UNIVERSITY OF WASHINGTON
CONSENT FORM

The NEXT Medicine Study (New EXome Technology in Medicine)
For Adult Participants

Researchers:

Gail P. Jarvik, MD, PhD	Division Head, Professor, Div. Med. Genetics	206-543-4259
Fuki Hisama, MD	Clinical Assistant Professor, Div. Med. Genetics	206-598-4030
Laura Amendola, MS, CGC	Genetic Counselor, Dept. of Medicine	206-685-8886

Contact: Martha Horike-Pyne, MPH, Research Coordinator, Div. Med. Genetics 206-221-0971

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether or not to be in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all of your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

We are asking you to be in this study because you have colorectal cancer or polyposis (excess growths in the intestines) or a close family member with this. This syndrome can be due to hereditary (genetic) reasons. We know of multiple possible genes that can have changes that cause colon cancer or polyps and we believe there are more genes yet to be identified. The purpose of this study is to compare a new genetic tool called whole exome sequencing with the standard clinical practices for genetic testing in patients with or at risk for colorectal cancer or polyposis. Standard clinical practice involves testing tumor tissue and/or single known colorectal cancer/polyposis genes individually. Then, depending on the result, choosing another gene to test until the causal gene is found or until all known genes are investigated. Analyzing many gene tests all at once that has a much broader search of DNA (the source of genetic material) is called "whole exome sequencing". There are pluses and minuses to both approaches, and we hope to determine which method is better in terms of efficiencies of time, cost, and medically relevant information, as well as which method patients prefer.

STUDY PROCEDURES

All participants in this research receive usual care at the Medical Genetics Clinic at the University of Washington Medical Center (UWMC) or at Group Health Cooperative (GHC).You are responsible for your usual care costs (insurance co-pays, etc). You are not responsible for costs related to research study procedures that go beyond usual care.

We would like to collect, study and store DNA and information from approximately 450 people who have colorectal cancer and/or polyps (CRCP) or are at risk. We will also want to study approximately 250 relatives of people enrolled in this study whose CRCP risk genes are not identified. We may ask your family members to also join this study. Your relatives may or may not also have CRCP. We will not ask any of your relatives to join this study if you don't want us to. We will not ask your relatives if we find the genetic cause for your CRCP. We expect that our study will take years to complete and we may never be able to identify the specific genetic change responsible for causing your CRCP. We will keep your samples and data indefinitely to use when needed for future research.

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Some people in this study will be asked to participate in extra research study questions and interviews. Those people will read and sign a separate consent form from this one. You can say no to the extra studies and still join this study. In order to capture a research subject's experience with this new technology study, we will ask your permission to audiotape the consenting process if we tape it. After you join this study, we will ask you questions about yourself (what is your race, collect a family tree and your CRCP medical history which will include your use of prescription and over the counter medications), and then you will be placed by chance (such as the flip of the coin) into one of the two groups being studied. One group will have their genetic causes for CRCP investigated under current medical genetics practice (Usual Care) which may include testing (sequencing) for one or for several genes known to cause CRCP. The other group will have the same usual care practice, and in addition will have nearly all of their genes "whole exome" sequenced. Whole exome sequencing looks at much larger portions of your DNA than targeted gene sequencing, and will show known genes for CRCP all at once. The new technique is also more likely to find unexpected genetic changes that are not related to CRCP. People in both groups will be told of the genetic results found from both methods as they relate to CRCP. People in the whole exome group will be asked if they want to hear about extra genetic findings that are not related to CRCP. If we do not find any extra genetic findings for risk, this does not mean that you do not have any other risks—it means we did not find any.

This project will collect information on how useful, efficient and beneficial the new technology of whole exome sequencing is, along with possible extra genetic results. We will then compare that information to standard genetic clinic practices to try and determine which method is best for patients and doctors. Neither you nor the researcher can choose which group you are put in, but we will tell you which group you have been placed in.

Both the Usual Care and the Whole Exome groups may require multiple clinic visits to complete standard care at either institution (UWMC or GHC). At your 1st visit to the Genetics Clinic we will collect 80 cc (a little over 5 tablespoons) of blood from your arm to study your DNA (genes), collect a pedigree of your family, and ask you to fill out survey to learn what you think is important in receiving genetic results, and about your moods or anxiety levels and feelings of well being. These same surveys will be asked of you several times during your participation in the study. The survey can be completed with papers that you mail back to us, by phone or "on line" using your own computer. Some surveys are short (take about 15 minutes to complete) and others are longer (take about 30-45 minutes to complete). You may refuse to answer any question. Some questions ask about personal and sensitive issues like how happy you feel in different situations.All the information you give us is confidential. However, if we learn that you intend to harm yourself or others, we must report that to the authorities. This visit may take approximately 1 hour to complete.

For subjects who receive their standard care at UWMC, when your genetic tests results are ready in approximately 3 months, we will schedule another clinic visit where we will tell you what we learned about your genes in relation to CRCP, and tell you which study group you were placed in. This visit may take approximately 30 minutes to complete. With your permission and if you were placed in the Whole Exome group, we will audio-record this visit so that we can transcribe (write down) that experience. We will select only a few tapes to analyze to gain a deeper understanding of what happened in that visit. Most of the tapes will be destroyed without being listened to. We will not associate your name or any other identifying information with your comments. Within a few weeks after your clinic visit at UWMC, we will ask you to complete the survey again.

For subjects who receive their standard care at GHC, when your genetic tests results are ready in approximately 3 months, your Genetic Counselor at Group Health will call you or schedule a clinic visit

which study group you were placed in. This call may take up to 30 minutes to complete. Within a few weeks after your call from the study team, we will ask you to complete the survey again.

About a month later at the next visit that is not considered a clinic visit, but rather a research visit, we will return other genetic results to you. This visit will occur at the UWMC for all study subjects. The Usual Care group will learn more about the risk for developing other CRCP disorders and the risk for CRCP in family members. The Whole Exome group will hear about those risks and may also get information on risks for disorders not associated with CRCP. This meeting will occur by phone or in-person. Again, with your permission and if you were placed in the Whole Exome group, we will audio-record this visit so that we can transcribe (write down) that experience. We will select only a few tapes to analyze to gain a deeper understanding of what happened in that visit. Most of the tapes will be destroyed without being listened to. We will not associate your name or any other identifying information with your comments

Again, after a few weeks we will ask you to complete the surveys about your experiences and feelings of getting other genetic information and also what you consider to be important in getting genetic results. These surveys can occur "on-line" using your own computer, with written materials, in person, or by phone. We estimate these surveys can be completed in about 15-45 minutes to complete. Lastly, approximately 4, 7 and 10 months after you got your last genetic results we will send out more surveys. The surveys can be completed using your own computer, on written materials in-person, or by phone. Examples of questions in the survey are are: "Did you find the genetic information useful? Or "Did the genetic information cause you stress?" You can refuse to answer any question.

Starting after your first clinic visit we will also be in touch by mail or "on-line" multiple times for more than a year (approximately 15 months) with a survey to learn how often you are using medical services (doctor and mental health visits, use of medications, hospitalizations, etc). You may refuse to answer any question. This survey should take about 15 minutes to complete.

In summary of the research activities, you will be asked to come for (usually 1-3) clinic visits to start the usual care at the UW Medical Genetics Clinic or the Group Health Medical Genetics Clinic; you will have a single blood draw at the first visit, then you will hear your genetic results in a clinical visit at your home medical center. This clinical visit may be a phone call for GH patients. The third research visit is conducted at UWMC for all participants. You will be asked to complete a total of 14 surveys in approximately 15 months of research participation. If you are in the Whole Exome group, we tell you about genetic information (results) that may include risks for "extra" diseases other than CRCP. We will tell you broad categories of diseases that we may have information on such as heart or neurological diseases or cancers. You can tell us if you do <u>not</u> want to hear about any or all of the "extra" genetic disease risks. We will tell you the medical significance of that information <u>as it known to us today</u>. For approximately 15 months while you are still a part of this study, we will try to update your information as needed. In the future, and after your study participation ends, our understanding of the medical significance of information we gave you may change, and we cannot predict what those changes may be. If you already know that you do <u>not</u> want to hear about any "extra" genetic risks that might be uncovered in this study, or are bothered that we cannot tell you of all your genetic information with certainty, then you should not join this study. However, even if you say yes to participation now, you can always change your mind later.

The genetic results that are discussed with you during this study will be placed in your medical record.

When all the research data have been collected, research participants that were assigned to the Usual Care group may also have their DNA sample whole exome sequenced. Whole exome sequencing will only be done on samples where no causal gene was identified, and it is scientifically likely to discover a gene.

Usual Care participants in this group will only receive whole exome sequence findings that are associated with CRCP.

We may want to grow blood cells from people in both study groups to establish permanent cell lines for future studies. This means some blood cells can be kept alive and grown in the laboratory indefinitely. Permanent cell lines are necessary for long-term genetic research as it allows us to maintain a DNA source. It also allows us to study if the genes are properly copied by the cell. Once we establish a permanent cell line, we may want to "force" the blood cell into acting like another cell, such as an intestinal cell. These 'forced" cells are called iPSCs (induced pluripotent stem cells). We will test the biology of the forced intestinal cells in people with CRCP and compare it to forced cells from people without CRCP. This helps us understand how genes can affect CRCP. We may need to ask you at a later date for another 30cc (2 tablespoons) of blood to grow these cells. You are free to say no.

If you decide to participate in this study, samples from your blood will be stored indefinitely in freezers as DNA, serum, plasma, cell lines, iPSCs and RNA without your name and labeled only with coded IDs. All of your medical history and study information data will also be labeled only with coded IDs in the database and will remain private. We may want to share your samples and data with other qualified researchers, but they will not be given your name. Database information is stored in password protected computers in locked offices. We will keep a link between your name and the coded ID forever. Dr. Jarvik will be the gatekeeper of the link between your coded ID and your name, and will work to keep your information confidential by only allowing authorized research study personnel access to the link.

In our search for genes that cause or influence CRCP, we may also perform other analysis called genotyping or analyze your entire DNA called whole genome sequencing. Usually researchers study just parts of your genetic code that are linked to a disease or condition. In whole-genome studies, all or most of your genes are analyzed and used by researchers to study links to the disease under study. Even if your sample is whole genome sequenced we cannot promise any direct benefit to you personally, though some people might find satisfaction in contributing to scientific knowledge about genetic problems and medical conditions.

dbGaP (*database for Genotype (genes) and Phenotype (observable qualities such as race, age, gender).* In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies. The NIH and other data banks will store your genetic information and give it to other qualified researchers to do more studies. Qualified researchers that can access the national databases can be from the government, academic, or commercial institutions. We do not think that there will be further risks to your privacy and confidentiality by sharing your DNA analysis with these databanks; however, we cannot predict how genetic information will be used in the future. Your genetic and disease status information will be sent with only a code number attached. Your name and other information that could identify you will never be given to them. There are many safeguards in place to protect your information while it is stored in repositories and used for research. You will not receive any results produced from participation in the national databases unless it is considered medically relevant. You can withdraw your consent at anytime you no longer want your data in the national databases. There will be no consequences for withdrawing consent. However, data that has already been sent to researchers cannot be retrieved from those researchers. If you are not comfortable sharing your genetic information (never your name) with qualified researchers, you should not join this study.

There is a small chance that your genetic information could be shared with others by mistake. This information will be part of your medical record. Anyone who has access to the medical record may see your genetic results. In the unlikely event that your information was mistakenly shared and if it were linked with a medical condition, this could affect your ability to get or keep some kinds of insurance.

There is also the risk that data could be released to the public, employers, or law enforcement agencies. If family members were to see this information, it could also affect them. This could hurt family relationships. It is also possible that you could be identified from the sample if someone has another DNA sample from you. The two samples could be matched to identify you from the sample given for this study.

We may want to contact you in the future regarding other studies about CRCP. Please indicate your wishes about being re-contacted in the future at the end of this consent. We may also want to study some of your relatives (with and without CRCP) and we may ask you to contact them about joining this study. We will not share any information about you or your relatives with any study participant.

For some subjects, we may want to ask your physician to discuss their experiences having a patient involved in the new technology NEXT Medicine research project. Please indicate your wishes about contacting your relatives and your physician at the end of this consent. You may say no and still enroll in this study.

RISKS, STRESS, OR DISCOMFORT

Although we are very careful to protect your privacy, we cannot promise that there will never be a breach of your confidential information collected in this study.

Learning about your risks for a genetic disease is likely to be emotionally stressful. The uncertainty of knowing exactly how the genetic risk will affect you or how the risk may change as science advances in the future may be stressful to you. Learning that a condition runs in your family might cause some tension among family members.There may be unknown risks, stresses or discomforts that we haven't identified in this new research.

Talking about private matters and feelings may make you feel uncomfortable.

There is some discomfort when the needle enters your arm for a blood draw. You may get a bruise that should go away in a day or two. You may have wanted to be assigned to the other research group.

BENEFITS OF THE STUDY

We cannot promise any personal benefit from participating in this research. However, we may be able to answer why some people are more likely to get CRCP, while other people are not. We may uncover risk of a medical condition that can be helped by life-style changes, early detection or a therapy. We are hopeful that future generations may benefit from the scientific and medical knowledge we gain from your participation with better methods to predict, prevent, or treat disease. This knowledge may help society by advancing medical science.

MEDICAL RECORDS INFORMATION

As mentioned earlier, all genetic results that are given to you will be placed in your medical record. The Federal Genetics Information Nondiscrimination Act (GINA) of 2008 offers protection from discrimination by health insurers or employers. Although it is illegal, it is theoretically possible that taking part in any genetic study might hurt your access to health insurance if results of the study become part of your medical record. Because your genetic information is unique to you, it is also theoretically possible that someone could trace the information back to you.

If you are a Group Health member, Group Health Cooperative will not use your genetic information when making decisions about your medical coverage eligibility, premiums, or benefits.

SOURCE OF FUNDING

The study team and/or the University of Washington have received funds from the National Institutes of Health (NIH) grant to support genetic research.

CONFIDENTIALITY OF RESEARCH INFORMATION

All of the information you provide will be confidential. However, if we learn that you intend to harm yourself or others, we must report that to the authorities. Government or university staff sometimes reviews studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

We have a Certificate of Confidentiality from the federal National Institutes of Health (NIH). This helps us protect your privacy. The Certificate means that we do not have to give out identifying information about you even if we are asked to by a court of law. We will use the Certificate to resist any demands for identifying information.

We can't use the Certificate to withhold your research information if you give your written consent to give it to an insurer, employer, or other person. Also, you or a member of your family can share information about yourself or your part in this research if you wish.

There are some limits to this protection. We will voluntarily provide the information to:

- a member of the federal government who needs it in order to audit or evaluate the research;
- individuals at the University of Washington, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly;
- the federal Food and Drug Administration (FDA), if required by the FDA;
- the proper authorities, if we learn of child abuse, elder abuse, or the intent to harm yourself or others.

OTHER INFORMATION

We currently have no plans to develop commercial products using your samples. However, if commercial products using your samples are developed sometime in the future, there are no plans to provide financial compensation to you.
You will not be charged for any study procedures; however you or your insurance will be billed for usual care procedures at the Genetics Clinic.

Costs not covered by the research study

Please note that you or your health insurance will be billed for the initial and return medical genetics clinic visits and usual care tests, just as you would if you were not in this study. It is possible that this study will identify genetic risk of disease and that additional medical tests for those diseases will be suggested. This study will not pay for any additional or on-going medical care that is suggested to follow-up those risks. For example, if you are at a higher risk of breast cancer this study will not pay for a mammogram. Your health insurance may or may not pay for additional care that is suggested to follow-up genetic risks.

Costs covered by the research study

You or your health insurance will not be charged for any procedure conducted only for research purposes. You or your health insurance will not be billed for any extra visits that are part of the study and not part of usual care.

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled.

All of the information you provide will be confidential. However, if we learn that you intend to harm yourself or others, we must report that to the authorities. We will keep a link between your name and the coded ID forever.

We will keep your participation in this study confidential. Sometimes, government or university staffs review studies to make sure they are being done safely and legally. If a review happens, your records may be examined. The reviewers will protect your privacy. Your name will not be given on any scientific presentation or publication.

You will be given a $10 gift card when you return completed surveys that we ask you to fill out throughout the study period. If you do not return your survey within the allotted time, we will withhold the $10 gift card. You will receive reminder notices when each survey is due. You have the potential to receive $140 worth of gift cards. Additionally, you will be paid $50 at the end of the study when all study visits and surveys are completed.

COMPENSATION FOR INJURY

If you think you have an injury or illness related to this study, contact the study staff (Martha Pyne, 206-221-0971) right away. She will put you in contact with the study doctors. No money has been set aside to pay for things like lost wages, lost time, or pain because we do not expect these to occur. However, you do not waive any rights by signing this consent form. The UW will pay up to $10,000 to reimburse for treatment of injury or illness resulting from the study.

Printed name of study staff obtaining consent Signature of staff Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, I can ask one of the researchers listed above. If I have questions about my rights as a research subject, I can call the UW Human Subjects Division at (206) 543-0098. I will receive a copy of this consent form.

Printed name of subject Signature of subject Date and Time

Please initial your preference below

1). You may contact my relatives who have given me permission to release contact information to the researchers.

Yes_____ No_____

2). You may contact my referring physician for his/her possible research participation.

Yes_____ No_____

3). I want to be contacted with any unexpected genetic research results that may have medical significance for me.

Yes_____ No_____

4). You may re-contact me regarding other research activities related to this study.

Yes_____ No_____

5). You may re-contact me regarding other research activities in the future not necessarily related to this study.

Yes_____ No_____

Copies to: Subject & Investigator