Project title:* *Metabolism of NNK Among Japanese Americans (Study 2: Clinical Protocol)

Investigator Team Contact Information:

For questions about research appointments, the research study, research results, or other concerns, call the study team at:

University of Hawaii Investigator Name: Loic Le Marchand University of Hawaii Cancer Center Phone Number: 808-237-3901 Email Address: Loic@cc.hawaii.edu	University of Minnesota Investigator Name: Dorothy Hatsukami University of Minnesota Masonic Cancer Center Phone Number: 612-626-2121 Email Address: hatsu001@umn.edu

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Key Information About This Research Study

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form. Please take time to read this entire consent form and ask questions before deciding whether to take part in this research project.

What is research?

Investigators are committed to your care and safety. There are important differences between research and treatment plans. This study does not offer any treatment for health care.

- The goal of research is to learn new information in order to help groups of people in the future. Investigators learn things by following the same study plan with a number of participants, so they do not usually make changes to the plan for individual research participants. You, as an individual, will not be helped by volunteering for this research study.

Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are a daily cigarette smoker who participated in Study 1: Observation Study, and you are Japanese-American or Native Hawaiian and willing to participate in this study. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

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Why is this research being done?

The purpose of this study is to better understand how people break down a cancer-causing chemical in cigarette smoke. Some people are able to get rid of this chemical as harmless agents better than others. Your participation will help us to understand how the differences in breaking down this chemical are related to cancer risk. We are recruiting Japanese Americans and Native Hawaiians because we have found that some have a particular gene that may help them eliminate one of the cancer-causing chemicals in cigarettes. This information will help us understand who may be at risk for tobacco-related cancer and develop measures that could help reduce risk. However, the results obtained when we analyze your samples will not tell us whether you personally are at risk for cancer.

To accomplish this purpose, you will receive special study cigarettes. The cigarettes used in the study are considered an investigational cigarette. This means that the cigarette is not approved by the FDA, but we have permission from the FDA to use these study cigarettes. The study cigarettes you will be asked to smoke were purchased in a regular tobacco shop and then modified. More information regarding these cigarettes can be found below under section "What happens if I say 'Yes, I want to be in this Research.'"

How long will the research last?

We expect that you will be in this research study for about two weeks and attend 6 visits (including today). One of the visits will be by phone. Each visit will be about 1 ½ hours.

What will I need to do to participate?

In addition to today's visit, you will be asked to attend a total of five 1 ½ hour visits over about two weeks. During the visits, you are asked to fill out several questionnaires, have vital signs taken and provide urine samples. Four of those urine samples will be a 24-hour collection. You will also smoke the investigational cigarettes for 1 week while in the study. You will collect the study cigarette butts. Three days after you have finished smoking the study cigarettes, you will receive a final phone call to complete the study.

Is there any way that being in this study could be bad for me? What are the risks of the study?

The risk of using the study cigarettes is comparable to the risk you expose yourself to when you smoke your regular cigarettes. Both your usual cigarette and the study cigarette contain about the same amount of the tobacco-specific cancer-causing agent NNK and other harmful toxins. The deuterium added to the study cigarettes is non-radioactive and non-hazardous and has been reviewed by the FDA for safety. If you are concerned about your cigarette smoking, speak to the study coordinator about referrals for quitting.

Will being in this study help me in any way?

Participation in this study will not benefit you.

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What happens if I do not want to be in this research?
You may choose not to participate in this study.

Detailed Information About This Research Study
The following is more detailed information about this study in addition to the information listed above.

How many people will be studied?
We expect about 20 people to complete this study.

What happens if I say "*Yes, I want to be in this research*"?
First, you will attend a screening visit where you complete several forms regarding your history of cigarette smoking, health, and use of certain drugs. We will also use the information that was collected from you in Study 1: Observation Study. The information will be reviewed by our study physician. If you are eligible after the review, you will be invited to our clinic for the first study visit. At this visit, you will be provided with a personal schedule for the study.

Prior to each visit, we will contact you to ask about symptoms or exposure to COVID-19. When you come to the visit, you will be provided a mask to wear during the visit and we will take your temperature. At each of the study visits, you will have your blood pressure and heart rate taken and at the screening visit your weight will be measured. You will be asked about any changes in your health or medications and complete a few forms about using cigarettes.

At four of the visits, you will bringing a 24-hour urine sample in the containers provided. You will collect the first sample while smoking your regular cigarettes and then during 3 of the days you are smoking study cigarettes. You will collect the urine every time you urinate throughout the day and night on those days. At two visits, we will collect three tubes of blood sample (about 6 teaspoons).

You will receive special study cigarettes. The study cigarettes you will be asked to smoke were purchased in a regular tobacco shop and then modified. These cigarettes normally have a low concentration of the cancer-causing agent NNK that is found only in tobacco (0.12 μg per cigarette for non-menthol and 0.16 μg per cigarette for menthol). We have changed the tobacco in these cigarettes by adding back NNK to equal the level in your regular cigarette, which is about 0.70 μg per cigarette. Therefore, when you smoke the cigarettes we provide, there will be no additional risk compared to your usual smoking. The NNK we have used to modify the cigarette is called [pyridine-D4]NNK. This is the same as NNK, except that it has 4 deuterium atoms (heavy hydrogen) which are necessary to follow the path this chemical takes in your system as it breaks down NNK. Deuterium is non-radioactive and safe.

You will be asked to smoke about the same number of study cigarettes as you normally smoke per day for 1 week. During 3 of the days you smoke the study cigarettes you will collect all of your urine, beginning with the first time you urinate on the 5th day and ending 3 days later (72 hours). To collect the urine sample, you will be given large containers, one for each day of collection. We will also give you a small plastic container so you can collect and return all of your smoked cigarette butts. When you have completed a 24-hour sample, you will drop it off at the clinic. The urine and blood samples will be

analyzed for break-down products of tobacco-specific toxins. We will also have you breathe into the CO monitoring device to determine how much you have smoked. At each visit, you will be provided with enough study cigarettes to last until the next visit. At your last visit, we will ask you to return all unsmoked cigarettes.

About three days after you stop the study cigarettes, we will call you with some follow up questions.

Your blood and urine samples will be used for research purposes only. Some of the samples will be sent to the University of Minnesota Masonic Cancer Center Biomarker Laboratory for storage and analysis. Your biological samples will be deidentified with a barcode to protect your confidentiality. Background information about you that accompanies these samples will only be identified with a study number. None of the information or samples will contain any personally identifying information. There will be no way for the laboratory staff to identify or contact you.

What are my responsibilities if I take part in this research?

You will be expected to attend all of the visits, smoke only the cigarettes provided to you by the study, and provide the blood samples and collect the 24-hour urine samples.

What happens if I say "Yes", but I change my mind later?

You can leave the research study at any time and no one will be upset by your decision. **I**f you decide to leave the research study, contact the researchers so that we can set up at time for you to come in and return all of the study cigarettes.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. This means that your choice not to be in this study will not negatively affect your right to any present or future medical care, or your present or future employment.

If you stop being in the research, information about you that has already been collected may not be removed from the study database.

What are the risks of being in this study? Is there any way being in this study could be bad for me? (Detailed Risks)

The risk of using the study cigarettes is comparable to the risk you expose yourself to when you smoke your regular cigarettes. Both contain the tobacco-specific cancer-causing agent NNK and other harmful toxins. The deuterium added to the study cigarettes is non-radioactive and non-hazardous. There are risks associated with having your blood drawn including mild pain or bruising at the place where blood is drawn. Rarely, a person may faint or feel faint during the blood draw. The risk of infection is slight since only sterile, one-time use equipment is used.

If you are using public transportation to get to your appointment, you may put yourself at increased risk for exposure to the COVID-19 virus. We advise you to wear a mask and practice social distancing when possible while using public transportation.

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What do I need to know about reproductive health and/or sexual activity if I am in this study?

You should not be or become pregnant while on this research study. We will conduct a pregnancy test prior to entering you in the study. Cigarette smoking is known to harm a fetus in the following ways: Miscarriage, birth defects, premature birth, low birth weight, sudden infant death syndrome (SIDS).

If you are sexually active, women should use at least one effective means of birth control while participating in this research study. According to the World Health Organization and the United States Center for Disease Control and Prevention, the most effective forms of birth control include complete abstinence, surgical sterilization (both male and female), intrauterine devices (IUDs), and the contraceptive implant. The next most effective forms of birth control include injectable hormones, oral contraceptive pills, the contraceptive ring, or the contraceptive patch. Acceptable, but least effective, methods of birth control include male condoms (with or without spermicide) and female condoms.

While use of prescribed "birth control" pills, injections, or implants is an acceptable method of birth control to be in this study, you should be aware that use of this type of birth control is not recommended for women who smoke. Smoking greatly increases the chance of serious heart or blood vessel side effects from oral contraceptive (birth control pills) use. The risk increases with age and with heavy smoking (about 15 or more cigarettes per day) especially in women over 35 years of age. It is unclear whether smoking while using birth control injections or implants increases the risks of heart attack and stroke, so it is recommended that women who use injections or implants do not smoke.

If you are considered to be postmenopausal, you are not required to use contraception while participating in this research study. Postmenopausal women rarely become pregnant.

If you become pregnant while participating in this research study, it is important that you tell the study doctor or other research team member immediately. You will be required to stop participation in this study. We will want to follow pregnancy outcomes in the event of a pregnancy. Your permission will be obtained prior to seeking follow-up on any pregnancy outcomes.

Notification of Significant New Findings

You will be told of any important new information that is learned during the course of this research study, which might affect your willingness to continue participation in this study.

Will it cost me anything to participate in this research study?

- There will be no cost to you for any of the study activities or procedures.
- You will have to pay for basic expenses like any childcare, food, or transportation related to study activities.
- If you need treatment for side effects while you are on the study, you or your insurance will need to pay for this treatment.

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information, including research

study records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of the University of Hawaii and the University of Minnesota (who oversees this study), including those that have responsibilities for monitoring or ensuring compliance. This includes representatives from Food and Drug Administration, National Cancer Institute (funder of the study).

The sponsor, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We will not ask you about child [or vulnerable adult] abuse, but if you tell us about child [or vulnerable adult] abuse or neglect, we may be required or permitted by law or policy to report to authorities.

A description of this clinical trial will be available at 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 Web site at any time.

Data or Specimens Collected

Data and specimen samples collected from you in this study will be used for future research. These samples will be kept until they are used up or no longer needed and destroyed. This data and specimens will be kept at the University of Hawaii and the University of Minnesota Masonic Cancer Center Biomarker Laboratory. All Identifiers are removed from your private information or samples that are collected during this research, that information or those samples could be used for future research studies or distributed to another approved investigator for future research studies without your additional informed consent. Any studies using these stored samples for other purposes will be submitted to the Committee on Human Studies, University of Hawaii, and the Institutional Review Board at the University of Minnesota for review and approval. All studies will be done in accordance with the guidelines of the Committee on Human Studies and with federal regulations for the protection of human subjects.

Your biological samples will be barcoded to protect your confidentiality. Background information about you that accompanies these samples will only be identified with a study number. None of the information or samples will contain any personally identifying information. There will be no way for the laboratory staff to identify or contact you.

Consent for future research uses of your biological specimens

The following questions ask whether biological specimens [urine, blood] collected from you during this research project may be stored and used to support future research.

- My specimens may only be stored and used for future research that relates to the clinical area [smoking and cancer] being investigated under this study.

Initial one: Yes _____ No _____

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- My specimens may be stored and used to support any future research.

Initial one: Yes _____ No _____

- I will consider providing consent to use my specimens to support future research. Prior to any future research use, please provide me with a consent form that describes the protocol.

Initial one: Yes _____ No _____

- My specimens may be stored and used for the development of commercial products without any financial compensation to me.

Initial one: Yes _____ No _____

Will I receive research test results?

Most tests done on samples in research studies are only for research and have no clear meaning for health care. The investigator(s) will not contact you or share your individual test results.

Whom do I contact if I have questions, concerns or feedback about my experience?

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately you may contact the UH Human Studies Program at (808) 956-5007 or uhirb@hawaii.edu to discuss problems, concerns and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol. Please visit http://go.hawaii.edu/jRd for more information on your rights as a research participant.

In addition, you can contact HRPP at the University of Minnesota about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

The HRPP may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Investigator Contact Information" of this form for study team contact information and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

Can I be removed from the research?

The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include health problems or not following the researcher's instructions.

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What happens if I am injured while participating in this research?

Please inform the researcher(s) if you have any injuries or problems related to your participation. You should also notify your regular doctor(s). If you become injured or ill as a result of participation in this research project, you or your insurance company may be responsible for the costs of any treatment or care. The University of Hawaii / study sponsor have not set aside any funds to assist in treatment or care for injuries or illness.

Will I be compensated for my participation?

If you agree to take part in this research study, we will pay you $750 for your time and effort if you complete the study. You will receive $50 for each of the 6 clinic visits ($10 for travel (except the phone visit) and $40 for the visit); $30 for each of the four 24 hour urine collections ($120); $10 for each cigarette filter collection ($80); and $260 bonus for completing the study. If you withdraw from the study prior to completing you will receive payment for all procedures you have completed.

Payment you receive as compensation for participation in research is considered taxable income. If payment to an individual equals or exceeds $600 in any one calendar year, the University is required to report this information to the Internal Revenue Service (IRS). Research payments to study participants that equal or exceed $600 during any calendar year will result in a FORM 1099 (Miscellaneous Income) being issued to you and a copy sent to the IRS.

Use of Identifiable Health Information

We are committed to respect your privacy and to keep your personal information confidential. When choosing to take part in this study, you are giving us the permission to use your personal health information and information that can identify you. For example, personal health information may include your name, address, phone number or social security number. Those persons who get your health information may not be required by Federal privacy laws (such as the 1099 Rule) to protect it. Some of those persons may be able to share your information with others without your separate permission. Please read the HIPAA Authorization form that we have provided and discussed.

The results of this study may also be used for teaching, publications, or for presentation at scientific meetings.

We are required by the National Institutes of Health to provide de-identified data to other researchers who request our data. All efforts will be made to keep your identity confidential. Any data requests will be reviewed by the investigators to make sure that the requestors are credible. The de-identified data released to these researchers will be asked to destroy this data upon completion of the use of the data.

You will be provided a copy of this signed document.

I have read the above information. I have asked questions and have received answers. My signature documents my permission to take part in this research. I will be provided a copy of this signed document.

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I understand that the samples collected from me may be used for research in the future. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the blood or samples that will allow laboratory staff to readily ascertain my identity.

I have been advised that I am free to withdraw (take away) my consent and can refuse to take further part in the study at any time without it making any difference to my care in the future.

I give my consent to be part of this study with the understanding that such consent does not take away any of my legal rights nor does it release the investigators or the institution or any employee or agent thereof from liability for negligence.

_____	_____	_____
Signature of Participant	**Participant's Name (please print)**	**Date**
_____	_____	_____
Signature of Staff Obtaining Consent	**Staff Name (please print)**	**Date**