or the misuse of their information. All of your personal information will be removed. Only your genetic information and condition will be sent to the databases.

If genetic testing occurs in the future, do you agree to allow your genetic information to be sent to genetic databases? Please initial your selection below.

Yes _____ No _____ Date: _____

The data and specimens will be studied, tested, and used by medical scientists. If this information helps lead to the creation of a product or idea, whoever creates that product or idea will own it. You will not receive any financial benefit from the creation, development, use or sale of that product or idea.

3. WHAT ARE THE POSSIBLE RISKS?

There are minimal risks to participating in this study. 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. **All**

subjects will be assigned a coded subject ID, which will be used on forms and the samples to help protect your identity. Any link between clinical information about your sample and personal information that could identify you will be maintained in a restricted access research office at the Cedars Sinai Medical Center. The potential use of a small portion of tumor tissue collected as part of your routine medical care which would be tested for research purposes does not pose any additional risk. Also, there is a minimal risk associated with collection of urine samples.

There may be other side effects or risks that we cannot predict. Many side effects may go away shortly after standard of care procedures are stopped.

4. ARE THERE BENEFITS IN TAKING PART IN THE STUDY?

You should not expect to benefit from taking part in this research study. We hope the information learned from this research study will benefit other individuals with blood in their urine in the future by helping us to learn who may require further invasive evaluation to determine the cause of the bleeding.

5. WILL I BE INFORMED OF RESEARCH RESULTS?

The research tests done in this study are performed in a research only lab (not a certified clinical lab) where the results are intended for research purposes only. Therefore, we will not inform you or your physician of the test results obtained from this study or include them in your Cedars-Sinai medical record.

Unanticipated Incidental Findings
If, unexpectedly, we find that results of your research procedures could suggest important medical information and we determine there is something you or your doctors can do in response to this finding, we will contact you using the last contact information provided by you. If necessary, we may recommend additional clinical testing to confirm the research finding. The cost of any additional testing and any related treatment will be your responsibility.

6. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

- The study is stopped or suspended;
- Funding for the study is reduced, stopped or withdrawn;
- If it is in your best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect you;
- You do not follow the study procedures.

7. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary, so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

When you withdraw your permission, no new data will be gathered after that date. Information that has already been gathered may still be used and given to others. You may withdraw from the study anytime. If you wish to withdraw, please notify the study staff immediately. If you withdraw, it will not interfere with the future care you receive at your medical care facility.

8. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not be used. Organizations that may look at and/or copy your medical records for research oversight, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.

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

We might share your information and/or research samples collected in this study 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.

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

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the U.S. government. This Certificate helps protect the confidentiality of information about people who join this study. If you join the study, the Certificate means that generally we would not have to give out identifying information about you even if we were asked to by a court of law. We would use the Certificate to resist any demands for identifying information.

We could not use the Certificate to withhold research information if you give written consent to give it to an insurer, employer, or other person.

This protection has some limits. We would voluntarily provide the information:

- To a member of the federal government who needs it in order to audit or evaluate the research.
- To the funding agency and groups involved in the research, if they need the information to make sure the research is being done correctly.
- To the federal Food and Drug Administration (FDA), if required by the FDA.
- To someone who is accused of a crime, if he or she believes that our research records could be used for defense.

- To authorities, if we learn of child abuse, elder abuse, or if participants might harm themselves or others.

Protections from Forced Disclosures (Subpoenas) – Certificates of Confidentiality

To further protect your private identifiable information, we intend to apply for a Certificate of Confidentiality (Certificate) from the federal government.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law such as child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as including research data in the medical record.

9. WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?

You will not be in danger of any illness or injury from this research study. However, should you believe that you are ill or have been injured as a result of your participation, please contact the study team at the phone number listed on page 1 of this consent form.

10. FINANCIAL CONSIDERATIONS

Costs of Participation

You will not have to pay for this testing.

Please review the attached flowchart for a listing of items, drugs and services that will be billed to you and/or your insurance and those that will be covered by the study sponsor.

Standard of care procedures and the cost of the study device, implant procedure, and related items, drugs and procedures will be charged to you or your insurance company. You remain responsible for all deductibles, co-pays, and balances under your health benefit plan.

The Researcher and/or research staff will seek pre-authorization from your insurance company for the device and related procedures. Before any study procedures are performed, pre-authorization must be received from your insurance company. If your insurance company denies coverage, you may decline to participate in the Study or you may choose to pay out of pocket. You should check with your health benefit plan if you have questions or concerns about your insurance coverage.

Compensation for Participating

You will not be paid for taking part in this research study.

Financial Interest in the Research

Conflict of interest is a situation where a person or an organization has a financial or other interest large enough to appear as if it could influence their judgment.

Dr. Charles Rosser, the person responsible for the conduct of this study 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.

The PI and institution have no other potential financial conflict of interest with respect to this study.

11. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact one of the investigators listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, or concerns that you want to discuss with someone who is not associated with this study, or want to offer suggestions or feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP) Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

12. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;

(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that by consenting to participate in the research, you are not giving up any of your legal rights (other than the postponement of your access to certain health information as described in this informed consent form);
(7) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and
(8) You have been provided with a copy of the "Experimental Subject's Bill of Rights", if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and the Experimental Subject's Bill of Rights.

SIGNATURE PAGE

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

SIGNATURE BY THE PARTICIPANT

Main Research Study: *I hereby agree to participate in the research study described to me during the informed consent process and described in this informed consent form.* ***You will be given a signed copy of this form.***

Name of Participant (Print)	Signature	Date Signed

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 this "Authorization for Use and Disclosure of Identifiable Health Information (Research)" form attached as Appendix to this form.*

Name of Participant (Print)	Signature	Date Signed

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.*

Name of Investigator (Print)	Signature	Date Signed

SIGNATURE BY THE INTERPRETER/WITNESS

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

Name of Witness (Print)	Signature	Date Signed

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APPENDIX: 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.

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AUTHORIZATION FOR USE AND DISCLOSURE OF IDENTIFIABLE HEALTH INFORMATION FOR RESEARCH

- **USE AND DISCLOSURE OF HEALTH INFORMATION**

If you agree to this Authorization, you give permission to the research team at Cedars-Sinai Medical Center ("CSMC") to use or disclose your identifiable health information ("private information") for the research study titled "A NOVEL MULTIPLEX ELISA ASSAY FOR EVALUATING PATIENTS WITH GROSS HEMATURIA FOR 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
- ☐ Other tests or other types of medical information: Click or tap here to enter text.

- **WHO WILL HAVE ACCESS TO YOUR PRIVATE INFORMATION?**

Your private information will be used by and/or shared with the CSMC investigators listed in Section A of the Consent Form and their research staff.

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 CSMC 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 and its business partners, for matters related to research study oversight, data analysis and use of research results in product development.
- 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.

CSMC is required by law to protect your private information. However, the recipients described above may re-disclose (or share) your information with other parties unless such sharing is prohibited by law.

- **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.

- **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. The mailing address is: Charles Rosser, MD; Cedars-Sinai Medical Center Davis Research Building; 110 N. George Burns Rd., D4094G; Los Angeles, CA 90048.

- **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. CSMC may not condition (withhold or refuse) treating you on whether you agree to this Authorization.

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

APPENDIX: FLOWCHART OF PROCEDURES – Medicare Coverage Analysis (MCA) Review

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

FLOWCHART OF PROCEDURES

	Screening	Testing	Month 12
Visit Window	**~28 days**		
Informed Consent	R	-	-
Medical History and Demographics	R		
Physical Exam	S		
Concurrent Medications		R	
Disease/Survival Follow-up			R
Urinalysis		S	
Urine Culture		S	
Urine Cytology		S	
NMP-22		R	
Cystoscopy and biopsy[1,2]		S	
Upper tract imaging [2]		S	
Urinary multiplex ELISA assay		R	
Specimen collection [3]		R	
Medical Record Review			R

Footnotes:

[1] biopsy performed only when medically indicated.

[2]Procedure can take place in subsequent visits related to the work-up of hematuria but no more than 30 days from signing study consent.

[3] Collection of urine and (if performed per standard of care) tissue.