The Ohio State University Consent to Participate in Research

Study Title: Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome

Principal Investigator: Heather Hampel, MS, LGC

Sponsor: The Ohio State University Comprehensive Cancer Center

- **This is a consent form for research participation and if you participate, you will have to sign this form.** This document contains important information about this study and what to expect if you decide to participate. We are asking you to donate your medical information and biological samples to The Ohio State University (OSU) for research. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate. If you are not comfortable with parts of this study, then discuss this with the consenter. It may be that this study is not right for you.

- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with OSU, your doctors or your hospitals.

- **You may or may not benefit as a result of participating in this study.** Almost all risks to this study are very small. The risks will be explained below. Additionally, we will do our best to protect your privacy.

- **You may receive the results of the research on your samples and you will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.**
1. Why is this study being done?

You are being asked to join the Ohio Colorectal Cancer Prevention Initiative (OCCPI) because your family member was recently diagnosed with colorectal cancer (CRC). Over 50 hospitals in Ohio are participating in the OCCPI to understand how better to prevent CRC in family members, as well as to increase length of life and quality of life for people who have been diagnosed with CRC.

We know that there are many causes of CRC and we need to fully understand each cause so that we can help prevent these cancers from happening, how to find them earlier and how to treat them better. The majority of CRC is caused by the normal aging process, lifestyle factors and environmental exposures. CRC is also caused by factors that we cannot yet explain. Individuals with CRC (and their family members) can help us answer many important questions that have not been answered before.

2. How many people will take part in this study?

We plan to study as many as 13,068 individuals from about 4,400 families in Ohio.

3. What will happen if I take part in this study?

After you sign the consent form, several things will happen:

- You will be asked to donate a saliva sample.
- You will be asked to release your medical records (past/present) by signing a Medical Records Release form.
- You will be asked to allow us to contact you in the future to see how you are doing and to possibly request that you sign additional Medical Records Release forms so that we may look at your future colonoscopies, surgeries and treatments (if applicable).
- You will be asked to complete a questionnaire that will ask about your age, medical history, family history, lifestyle factors and environmental exposures.
  - The questionnaire will take approximately one hour to complete and you will complete the questionnaire at home at your convenience.
    - If you have Internet access, you can complete the questionnaire yourself using your home Internet. You will receive an e-mail invitation from occpi.study@osumc.edu that will provide you with a link to your specific questionnaire. If you do not complete the questionnaire after one week, we will send you a reminder e-mail. If you do not complete the questionnaire within two weeks of receiving the e-mail invitation, we will contact you by telephone to make sure you received the e-mail or to do the questionnaire with you over the phone in case you had difficulty accessing it.
    - If you do not have Internet access or prefer not to complete the questionnaire yourself, a member of our study team will call you on the telephone to help you complete the questionnaire.
4. **How long will I be in the study?**

Your active involvement will take about 15 minutes on the day that you provide your saliva sample and consent (by completing this form and the teleform) and about 60 minutes when you complete the questionnaire from home. If you elect to join the biorepository, your samples will be available for research indefinitely.

In addition, we would like to stay in touch with you for as long as this study is open to update your personal and family medical history information. We may also want access to your medical records from the hospitals and doctor's offices where you have had/will have treatment. You may choose whether or not you would like to allow OCCPI study team to contact you in the future to update your personal and family medical history information.

**Choose one option and initial:**

_____ Yes, study personnel may contact me in the future in order to update my personal and family medical history information.

_____ No, study personnel may *not* contact me in the future in order to update my personal and family medical history information.

5. **What type of research will be done with my sample?**

Your sample and information will be used for cancer research, including genetic research. Your sample may be requested by researchers who are doing cancer research at OSU or other institutions. Any external researchers who might study your sample and information will not know who you are. We will give them the code numbers and the minimal amount of potentially identifying information that is necessary for the research. The research must be approved by an Institutional Review Board (IRB) (a university committee that reviews all research for protection of the study participants) before samples/information will be released. Some of your genetic and health information might also be placed into one or more external scientific or publicly-accessible databases. For example, the National Institutes of Health (an agency of the federal government) maintains a database called “dbGaP.” A researcher who wants to study the information must have an approved study and apply to the dbGaP database.

You have the option of receiving any clinically relevant cancer genetics research results that become available and involve your sample. However, please note, some cancer genetics research studies may not provide results. In order for you to receive any results from another study, the other researchers would report the result to the OCCPI study personnel. Using the sample code, the OCCPI study personnel would then be able to link your identifying information with the sample result. If clinically relevant results become available, and if you have elected to receive results, genetic counseling will be
available, and you may be offered clinical genetic testing to confirm the research results (if available). These services may be at your or your insurance company’s cost.

**Choose one option and initial:**

___ Yes, I would like to be contacted if clinically relevant research results become available.

___ No, I do not wish to be contacted if clinically relevant research results become available.

6. **Family Member Contact**

In the event that we cannot contact you in the future, we ask you to name a Family Member Contact who will receive notices concerning any study related issue (the storage of your samples, the results of any future cancer research studies performed on your samples, etc). You may change your Family Member Contact person at any time by notifying the Clinical Cancer Genetics Program in writing. You do not have to do this.

Name: _________________________________________
Address: _______________________________________
City, State, Zip: _________________________________
Telephone number: _______________________________
Relationship to me: _______________________________

___ I do not wish to name a Family Member Contact.
Initial

7. **Can I stop being in the study?**

You may request to withdraw from the biorepository at any time and researchers will not receive any more samples or information about you. However, your sample and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in the biorepository, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored sample be destroyed or otherwise transferred.

If you decide to withdraw from the study, you may be presented with additional options for continuing your participation at a reduced level.

To revoke your authorization, please contact:

Heather Hampel, MS, LGC  
Principal Investigator  
2012 Kenny Road  
Columbus, OH 43221  
614-293-7240

8. **What risks, side effects or discomforts can I expect from being in the study?**
In general, there are minimal risks for this study.

- **Financial Risk:**
  - If there is additional medical care that is needed because of the results of this study, you will be financially responsible.

- **Psychosocial Risk:**
  - You might find that being involved in cancer genetics research causes you anxiety or causes you to feel upset.
    - This is a long term study and you may never receive results. If you elect to be informed of clinically relevant results that become available through this study, these results may indicate you or your family members are at increased risk of developing cancer and this could be distressing.
  - You can contact the project manager, genetic counselor Rachel Pearlman, at 614-293-5740 any time during the research study to discuss the status of the study and any emotional responses that you are having.

- **Insurance Risk:**
  - A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may **not** request your genetic information from this research.
    - Health insurance companies and group health plans may **not** use your genetic information when making decisions about your eligibility or premiums.
    - Employers with 15 or more employees may **not** use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.
    - All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies **cannot** ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.

9. **What benefits can I expect from being in the study?**

You may benefit from knowing that your participation has helped researchers try to understand how to prevent CRC from being diagnosed in individuals in Ohio, as well as to understand how to improve quality of life and length of life for individuals diagnosed with CRC. Additionally, you may benefit from future cancer research studies if clinically relevant results are found and can be linked back to you.

10. **What are the costs of taking part in this study?**

There are no costs associated with participating in this study.
11. Will I be paid for taking part in this study?

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

12. What happens if I am injured because I took part in this study?

As this is a minimal-risk study, there is no injury expected from participation.

13. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

14. Will my study-related information be kept confidential?

Considerable effort will be made to keep your study-related information confidential. We use state-of-the-art technology to make sure only authorized personnel see any study related information that identifies you and then only for approved purposes or reasons you have authorized. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

We will work to make sure that no one sees your questionnaire responses without approval. However; because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you. Your data will be protected with a code to reduce the risk that other people can identify you.

Additionally, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](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 the website at any time.

15. Authorization to use and disclose information for research purposes

- Your information may be used and given to others.
  - The study doctor and study staff will get your personal and medical information including:
• Past and present medical records
• Research records
• Records about phone calls made as part of this research
• Records about your study visits
• Information that includes personal identifiers, such as your name, or a number associated with you as an individual
• Information gathered for this research about physical exams, laboratory and other test results, questionnaires, HIV/AIDS, hepatitis infection, sexually transmitted diseases and other reportable infectious diseases

• Who may use and give out information about you?
  o The study doctor and the study staff may also use and give out information about you.

• Who might get this information?
  o The sponsor of this research
    ▪ “Sponsor” means any persons or companies that are working for or with the sponsor, or owned by the sponsor
  o Members and staff of the OSU Institutional Review Boards, including the Western Institutional Review Board
  o The Office of Responsible Research Practices
  o University data safety monitoring committees
  o The OSU Office of Sponsored Programs
  o Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information
  o If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician’s office record

• Your information may be given to:
  o The U.S. Food and Drug Administration (FDA)
  o Department of Health and Human Services (DHHS) agencies
  o Governmental agencies in other countries
  o Governmental agencies to whom certain diseases (reportable diseases) must be reported
  o The Ohio State University units involved in managing and approving the research study including the University Research Foundation and the Office of Responsible Research Practices
  o Western Institutional Review Board® (WIRB®)

• Why will this information be used and/or given to others?
  o to do the research
  o to study the results
  o to make sure that the research was done right

If the results of this study are made public, information that identifies you will not be used.

• What if you decide not to give permission to use and give out your health information?
  o Then you will not be able to be in this research study. The Ohio State University Wexner Medical Center may not condition (withhold or refuse) treating you on whether you sign this Authorization.

• Can you review or copy your information?
• **When will your permission end?**
  
  o There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

• **Can you withdraw or revoke (cancel) your permission?**
  
  o Yes. Your authorization will not expire unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

• **Is your health information protected after it has been given to others?**
  
  o There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

16. **What are my rights if I take part in this study?**

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a subject in this study.

You will be provided with any new information that develops during the course of this research that may affect your decision whether or not to continue participation in the study.

An Institutional Review Board responsible for human subjects research at OSU reviewed this research study and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

17. **Who can answer my questions about the study?**

For questions, concerns, complaints, or if you are injured as a result of participating in this study, please contact:

Rachel Pearlman, MS, LGC
Project Manager
614-293-5740

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, please contact:

Sandra Meadows
For questions about how protected health information is collected, maintained, used, and disclosed, please contact:
OSU HIPAA Privacy Officer
614-293-4477
**Signing the Consent Form**

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

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**Investigator/Research Staff**

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

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**Witness(es)** - *May be left blank if not required by the IRB*

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The Ohio State University Consent to Participate in Research

Study Title: Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome

Principal Investigator: Heather Hampel, MS, LGC

Sponsor: The Ohio State University Comprehensive Cancer Center

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- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with OSU, your doctors or your hospitals.

- **You may or may not benefit as a result of participating in this study.** Almost all risks to this study are very small. The risks will be explained below. Additionally, we will do our best to protect your privacy.

- **You may receive the results of the research on your samples and you will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.**
18. Why is this study being done?

You are being asked to join the Ohio Colorectal Cancer Prevention Initiative (OCCPI) because you have recently been diagnosed with colorectal cancer (CRC). Over 50 hospitals in Ohio are participating in the OCCPI to understand how better to prevent CRC in other individuals in Ohio, as well as to increase length of life and quality of life for people who have been diagnosed with CRC. There are currently two studies being done through the OCCPI: Universal Screening for Lynch Syndrome (USLS) and Adherence to Colorectal Cancer Screening (ACCS). The studies are related, but require separate consent forms. **This consent form is for the USLS study, which will focus on identifying individuals at high-risk for CRC (hereditary predisposition).** The ACCS study will focus on providing screening recommendations to you and your close relatives to try to prevent future CRCs.

We know that there are many causes of CRC and we need to fully understand each cause so that we can help prevent these cancers from happening, learn how to find them earlier and learn how to treat them better. The majority of CRC is caused by the normal aging process, lifestyle factors and environmental exposures. CRC is also caused by factors that we cannot yet explain. Individuals with CRC can help us answer many important questions that have not been answered before.

Sometimes, CRC can appear to run in families or be hereditary. Hereditary cancer syndromes are caused by a non-working gene passed down in a family that increases the risk for specific types of cancer. Lynch syndrome (LS) is a hereditary cancer syndrome caused by a non-working gene that significantly increases the risk for an individual to develop CRC, endometrial cancer (EC; also known as uterine cancer) and other cancers during one’s lifetime. There are certain features in colorectal tumors that can suggest they are caused by LS. This study will include free tumor testing to see if you are likely to have LS and if those tests suggest that it is likely, this study will also include free genetic testing to confirm whether or not you have LS. In addition, if you are found to have LS, this study will provide free genetic counseling and testing to your at-risk relatives.

19. How many people will take part in this study?

We plan to include about 4,000 individuals with newly diagnosed CRC across the state of Ohio, as well as 400 individuals newly diagnosed with EC (OSU only). In addition, the relatives of those found to have LS (around 768 individuals) and close relatives of the CRC participants found not to have LS (around 8,000 individuals) will be invited to participate in this study. In total, about 13,068 individuals will participate in the OCCPI.

20. What will happen if I take part in this study?

After you sign the consent form, several things will happen:

- You will be asked to donate a few tablespoons of blood.
- A small piece of your colorectal tumor will be obtained from the hospital where you had (or will be having) your surgery.
  - This signed consent form will serve as a release form for your tumor sample.
In order for you to stay in this study, the final pathology report must confirm that you have an invasive colorectal adenocarcinoma (a specific type of CRC), and the tumor sample must be large enough for at least one of the tumor screening tests to work.

- You will be asked to release your medical records (past/present) by signing a Medical Records Release form.
- You will be asked to allow us to contact you in the future to see how you are doing from your CRC and to possibly request that you sign additional Medical Records Release forms so that we may look at your future colonoscopies, surgeries and treatments.
- You will be asked to join the OCCPI biorepository (sample bank) to help with future research on the causes, treatment and survival of cancer.
  - You will be asked to contribute your leftover samples (tumor and blood), as well as a saliva sample, and complete a questionnaire that will ask about your age, medical history, family history, lifestyle factors and environmental exposures.
- We will screen your tumor for features of LS.
- You may have free genetic testing and genetic counseling.
- If you are found to have LS, your at-risk relatives will be offered free genetic counseling and genetic testing.

21. How long will I be in the study?

Your active involvement will take about 15 minutes on the day that you provide consent and about 60 minutes when you complete the questionnaire from home. The LS tumor screening will take 1-4 months from the time we receive your tumor sample. If you proceed to genetic testing, results should be ready in an additional 3-6 months. If you have genetic counseling, sessions usually last around 60-90 minutes. Overall, your participation in the LS screening portion of the OCCPI is expected to take about 1 year. Most of this time will be spent waiting for results.

In addition, we would like to stay in touch with you for as long as this study is open to update your personal and family medical history information so that we know more about your treatment and outcome from this CRC. We may also want access to your medical records from the hospitals and doctor’s offices where you have had/will have treatment. You may choose whether or not you would like to allow OCCPI study team to contact you in the future to update your personal and family medical history information.

Choose one option and initial:

______ Yes, study personnel may contact me in the future in order to update my personal and family medical history information.

______ No, study personnel may not contact me in the future in order to update my personal and family medical history information.

22. What type of research will be done with my samples for this study?

There are a few screening tests that can be done using your tumor sample in order to determine if you are “more likely” to have LS or “less likely” to have LS.
• Microsatellite Instability (MSI):
  o CRC from individuals with LS will usually show changes in areas of DNA called “microsatellites”. The majority of CRC from LS patients have MSI (MSI positive).
  o If your tumor is MSI positive, it is more likely that you have LS.
  o If your tumor does not have MSI (MSI negative), you are less likely to have LS.

• Immunohistochemistry (IHC):
  o There are four different LS proteins (substances in the body) that are normally present in CRC tumors. There are IHC stains that can show whether or not these proteins are present in your tumor. If one or more of the LS proteins are missing in your tumor, it means that it is more likely that you have LS.
  o If all four proteins are present in your tumor, you are less likely to have LS.

• Methylation:
  o The Methylation test helps to show the difference between hereditary and sporadic (non-hereditary) CRC and is only performed if the MSI or IHC test results show that you are more likely to have LS.
  o If your tumor is methylated, it is very unlikely that you have LS.
  o If your tumor is not methylated, it means that it is more likely that your CRC was caused by LS.

Sometimes a different screening test may need to be substituted for a planned test due to insufficient tumor quantity or other technical issues. In addition, other test(s) may need to be added to help clarify results. In all cases, these tests will be to help determine whether or not the tumor was due to LS or another hereditary cancer susceptibility syndrome.

You will proceed to genetic testing if:
• You were diagnosed with CRC under age 50 OR
• The tumor screening tests suggest that you are more likely to have LS OR
• You have a strong family history of CRC and EC OR
  You have been diagnosed with more than one primary CRC AND/OR you have had both CRC and EC

If you proceed to genetic testing, your blood and/or tumor sample will be tested for mutations (harmful changes) in the five genes known to cause LS (MLH1, MSH2, MSH6, PMS2, EPCAM). You will also be tested for several other genes that increase the risk for hereditary cancers. This additional testing could include (but is not limited to) some of the following genes: BRCA1, BRCA2, PALB2, CDKN2A, CDK4, ATM, CHEK2, RAD51C, RAD51D, BRIP1, BARD1, NBN, MUTYH, APC, CDH1, PTEN, TP53, SMAD4, BMPR1A and STK11. Genetic testing will primarily be done on your blood sample, but in some cases, additional genetic testing will be done on your tumor sample to help determine if your CRC was hereditary.

23. How will I receive my results from this study?
If you do NOT have genetic testing, your active involvement in the study will be completed and you will be notified by mail of your tumor screening test results and that you will not have genetic testing. This letter will also be sent to your accrual nurse and your treating physician.

If you have genetic testing, you could have one of three different results.

- You could have a **negative genetic test result** (meaning no mutations or changes were found in any of the genes that were tested).
  - If you have a negative genetic test result and the tumor screening tests suggested that you were unlikely to have LS, you will receive a letter in the mail detailing your tumor screening test results and genetic test result. The letter will also be sent to your accrual nurse and your treating physician. If you are still concerned about your personal or family history of cancer, please call the telephone number listed on the letter to schedule an appointment with a genetic counselor in your area at your expense. The genetic counseling will not be covered as part of the study because LS has primarily been ruled out.
  - If you have a negative genetic test result in your blood and additional tumor genetic testing indicates that your CRC is most likely not hereditary, you will receive a letter in the mail detailing your tumor screening test results and genetic test results. The letter will also be sent to your accrual nurse and your treating physician. If you are still concerned about your personal or family history of cancer, please call the telephone number listed on the letter to schedule an appointment with a genetic counselor in your area at your expense. The genetic counseling will not be covered as part of the study because LS has primarily been ruled out.
  - If you have a negative genetic test result but you had abnormal tumor screening tests NOT explained by methylation or additional tumor genetic testing, you will be contacted to schedule a free genetic counseling appointment at a location convenient for you. You may also be provided with the option to be counseled over the telephone. After counseling, you will receive a letter in the mail detailing your tumor screening test results, genetic test result and management recommendations. This letter will also be sent to your accrual nurse and your treating physician.

- You could have a **positive genetic test result** (meaning a gene mutation was found).
  - If you have a positive result, you will be contacted to schedule a free genetic counseling appointment at a location convenient for you. You may also be provided with the option to be counseled over the telephone. After your genetic counseling session, you will receive a letter in the mail detailing your tumor screening test results, genetic test result and management recommendations. This letter will also be sent to your accrual nurse and your treating physician. If you do not want to know your genetic test result, you can choose not to schedule an appointment for genetic counseling.
  - If you are found to have LS, your relatives will have the opportunity to learn whether or not they have inherited the same gene mutation and increased cancer risks. You can arrange a group appointment for your relatives, your relatives can contact us or your local genetic counselor directly to schedule a genetic counseling appointment or you can provide
them with a Family Member Consent for Contact form that they can complete and return to us, allowing us to contact them directly to schedule an appointment for genetic counseling. At their appointment, a genetic counselor will offer your relatives genetic testing for the mutation that was found to cause your cancer. Genetic counseling and testing for your relatives will be free of charge as part of this study if you are found to have LS. However, if you are found to have one of the other hereditary forms of cancer, your relatives will be offered genetic counseling and mutation testing at their own expense.

- You could have an **unclear genetic test result** (meaning a change in a gene was found, but it is unclear if that change increases the risk for cancer, or if the change is a normal variation that is not frequently seen).
  - If you have an unclear genetic test result (also known as a variant of uncertain significance (VUS)), you will receive a letter in the mail detailing your tumor screening test results and genetic test result. This letter will also be sent to your accrual nurse and your treating physician. If you are concerned about your genetic test result or your personal or family history of cancer, please call the telephone number listed on the letter to schedule an appointment with a genetic counselor in your area. If you are found to have a variant in a LS gene (*MLH1, MSH2, MSH6, PMS2, EPCAM*) and elect to have genetic counseling, this will be free to you as part of the study. If you are found to have a variant in a non-LS gene and elect to have genetic counseling, this will be at your own expense.

### 24. OCCPI Biorepository

You are being asked to contribute to the OCCPI biorepository, which is being created for future studies that will try to understand the causes of cancer, how better to prevent cancer in family members, as well as to increase length of life and quality of life for people who have been diagnosed with cancer.

We are asking that you allow us to use your medical information (obtained from past/present/future medical records and the baseline questionnaire) and donate your leftover samples from the LS screening portion of the OCCPI (tissue from your CRC surgery and blood sample), as well as donate a saliva sample.

The questionnaire will take approximately one hour to complete and you will complete the questionnaire at home at your convenience.

- If you have Internet access, you can complete the questionnaire yourself using your home Internet. You will receive an e-mail invitation from occpi.study@osumc.edu that will provide you with a link to your specific questionnaire. If you do not complete the questionnaire after one week, we will send you a reminder e-mail. If you do not complete the questionnaire within two weeks of receiving the e-mail invitation, we will contact you by telephone to make sure you received the e-mail or to do the questionnaire with you over the phone in case you had difficulty accessing it.
- If you do not have Internet access or prefer not to complete the questionnaire yourself, a member of our study team will call you on the telephone to help you complete the questionnaire.
Preference:

☐ Telephone: __________________________

☐ Email: __________________________

Your samples and information will be used for cancer research, including genetic research. Your samples may be requested by researchers who are doing cancer research at OSU or other institutions. Any external researchers who might study your sample and information will not know who you are. We will give them the code numbers and the minimal amount of potentially identifying information that is necessary for the research. The research must be approved by an Institutional Review Board (IRB) (a university committee that reviews all research for protection of the study participants) before samples/information will be released. Some of your genetic and health information might also be placed into one or more external scientific or publicly-accessible databases. For example, the National Institutes of Health (an agency of the federal government) maintains a database called “dbGaP.” A researcher who wants to study the information must have an approved study and apply to the dbGaP database.

If you elect to join the biorepository, your samples will be available for research indefinitely. You may request to withdraw from the biorepository at any time and researchers will not receive any more samples or information about you. However, your samples and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in the biorepository, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored samples be destroyed or otherwise transferred. You can still participate in the LS screening portion of the OCCPI even if you do not wish to participate in the OCCPI biorepository.

Choose one option and initial:

_____ Yes, I would like to contribute my leftover tumor and blood samples, as well as donate a saliva sample for the OCCPI biorepository.

_____ No, I do not want to contribute my leftover tumor and blood samples to the OCCPI biorepository. Destroy any of my leftover samples that are not used for the LS screening.

If you agreed to participate in the biorepository:

You have the option of receiving any clinically relevant cancer genetics research results that become available and involve your sample. However, please note, some cancer genetics research studies may not provide results. In order for you to receive any results from another study, the other researchers would report the result to the OCCPI study personnel. Using the sample code, the OCCPI study personnel would then be able to link your identifying information with the sample result. If clinically relevant results become available, and if you have elected to receive results, genetic counseling will be available, and you may be offered clinical genetic testing to confirm the research results (if available). These services may be at your or your insurance company’s cost.

Choose one option and initial:
_____ Yes, I would like to be contacted if clinically relevant research results become available.

_____ No, I do not wish to be contacted if clinically relevant research results become available.

25. What about other research studies?

There may be additional studies that will try to discover possible causes of CRC or ways to improve the prevention, treatment or survival of CRC. For example, the OCCPI's Adherence to Colorectal Cancer Screening (ACCS) study focuses on making sure that you and your relatives receive proper screening recommendations for CRC, as well as follow-through on those recommendations. If you enroll in ACCS, your first-degree relatives (parents, siblings, adult children at least 25 years old) will be eligible to participate in ACCS as well.

The OCCPI would like to contact you to offer you participation in studies like the ACCS and other future studies for which you may be eligible. Agreeing to be contacted does not imply that you will agree to join these studies; you can choose the studies in which you would or would not like to participate at the time you are contacted.

Choose one option and initial:

_____ Yes, I would like to be contacted if I am eligible for future research studies.

_____ No, I do not wish to be contacted if I am eligible for future research studies.

26. Family Member Contact

In the event that we cannot contact you in the future, we ask you to name a Family Member Contact who will receive notices concerning any study related issue (genetic test results from the OCCPI, the storage of your samples, the results of any future cancer research studies performed on your samples, etc). You may change your Family Member Contact person at any time by notifying the Clinical Cancer Genetics Program in writing. You do not have to do this.

Name: _________________________________________
Address: _______________________________________
City, State, Zip: _________________________________
Telephone number: ______________________________
Relationship to me: ______________________________

_____ I do not wish to name a Family Member Contact.
Initial

27. Can I stop being in the study?
You may request to withdraw from the study at any time and researchers will not receive any more samples or information about you. However, your samples and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in this study, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored samples be destroyed or otherwise transferred.

If you decide to withdraw from the study, you may be presented with additional options for continuing your participation at a reduced level.

To revoke your authorization, please contact:

Heather Hampel, MS, LGC
Principal Investigator
2012 Kenny Road
Columbus, OH 43221
614-293-7240

28. What risks, side effects or discomforts can I expect from being in the study?

In general, there are minimal risks for this study.

- **Risk of taking blood from you:**
  - When blood is drawn you may feel some pain and you may feel faint.
  - After blood is collected, you may have a bruise and a very slight risk of infection at the site where the blood was taken.

- **Financial Risk:**
  - If there is additional medical care that is needed because of the results of this study, you will be financially responsible.

- **Psychosocial Risk:**
  - Some people find it upsetting to go through the genetic testing process because it has implications for their children, siblings, and other family members.
    - Genetic test results could also suggest that you are at an increased risk for developing cancer again in the future.
    - It may be difficult to wait for the full results of this study.
    - Some individuals may be upset to learn that their tumor does not show features of LS and they will not have genetic testing.
  - You can contact the project manager, genetic counselor Rachel Pearlman, at 614-293-5740 any time during the research study to discuss the status of the study and any emotional responses that you are having.

- **Insurance Risk:**
  - A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may **not** request your genetic information from this research.
• Health insurance companies and group health plans may **not** use your genetic information when making decisions about your eligibility or premiums.
• Employers with 15 or more employees may **not** use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.
• All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies **cannot** ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.

29. **What benefits can I expect from being in the study?**

There are several possible benefits to participating in the study.

- You may benefit from knowing that your participation has helped researchers try to understand how to prevent CRC from being diagnosed in other individuals in Ohio, as well as to understand how to improve quality of life and length of life for individuals diagnosed with CRC.
- Genetic test results can help us to provide personalized cancer screening recommendations for you.
- Genetic test results can provide information to family members including their future cancer risks and personalized cancer screening recommendations.
- If you are participating in the biorepository and you elected to receive any clinically relevant results, you may benefit from future cancer research studies if clinically relevant results are found and can be linked back to you.

30. **What are the costs of taking part in this study?**

Some hospitals already perform some or all of the tumor tests required for this study as part of your regular clinical care.

- If your hospital performs all of the tumor tests required for this study, your tumor testing will be billed to your insurance company as part of your clinical care.
- If your hospital performs some (but not all) of the tumor tests required for this study, the testing performed by your hospital will be billed to your insurance company as part of your clinical care. The remaining tumor test(s) not performed by your hospital will be done at OSU for free as part of this study.
- If your hospital does not perform any of the tumor tests required for this study, the testing will be done at OSU for free as part of this study.

There are no costs associated with the genetic testing and genetic counseling for the participants of this study.

31. **Will I be paid for taking part in this study?**

You will not be paid for taking part in this study.
32. What happens if I am injured because I took part in this study?

As this is a minimal-risk study, there is no injury expected from participation.

33. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. You may choose to have clinical genetic testing and genetic counseling (at your expense) if you do not take part in the study.

34. Will my study-related information be kept confidential?

Considerable effort will be made to keep your study-related information confidential. We use state-of-the-art technology to make sure only authorized personnel see any study related information that identifies you and then only for approved purposes or reasons you have authorized. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

We will work to make sure that no one sees your questionnaire responses without approval. But, because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you. Your data will be protected with a code to reduce the risk that other people can identify you.

Additionally, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

Because this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician’s office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](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 the website at any time.

35. Authorization to use and disclose information for research purposes

- Your information may be used and given to others.
The study doctor and study staff will get your personal and medical information including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual
- Information gathered for this research about physical exams, laboratory and other test results, questionnaires, HIV/AIDS, hepatitis infection, sexually transmitted diseases and other reportable infectious diseases

Who may use and give out information about you?

- The study doctor and the study staff may also use and give out information about you.

Who might get this information?

- The sponsor of this research
  - “Sponsor” means any persons or companies that are working for or with the sponsor, or owned by the sponsor
- Members and staff of the OSU Institutional Review Boards, including the Western Institutional Review Board
- The Office of Responsible Research Practices
- University data safety monitoring committees
- The OSU Office of Sponsored Programs
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician’s office record

Your information may be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- The Ohio State University units involved in managing and approving the research study including the University Research Foundation and the Office of Responsible Research Practices
- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research
- to study the results
- to make sure that the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if you decide not to give permission to use and give out your health information?
Then you will not be able to be in this research study. The Ohio State University Wexner Medical Center may not condition (withhold or refuse) treating you on whether you sign this Authorization.

- **Can you review or copy your information?**
  - Yes, but only after the research is over.

- **When will your permission end?**
  - There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

- **Can you withdraw or revoke (cancel) your permission?**
  - Yes. Your authorization will not expire unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

- **Is your health information protected after it has been given to others?**
  - There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

36. What are my rights if I take part in this study?

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a subject in this study.

You will be provided with any new information that develops during the course of this research that may affect your decision whether or not to continue participation in the study.

An Institutional Review Board responsible for human subjects research at OSU reviewed this research study and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

37. Who can answer my questions about the study?

For questions, concerns, complaints, or if you are injured as a result of participating in this study, please contact:

Rachel Pearlman, MS, LGC
Project Manager
614-293-5740
For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, please contact:
  Sandra Meadows
  The Office of Responsible Research Practices
  1-800-678-6251

For questions about how protected health information is collected, maintained, used, and disclosed, please contact:
  OSU HIPAA Privacy Officer
  614-293-4477
Signing the Consent Form
I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of subject ____________________________ Signature of subject ____________________________ AM/PM
Date and time ____________________________

Printed name of person authorized to consent for subject (when applicable) ____________________________ Signature of person authorized to consent for subject (when applicable) ____________________________ AM/PM

Relationship to the subject ____________________________ Date and time ____________________________

Investigator/Research Staff
I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent ____________________________ Signature of person obtaining consent ____________________________ AM/PM
Date and time ____________________________

Witness(es) - May be left blank if not required by the IRB

Printed name of witness ____________________________ Signature of witness ____________________________ AM/PM
Date and time ____________________________

Printed name of witness ____________________________ Signature of witness ____________________________ AM/PM
Date and time ____________________________
The Ohio State University Consent to Participate in Research

Study Title: Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome

Principal Investigator: Heather Hampel, MS, LGC

Sponsor: The Ohio State University Comprehensive Cancer Center

- This is a consent form for research participation and if you participate, you will have to sign this form. This document contains important information about this study and what to expect if you decide to participate. We are asking you to donate your medical information and biological samples to The Ohio State University (OSU) for research. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate. If you are not comfortable with parts of this study, then discuss this with the consenter. It may be that this study is not right for you.

- Your participation is voluntary. You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with OSU, your doctors or your hospitals.

- You may or may not benefit as a result of participating in this study. Almost all risks to this study are very small. The risks will be explained below. Additionally, we will do our best to protect your privacy.

- You may receive the results of the research on your samples and you will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.
38. Why is this study being done?

You are being asked to join the Ohio Colorectal Cancer Prevention Initiative (OCCPI) because you have recently been diagnosed with endometrial cancer (EC; also known as uterine cancer). This study is being done to understand how better to prevent EC in other individuals in Ohio, as well as to increase length of life and quality of life for people who have been diagnosed with EC.

We know that there are many causes of EC and we need to fully understand each cause so that we can help prevent these cancers from happening, learn how to find them earlier and learn how to treat them better. The majority of EC is caused by the normal aging process, lifestyle factors and environmental exposures. EC is also caused by factors that we cannot yet explain. Individuals with EC can help us answer many important questions that have not been answered before.

Sometimes, EC can appear to run in families or be hereditary. Hereditary cancer syndromes are caused by a non-working gene passed down in a family that increases the risk for specific types of cancer. Lynch syndrome (LS) is a hereditary cancer syndrome caused by a non-working gene that significantly increases the risk for an individual to develop colorectal cancer (CRC), EC and other cancers during one’s lifetime. There are certain features in endometrial tumors that can suggest they are caused by LS.

This study will include free tumor testing to see if you are likely to have LS and if those tests suggest that it is likely, this study will also include free genetic testing to confirm whether or not you have LS. In addition, if you are found to have LS, this study will provide free genetic counseling and testing to your at-risk relatives. This important because if you are found to have LS, we can hopefully prevent you from getting CRC by recommending that you have colonoscopy screening procedures more frequently and starting at an earlier age. This is why this testing is being done in EC patients under a study called the Ohio Colorectal Cancer Prevention Initiative.

39. How many people will take part in this study?

We plan to include about 400 newly diagnosed EC patients who undergo surgery exclusively at OSU. In addition, the relatives of those found to have LS (around 48 individuals) will be invited to participate in this study.

40. What will happen if I take part in this study?

After you sign the consent form, several things will happen:

- You will be asked to donate a few tablespoons of blood.
- A small piece of your endometrial tumor will be obtained from OSU after your surgery.
  - This signed consent form will serve as a release form for your tumor sample.
  - In order for you to stay in this study, the final pathology report must confirm that you have any type of endometrial cancer except sarcoma (a
specific type of EC), and the tumor sample must be large enough for at least one of the tumor screening tests to work.

- You will be asked to release your medical records (past/present) by signing a Medical Records Release form.
- You will be asked to allow us to contact you in the future to see how you are doing from your EC and to possibly request that you sign additional Medical Record Release forms so that we may look at your future colonoscopies, surgeries and treatments.
- You will be asked to join the OCCPI biorepository (sample bank) to help with future research on the causes, treatment and survival of cancer.
  - You will be asked to contribute your leftover samples (tumor and blood) to the OCCPI biorepository, as well as complete a questionnaire that will ask about your age, medical history, family history, lifestyle factors and environmental exposures.
- We will screen your tumor for features of LS.
- You may have free genetic testing and genetic counseling.
- If you are found to have LS, your at-risk relatives will be offered free genetic counseling and genetic testing.

41. How long will I be in the study?

Your active involvement will take about 15 minutes on the day that you provide consent and about 60 minutes when you complete the questionnaire from home. The LS tumor screening portion of the OCCPI will take 1-4 months. If you undergo genetic testing for LS, results should be ready in an additional 3-6 months. If you have genetic counseling, sessions usually last around 60-90 minutes. Overall, your participation in the OCCPI is expected to take about 1 year. Most of this time will be spent waiting for results.

In addition, we would like to stay in touch with you for as long as this study is open to update your personal and family medical history information so that we know more about your treatment and outcome from this endometrial cancer. We may also want access to your medical records from the hospitals and doctor’s offices where you have had/will have treatment. You may choose whether or not you would like to allow OCCPI study team to contact you in the future to update your personal and family medical history information.

Choose one option and initial:

_____ Yes, study personnel may contact me in the future in order to update my personal and family medical history information.

_____ No, study personnel may not contact me in the future in order to update my personal and family medical history information.

42. What type of research will be done with my samples for this study?

There are a few screening tests that will be done using your tumor sample in order to determine if you are “more likely” to have LS or “less likely” to have LS.
• **Microsatellite Instability (MSI):**
  - EC from individuals with LS will usually show changes in areas of DNA called “microsatellites”. The majority of EC from LS patients have MSI (MSI positive).
  - If your tumor is MSI positive, it is more likely that you have LS.
  - If your tumor does not have MSI (MSI negative), you are less likely to have LS.

• **Immunohistochemistry (IHC):**
  - There are four different LS proteins (substances in the body) that are normally present in EC tumors. There are IHC stains that can show whether or not these proteins are present in your tumor. If one or more of the LS proteins are missing in your tumor, it means that it is more likely that you have LS.
  - If all four proteins are present in your tumor, you are less likely to have LS.

• **Methylation:**
  - The Methylation test helps to show the difference between hereditary and sporadic (non-hereditary) EC and is only performed if the MSI or IHC test results show that you are more likely to have LS.
  - If your tumor is methylated, it is very unlikely that you have LS and you will be notified by mail that you will not have genetic testing.
  - If your tumor is not methylated, it means that it is more likely that your EC was caused by LS and you will proceed to the genetic testing portion of this study.

Sometimes a different screening test may need to be substituted for a planned test due to insufficient tumor quantity or other technical issues. In addition, an additional test(s) may sometimes need to be added to help clarify the rest of the results. In all cases, these tests will be to help determine whether or not the tumor was due to LS.

**You will NOT proceed to genetic testing if:**
- The tumor screening tests suggest that you are unlikely to have LS

**You will proceed to genetic testing if:**
- The tumor screening tests suggest that you are more likely to have LS

If you proceed to the genetic testing portion of the study, your blood sample will be tested for mutations (harmful changes) in several genes that increase the risk for hereditary cancers including the five genes known to cause LS (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and other genes (e.g. *MUTYH, APC, CDH1, PTEN, TP53, STK11, SMAD4, BMPR1A*). Genetic testing will primarily be done on your blood sample, but in some cases, additional genetic testing will be done on your tumor sample to help determine if your EC was hereditary.

**43. How will I receive my results from this study?**

If you do NOT have genetic testing, your active involvement in the study will be completed and you will be notified by mail of your tumor screening test results and that
you will not have genetic testing. This letter will also be sent to your accrual nurse and your treating physician.

**If you have genetic testing**, you could have one of three different results.

- **You could have a negative genetic test result** (meaning no mutations or changes were found in any of the genes that were tested).
  - If you have a negative genetic test result in your blood and additional tumor genetic testing indicates that your EC is most likely not hereditary, you will receive a letter in the mail detailing your tumor screening test results and genetic test results. The letter will also be sent to your accrual nurse and your treating physician. If you are still concerned about your personal or family history of cancer, please call the telephone number listed on the letter to schedule an appointment with a genetic counselor in your area at your expense. The genetic counseling will not be covered as part of the study because LS has primarily been ruled out.
  - If you have a negative genetic test result but you had abnormal tumor screening tests NOT explained by methylation or additional tumor genetic testing, you will be contacted to schedule a free genetic counseling appointment at OSU. You may also be provided with the option to be counseled over the telephone. After counseling, you will receive a letter in the mail detailing your tumor screening test results, genetic test result and management recommendations. This letter will also be sent to your accrual nurse and your treating physician.

- **You could have a positive genetic test result** (meaning a gene mutation was found).
  - If you have a positive result, you will be contacted to schedule a free genetic counseling session at OSU. You may also be provided with the option to be counseled over the telephone. After counseling, you will receive a letter in the mail detailing your tumor screening test results, genetic test result and management recommendations. This letter will also be sent to your accrual nurse and your treating physician. If you do not want to know your genetic test result, you can choose not to schedule an appointment for genetic counseling.
  - If you are found to have LS, your relatives will have the opportunity to learn whether or not they have inherited the same gene mutation and increased cancer risks. You can arrange a group appointment for your relatives, your relatives can contact us directly to schedule a genetic counseling appointment or you can provide them with a Family Member Consent for Contact form that they can complete and return to us, allowing us to contact them directly to schedule an appointment for genetic counseling. At their appointment, a genetic counselor will offer them genetic testing for the mutation that was found to cause your cancer. Genetic counseling and testing for your relatives will be free of charge as part of this study if you are found to have LS. However, if you are found to have one of the other hereditary forms of cancer, your relatives will be offered genetic counseling and mutation testing at their own expense.

- **You could have an unclear genetic test result** (meaning a change in a gene was found, but it is unclear if that change increases the risk for cancer, or if the change is a normal variation that is not frequently seen).
If you have an unclear genetic test result (also known as a variant of uncertain significance (VUS)) and you had abnormal tumor screening tests NOT explained by methylation or additional tumor genetic testing, you will be contacted to schedule a free genetic counseling appointment at OSU. You may also be provided with the option to be counseled over the telephone. After counseling, you will receive a letter in the mail detailing your tumor screening test results, genetic test result and management recommendations. This letter will also be sent to your accrual nurse and your treating physician.

- If you have an unclear genetic test result in your blood and additional tumor genetic testing indicates that your EC is most likely not hereditary, you will receive a letter in the mail detailing your tumor screening test results and genetic test result. This letter will also be sent to your accrual nurse and your treating physician. If you are concerned about your genetic test result or your personal or family history of cancer, please call the telephone number listed on the letter to schedule an appointment with a genetic counselor at OSU. If you are found to have a variant in a non-LS gene (MLH1, MSH2, MSH6, PMS2, EPCAM) and elect to have genetic counseling, this will be at your own expense.

44. OCCPI Biorepository

You are being asked to contribute to the OCCPI biorepository, which is being created for future studies that will try to understand the causes of cancer, how better to prevent cancer in family members, as well as to increase length of life and quality of life for people who have been diagnosed with cancer.

We are asking that you allow us to use your medical information (obtained from past/present/future medical records and the baseline questionnaire) and donate your leftover samples from the LS screening portion of the OCCPI (tissue from your EC surgery and blood sample).

The questionnaire will take approximately one hour to complete and you will complete the questionnaire at home at your convenience.

- If you have Internet access, you can complete the questionnaire yourself using your home Internet. You will receive an e-mail invitation from occpi.study@osumc.edu that will provide you with a link to your specific questionnaire. If you do not complete the questionnaire after one week, we will send you a reminder e-mail. If you do not complete the questionnaire within two weeks of receiving the e-mail invitation, we will contact you by telephone to make sure you received the e-mail or to do the questionnaire with you over the phone in case you had difficulty accessing it.
- If you do not have Internet access or prefer not to complete the questionnaire yourself, a member of our study team will call you on the telephone to help you complete the questionnaire.

Preference:
Your samples and information will be used for cancer research, including genetic research. Your samples may be requested by researchers who are doing cancer research at OSU or other institutions. Any external researchers who might study your sample and information will not know who you are. We will give them the code numbers and the minimal amount of potentially identifying information that is necessary for the research. The research must be approved by an Institutional Review Board (IRB) (a university committee that reviews all research for protection of the study participants) before samples/information will be released. Some of your genetic and health information might also be placed into one or more external scientific or publicly-accessible databases. For example, the National Institutes of Health (an agency of the federal government) maintains a database called “dbGaP.” A researcher who wants to study the information must have an approved study and apply to the dbGaP database.

If you elect to join the biorepository, your samples will be available for research indefinitely. You may request to withdraw from the biorepository at any time and researchers will not receive any more samples or information about you. However, your samples and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in the biorepository, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored samples be destroyed or otherwise transferred.

You can still participate in the LS screening portion of the OCCPI even if you do not wish to participate in the OCCPI biorepository.

Choose one option and initial:

_____ Yes, I would like to contribute my leftover tumor and blood samples to the OCCPI biorepository.

_____ No, I do not want to contribute my leftover tumor and blood samples to the OCCPI biorepository. Destroy any of my leftover samples that are not used for the LS screening.

If you agreed to participate in the biorepository:

You have the option of receiving any clinically relevant cancer genetics research results that become available and involve your sample. However, please note, some cancer genetics research studies may not provide results. In order for you to receive any results from another study, the other researchers would report the result to the OCCPI study personnel. Using the sample code, the OCCPI study personnel would then be able to link your identifying information with the sample result. If clinically relevant results become available, and if you have elected to receive results, genetic counseling will be available, and you may be offered clinical genetic testing to confirm the research results (if available). These services may be at your or your insurance company’s cost.

Choose one option and initial:
Yes, I would like to be contacted if clinically relevant research results become available.

No, I do not wish to be contacted if clinically relevant research results become available.

45. What about future research studies?

There may be additional studies that will try to discover possible causes of EC or ways to improve the prevention, treatment or survival of EC in the future. If such studies occur, we would like to contact you and offer you participation. It is your decision whether or not you would like us to contact you about future studies for which you may be eligible. Agreeing to be contacted does not imply that you will agree to join these studies; you can choose the studies in which you would or would not like to participate at the time you are contacted.

Choose one option and initial:

Yes, I would like to be contacted if I am eligible for future research studies.

No, I do not wish to be contacted if I am eligible for future research studies.

46. Family Member Contact

In the event that we cannot contact you in the future, we ask you to name a Family Member Contact who will receive notices concerning any study related issue (genetic test results from the OCCPI, the storage of your samples, the results of any future cancer research studies performed on your samples, etc). You may change your Family Member Contact person at any time by notifying the Clinical Cancer Genetics Program in writing. You do not have to do this.

Name: _________________________________________
Address: _______________________________________
City, State, Zip: _________________________________
Telephone number: _______________________________
Relationship to me: _______________________________

I do not wish to name a Family Member Contact.
Initial

47. Can I stop being in the study?

You may request to withdraw from the study at any time and researchers will not receive any more samples or information about you. However, your samples and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in this study, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored samples be destroyed or otherwise transferred.

If you decide to withdraw from the study, you may be presented with additional options for continuing your participation at a reduced level.
To revoke your authorization, please contact:

Heather Hampel, MS, LGC
Principal Investigator
2012 Kenny Road
Columbus, OH 43221
614-293-7240

48. What risks, side effects or discomforts can I expect from being in the study?

In general, there are minimal risks for this study.

- **Risk of taking blood from you:**
  - When blood is drawn you may feel some pain and you may feel faint.
  - After blood is collected, you may have a bruise and a very slight risk of infection at the site where the blood was taken.

- **Financial Risk:**
  - If there is additional medical care that is needed because of the results of this study, you will be financially responsible.

- **Psychosocial Risk:**
  - Some people find it upsetting to go through the genetic testing process because it has implications for their children, siblings, and other family members.
    - Genetic test results could also suggest that you are at an increased risk for developing cancer again in the future.
    - It may be difficult to wait for the full results of this study.
    - Some individuals may be upset to learn that their tumor does not show features of LS and they will not have genetic testing.
  - You can contact the project manager, genetic counselor Rachel Pearlman, at 614-293-5740 any time during the research study to discuss the status of the study and any emotional responses that you are having.

- **Insurance Risk:**
  - A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may **not** request your genetic information from this research.
    - Health insurance companies and group health plans may **not** use your genetic information when making decisions about your eligibility or premiums.
    - Employers with 15 or more employees may **not** use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.
    - All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health
insurance companies cannot ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.

49. What benefits can I expect from being in the study?

There are several possible benefits to participating in the study.

- You may benefit from knowing that your participation has helped researchers try to understand how to prevent EC from being diagnosed in other individuals in Ohio, as well as to understand how to improve quality of life and length of life for individuals diagnosed with EC.
- Genetic test results can help us to provide personalized cancer screening recommendations for you.
- Genetic test results can provide information to family members including their future cancer risks and personalized cancer screening recommendations.
- If you are participating in the biorepository and you elected to receive any clinically relevant results, you may benefit from future cancer research studies if clinically relevant results are found and can be linked back to you.

50. What are the costs of taking part in this study?

OSU already performs some of the tumor tests required for this study as part of your regular clinical care. The testing already performed by OSU will be billed to your insurance company as part of your clinical care. The remaining tumor test(s) not routinely performed by OSU will be done for free as part of this study.

There are no costs associated with the genetic testing and genetic counseling for the participants of this study.

51. Will I be paid for taking part in this study?

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

52. What happens if I am injured because I took part in this study?

As this is a minimal-risk study, there is no injury expected from participation.

53. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. You may choose to have clinical genetic testing and genetic counseling (at your expense) if you do not take part in the study.

54. Will my study-related information be kept confidential?

Considerable effort will be made to keep your study-related information confidential. We use state-of-the-art technology to make sure only authorized personnel see any study related information that identifies you and then only for approved purposes or reasons you have authorized. However, there may be circumstances where this information must
be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

We will work to make sure that no one sees your questionnaire responses without approval. However; because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you. Your data will be protected with a code to reduce the risk that other people can identify you.

Additionally, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

Because this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician’s office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](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 the website at any time.

55. Authorization to use and disclose information for research purposes

- **Your information may be used and given to others.**
  - The study doctor and study staff will get your personal and medical information including:
    - Past and present medical records
    - Research records
    - Records about phone calls made as part of this research
    - Records about your study visits
    - Information that includes personal identifiers, such as your name, or a number associated with you as an individual
    - Information gathered for this research about physical exams, laboratory and other test results, questionnaires, HIV/AIDS, hepatitis infection, sexually transmitted diseases and other reportable infectious diseases

- **Who may use and give out information about you?**
  - The study doctor and the study staff may also use and give out information about you.

- **Who might get this information?**
The sponsor of this research
  ▪ “Sponsor” means any persons or companies that are working for
    or with the sponsor, or owned by the sponsor

Members and staff of the OSU Institutional Review Boards, including the
Western Institutional Review Board

The Office of Responsible Research Practices

University data safety monitoring committees

The OSU Office of Sponsored Programs

Authorized Ohio State University staff not involved in the study may be
aware that you are participating in a research study and have access to
your information

If this study is related to your medical care, your study-related information
may be placed in your permanent hospital, clinic or physician’s office record

Your information may be given to:
  ▪ The U.S. Food and Drug Administration (FDA)
  ▪ Department of Health and Human Services (DHHS) agencies
  ▪ Governmental agencies in other countries
  ▪ Governmental agencies to whom certain diseases (reportable diseases)
    must be reported
  ▪ The Ohio State University units involved in managing and approving the
    research study including the University Research Foundation and the Office
    of Responsible Research Practices
  ▪ Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?
  ▪ to do the research
  ▪ to study the results
  ▪ to make sure that the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if you decide not to give permission to use and give out your health
information?
  ▪ Then you will not be able to be in this research study. The Ohio State
    University Wexner Medical Center may not condition (withhold or refuse)
    treating you on whether you sign this Authorization.

Can you review or copy your information?
  ▪ Yes, but only after the research is over.

When will your permission end?
  ▪ There is no date at which your permission ends. Your information will be
    used indefinitely. This is because the information used and created during
    the study may be analyzed for many years, and it is not possible to know
    when this will be complete.

Can you withdraw or revoke (cancel) your permission?
  ▪ Yes. Your authorization will not expire unless you change your mind and
    revoke it in writing. You may withdraw or take away your permission to
    use and disclose your health information at any time. You do this by
    sending written notice to the study doctor. If you withdraw your
    permission, you will not be able to stay in this study. When you withdraw
    your permission, no new health information identifying you will be
gathered after that date. Information that has already been gathered may still be used and given to others.

- **Is your health information protected after it has been given to others?**
  - There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

56. **What are my rights if I take part in this study?**

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a subject in this study.

You will be provided with any new information that develops during the course of this research that may affect your decision whether or not to continue participation in the study.

An Institutional Review Board responsible for human subjects research at OSU reviewed this research study and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

57. **Who can answer my questions about the study?**

For questions, concerns, complaints, or if you are injured as a result of participating in this study, please contact:
- Rachel Pearlman, MS, LGC
  - Project Manager
  - 614-293-5740

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, please contact:
- Sandra Meadows
  - The Office of Responsible Research Practices
  - 1-800-678-6251

For questions about how protected health information is collected, maintained, used, and disclosed, please contact:
- OSU HIPAA Privacy Officer
  - 614-293-4477
**Signing the Consent Form**  
I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

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**Investigator/Research Staff**  
I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

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**Witness(es) - May be left blank if not required by the IRB**

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The Ohio State University Consent to Participate in Research

Study Title: Ohio Colorectal Cancer Prevention Initiative: Universal Screening for Lynch Syndrome

Principal Investigator: Heather Hampel, MS, LGC

Sponsor: The Ohio State University Comprehensive Cancer Center

- This is a consent form for research participation and if you participate, you will have to sign this form. This document contains important information about this study and what to expect if you decide to participate. We are asking you to donate your medical information and biological samples to The Ohio State University (OSU) for research. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate. If you are not comfortable with parts of this study, then discuss this with the consenter. It may be that this study is not right for you.

- Your participation is voluntary. You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with OSU, your doctors or your hospitals.

- You may or may not benefit as a result of participating in this study. Almost all risks to this study are very small. The risks will be explained below. Additionally, we will do our best to protect your privacy.

- You may receive the results of the research on your samples and you will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.
58. **Why is this study being done?**

You are being asked to join the Ohio Colorectal Cancer Prevention Initiative (OCCPI) because your family member was recently diagnosed with colorectal cancer (CRC) or endometrial cancer (EC; also known as uterine cancer) and found to have Lynch syndrome (LS). Over 40 hospitals in Ohio are participating in the OCCPI to understand how better to prevent cancer in family members, as well as to increase length of life and quality of life for people who have been diagnosed with CRC and EC. There are currently two studies being done through the OCCPI: Universal Screening for Lynch Syndrome (USLS) and Adherence to Colorectal Cancer Screening (ACCS). The studies are related, but require separate consent forms. **This consent form is for the USLS study, which will focus on identifying individuals at high-risk for CRC and EC (hereditary predisposition).** The first degree relatives (FDRs) of participants with CRC are eligible for the ACCS study, which will focus on providing screening recommendations to try to prevent CRC. FDRs of participants with CRC will be given a postcard with information about the ACCS study to take home and look over.

Sometimes, CRC and EC can appear to run in families or be hereditary. Hereditary cancer syndromes are caused by a non-working gene passed down in a family that increases the risk for specific types of cancer. Lynch syndrome (LS) is a hereditary cancer syndrome caused by one of five genes (MLH1, MSH2, MSH6, PMS2, EPCAM) not working the correct way in the body. A mutation (change) in a LS gene can significantly increase the risk for an individual to develop CRC, EC and other cancers during one’s lifetime.

This study will include free genetic counseling (unless otherwise specified) and free genetic testing to determine if you also have inherited LS.

59. **How many people will take part in this study?**

We plan to include about 4,000 individuals with newly diagnosed CRC across the state of Ohio, as well as 400 individuals newly diagnosed with EC (OSU only). In addition, the relatives of those found to have LS (around 768 individuals) and close relatives of the CRC participants found not to have LS (around 8,000 individuals) will be invited to participate in this study. In total, about 13,068 individuals will participate in the OCCPI.

60. **What will happen if I take part in this study?**

After you sign the consent form, several things will happen:

- You will be asked to donate a few tablespoons of blood and/or saliva in order to do the genetic testing.
- You will be asked to release your medical records (past/present) by signing a Medical Records Release form.
- You will be asked to allow us to contact you in the future to see how you are doing and to possibly request that you sign additional Medical Records Release forms so that we may look at your future colonoscopies, any surgeries and any new diagnoses.
- You will be offered free genetic counseling and free single site genetic testing for LS.
If you already had genetic testing for LS prior to joining this study, you will be offered free genetic counseling.

- You will be asked to join the OCCPI biorepository (sample bank) to help with future research on the causes, treatment and survival of cancer.
- You will be asked to contribute your leftover blood and/or saliva samples to the biorepository, as well as complete a questionnaire that will ask about your age, medical history, family history, lifestyle factors and environmental exposures.

61. How long will I be in the study?

In order to have genetic testing, you must have pre-test genetic counseling. Pre-test genetic counseling sessions usually last around 60-90 minutes. Your genetic test result should be ready 2-4 weeks after your pre-test genetic counseling session, but sometimes results can take around 3 months (depending on the type of mutation in your family). If your results are expected to take 3 months, you will be notified of this at the time you consent to the study. In addition, it takes about 60 minutes to complete the questionnaire from home. Overall, your participation in the genetic testing portion of the OCCPI is expected to take about 1-4 months.

In addition, we would like to stay in touch with you for as long as this study is open to update your personal and family medical history information. We may also want access to your medical records from the hospitals and doctor's offices where you have had/will have any treatments. You may choose whether or not you would like to allow OCCPI study team to contact you in the future to update your personal and family medical history information.

Choose one option and initial:

_____ Yes, study personnel may contact me in the future in order to update my personal and family medical history information.

_____ No, study personnel may not contact me in the future in order to update my personal and family medical history information.

62. What type of research will be done with my samples for this study?

Your blood or saliva sample will be tested for the exact gene mutation which your family member was found to have (single site testing).

When your result is ready you will be contacted by a genetic counselor and given the choice whether or not you would like to learn your test result. If you want your result, you will have the option to learn your result by telephone or in person. You can always receive your result by telephone and then decide to come in for additional genetic counseling if you would like to further discuss your result.

63. OCCPI Biorepository

You are being asked to contribute to the OCCPI biorepository, which is being created for future studies that will try to understand the causes of cancer, how better to prevent
cancer in family members, as well as to increase length of life and quality of life for people who have been diagnosed with cancer.

We are asking that you allow us to use your medical information (obtained from past/present/future medical records and the baseline questionnaire) and donate your leftover blood and/or saliva sample(s) from your genetic testing.

The questionnaire will take approximately one hour to complete and you will complete the questionnaire at home at your convenience.

- If you have Internet access, you can complete the questionnaire yourself using your home Internet. You will receive an e-mail invitation from occpi.study@osumc.edu that will provide you with a link to your specific questionnaire. If you do not complete the questionnaire after one week, we will send you a reminder e-mail. If you do not complete the questionnaire within two weeks of receiving the e-mail invitation, we will contact you by telephone to make sure you received the e-mail or to do the questionnaire with you over the phone in case you had difficulty accessing it.
- If you do not have Internet access or prefer not to complete the questionnaire yourself, a member of our study team will call you on the telephone to help you complete the questionnaire.

### Preference:

- Telephone:________________________
- Email:________________________

Your samples and information will be used for cancer research, including genetic research. Your samples may be requested by researchers who are doing cancer research at OSU or other institutions. Any external researchers who might study your sample and information will not know who you are. We will give them the code numbers and the minimal amount of potentially identifying information that is necessary for the research. The research must be approved by an Institutional Review Board (IRB) (a university committee that reviews all research for protection of the study participants) before samples/information will be released. Some of your genetic and health information might also be placed into one or more external scientific or publicly-accessible databases. For example, the National Institutes of Health (an agency of the federal government) maintains a database called “dbGaP.” A researcher who wants to study the information must have an approved study and apply to the dbGaP database.

If you elect to join the biorepository, your samples will be available for research indefinitely. You may request to withdraw from the biorepository at any time and researchers will not receive any more samples or information about you. However, your samples and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in the biorepository, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored samples be destroyed or otherwise transferred.
You can still participate in the genetic testing portion of the OCCPI even if you do not wish to participate in the OCCPI biorepository.

**Choose one option and initial:**

___ Yes, I would like to contribute my leftover blood and/or saliva sample(s) to the OCCPI biorepository.

___ No, I do not want to contribute my leftover blood and/or saliva sample(s) to the OCCPI biorepository. Destroy any of my leftover samples that are not used for the genetic testing.

**If you agreed to participate in the biorepository:**

You have the option of receiving any clinically relevant cancer genetics research results that become available and involve your sample. However, please note, some cancer genetics research studies may not provide results. In order for you to receive any results from another study, the other researchers would report the result to the OCCPI study personnel. Using the sample code, the OCCPI study personnel would then be able to link your identifying information with the sample result. If clinically relevant results become available, and if you have elected to receive results, genetic counseling will be available, and you may be offered clinical genetic testing to confirm the research results (if available). These services may be at your or your insurance company’s cost.

**Choose one option and initial:**

___ Yes, I would like to be contacted if clinically relevant research results become available.

___ No, I do not wish to be contacted if clinically relevant research results become available.

64. **What about other research studies?**

There may be additional studies that will try to discover ways to improve the prevention, treatment or survival of CRC or EC. For example, the OCCPI’s Adherence to Colorectal Cancer Screening (ACCS) study focuses on making sure that you and your relatives receive proper screening recommendations for CRC, as well as follow-through on those recommendations.

The OCCPI would like to contact you to offer you participation in studies for which you may be eligible. Agreeing to be contacted does not imply that you will agree to join these studies; you can choose the studies in which you would or would not like to participate at the time you are contacted.

**Choose one option and initial:**

___ Yes, I would like to be contacted if I am eligible for future research studies.

___ No, I do not wish to be contacted if I am eligible for future research studies.
65. Family Member Contact

In the event that we cannot contact you in the future, we ask you to name a Family Member Contact who will receive notices concerning any study related issue (genetic test results from the OCCPI, the storage of your samples, the results of any future cancer research studies performed on your samples, etc). You may change your Family Member Contact person at any time by notifying the Clinical Cancer Genetics Program in writing. You do not have to do this.

Name: _________________________________________
Address: _______________________________________
City, State, Zip: _________________________________
Telephone number: _______________________________
Relationship to me: _______________________________

_____ I do not wish to name a Family Member Contact.
Initial

66. Can I stop being in the study?

You may request to withdraw from the study at any time and researchers will not receive any more samples or information about you. However, your samples and information that has been used for studies already in progress or previously conducted cannot be undone. If you decide to stop participating in this study, your decision will not affect your medical care, your future relationship with OSU, your doctors or your hospitals. You may request to have your stored samples be destroyed or otherwise transferred. If you decide to withdraw from the study, you may be presented with additional options for continuing your participation at a reduced level.

To revoke your authorization, please contact:

Heather Hampel, MS, LGC
Principal Investigator
2012 Kenny Road
Columbus, OH 43221
614-293-7240

67. What risks, side effects or discomforts can I expect from being in the study?

In general, there are minimal risks for this study.

- **Risk of taking blood from you (if applicable):**
  - When blood is drawn you may feel some pain and you may feel faint.
  - After blood is collected, you may have a bruise and a very slight risk of infection at the site where the blood was taken.

- **Financial Risk:**
  - If there is additional medical care that is needed because of the results of this study, you will be financially responsible.

- **Psychosocial Risk:**
Some people find it upsetting to go through the genetic testing process because it has implications for their children, siblings, and other family members.

- Genetic test results could also suggest that you are at an increased risk for developing cancer in the future.
- It may be difficult to wait for the full results of this study.

You can contact the project manager, genetic counselor Rachel Pearlman, at 614-293-5740 any time during the research study to discuss the status of the study and any emotional responses that you are having.

• **Insurance Risk:**
  - A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
    - Health insurance companies and group health plans may **not** request your genetic information from this research.
    - Health insurance companies and group health plans may **not** use your genetic information when making decisions about your eligibility or premiums.
    - Employers with 15 or more employees may **not** use your genetic information from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.
    - All health insurance companies and group health plans must follow this federal law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies **cannot** ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.

68. **What benefits can I expect from being in the study?**

There are several possible benefits to participating in the study.

- You may benefit from knowing that your participation has helped researchers try to understand how to prevent CRC and EC from being diagnosed in individuals in Ohio, as well as to understand how to improve quality of life and length of life for individuals diagnosed with CRC and EC.
- Genetic test results can help us to provide personalized cancer screening recommendations for you.
- Genetic test results can provide information to family members including their future cancer risks and personalized cancer screening recommendations.
- If you are participating in the biorepository and you elected to receive any clinically relevant results, you may benefit from future cancer research studies if clinically relevant results are found and can be linked back to you.

69. **What are the costs of taking part in this study?**
There should not be any costs associated with participating in this study unless you opt to have the genetic counseling session billed to your insurance company (see number 15 below).

70. Will I be paid for taking part in this study?

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

71. What happens if I am injured because I took part in this study?

As this is a minimal-risk study, there is no injury expected from participation.

72. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

You may choose to have the free genetic testing provided by the study but have the genetic counseling billed to your insurance company if the hospital providing the genetic counseling is unable to provide the service without billing the full cost of the session.

You may choose to have clinical genetic testing and genetic counseling (at your expense) if you do not take part in the study.

73. Will my study-related information be kept confidential?

Considerable effort will be made to keep your study-related information confidential. We use state-of-the-art technology to make sure only authorized personnel see any study related information that identifies you and then only for approved purposes or reasons you have authorized. But, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

We will work to make sure that no one sees your questionnaire responses without approval. However; because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you. Your data will be protected with a code to reduce the risk that other people can identify you.

Additionally, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).
Because this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician’s office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

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 the website at any time.

74. Authorization to use and disclose information for research purposes

- **Your information may be used and given to others.**
  - The study doctor and study staff will get your personal and medical information including:
    - Past and present medical records
    - Research records
    - Records about phone calls made as part of this research
    - Records about your study visits
    - Information that includes personal identifiers, such as your name, or a number associated with you as an individual
    - Information gathered for this research about physical exams, laboratory and other test results, questionnaires, HIV/AIDS, hepatitis infection, sexually transmitted diseases and other reportable infectious diseases

- **Who may use and give out information about you?**
  - The study doctor and the study staff may also use and give out information about you.

- **Who might get this information?**
  - The sponsor of this research
    - “Sponsor” means any persons or companies that are working for or with the sponsor, or owned by the sponsor
  - Members and staff of the OSU Institutional Review Boards, including the Western Institutional Review Board
  - The Office of Responsible Research Practices
  - University data safety monitoring committees
  - The OSU Office of Sponsored Programs
  - Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information
  - If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician’s office record

- **Your information may be given to:**
- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- The Ohio State University units involved in managing and approving the research study including the University Research Foundation and the Office of Responsible Research Practices
- Western Institutional Review Board® (WIRB®)

**Why will this information be used and/or given to others?**

- to do the research
- to study the results
- to make sure that the research was done right

If the results of this study are made public, information that identifies you will not be used.

**What if you decide not to give permission to use and give out your health information?**

- Then you will not be able to be in this research study. The Ohio State University Wexner Medical Center may not condition (withhold or refuse) treating you on whether you sign this Authorization.

**Can you review or copy your information?**

- Yes, but only after the research is over.

**When will your permission end?**

- There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

**Can you withdraw or revoke (cancel) your permission?**

- Yes. Your authorization will not expire unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

**Is your health information protected after it has been given to others?**

- There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

**75. What are my rights if I take part in this study?**

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a subject in this study.
You will be provided with any new information that develops during the course of this research that may affect your decision whether or not to continue participation in the study.

An Institutional Review Board responsible for human subjects research at OSU reviewed this research study and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

**76. Who can answer my questions about the study?**

For questions, concerns, complaints, or if you are injured as a result of participating in this study, please contact:

Rachel Pearlman, MS, LGC
Project Manager
614-293-5740

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, please contact:

Sandra Meadows
The Office of Responsible Research Practices
1-800-678-6251

For questions about how protected health information is collected, maintained, used, and disclosed, please contact:

OSU HIPAA Privacy Officer
614-293-4477
**Signing the Consent Form**

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

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**Investigator/Research Staff**

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

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Ohio Colorectal Cancer Prevention Initiative:  
Universal Screening for Lynch Syndrome

Research Protocol

Principal Investigator:  Heather Hampel, MS, LGC

Co-Investigators:  Albert de la Chapelle, MD, PhD

Wendy Frankel, MD

Jo Freudenheim, PhD

Richard Goldberg, MD

Ilene Lattimer, RN, OCN, CCRC

Electra Paskett, PhD

Rachel Pearlman, MS, LGC

Peter Shields, MD

1. Introduction
While there have been remarkable advances in colorectal cancer (CRC) screening and treatment, CRC remains the third most common cancer (excluding non-melanoma skin cancer). The overall lifetime incidence for developing CRC is 1 in 20 Americans (5%). The American Cancer Society estimates 103,170 new cases of colon cancer and 40,290 new cases of rectal cancer will be diagnosed during 2012. Despite the benefits of advances in CRC screening, only 39% of cases are diagnosed today at the localized stage when there is a five-year survival rate of 90%\[1\]. In Ohio, the incidence rate is higher than the national average (51.1 v. 47.9 per 100,000) and results in approximately 6,370 newly diagnosed CRC cases per year\[1\]. In the U.S, there are 51,690 deaths per year related to CRC, of which 2,456 deaths occur in Ohio\[1\]. Thus, the high CRC incidence and mortality rates in the state of Ohio justify additional research that will translate into lives saved.

With the overall goal of reducing morbidity and mortality due to CRC in the state of Ohio, The Ohio State University Comprehensive Cancer Center (OSU-CCC) proposes to form by invitation, and initially commits to fully funding, the Ohio Colorectal Cancer Prevention Initiative (OCCPI). The OCCPI will facilitate the development of a CRC research infrastructure within the state of Ohio, and will be comprised of two arms (and two separate protocols): Universal Screening for Lynch Syndrome (USLS) and Adherence to Colorectal Cancer Screening (ACCS). The USLS arm of the OCCPI will focus primarily on identifying those at high-risk for CRC (genetically predisposed). The ACCS arm of the OCCPI will focus on providing screening recommendations for cancer risk reduction. Highlights of the second arm of the OCCPI are discussed in the paragraph below; however, the focus of this protocol is the USLS arm of the OCCPI.

Adherence to Colorectal Cancer Screening (ACCS) (OSU IRB\# 2013C0022, approved 3/6/2012) will focus on increasing adherence to CRC screening recommendations among persons diagnosed with CRC in Ohio and their first-degree relatives (FDR), as well as testing the comparative effectiveness of two behavioral interventions. In order to compare the effectiveness of different behavioral interventions, the ACCS developed two test methods in a randomized controlled trial on adherence to CRC screening recommendations. The individuals diagnosed with CRC (probands) will serve as the unit of randomization/analysis. The first test method, a website, will deliver a “personalized prescription for CRC prevention” based on age, cancer history, family history and screening history. The second test method, a patient navigator, will address individual barriers to adhering to the “personal prescription”. Twelve months after enrollment, the ACCS will contact participants by telephone and inquire about CRC screening compliance over the past year. Based on the results, a preferred and effective method for behavioral interventions for CRC screening compliance will be established.

A biorepository of tumor tissue, blood and saliva will be created from the efforts of both arms of the OCCPI. Both cancer patients and FDRs will be included, which is a unique component of the OCCPI biorepository. The biorepository is an optional part
of the study and participants will have the opportunity to “opt-out” of contributing their samples. After the USLS arm of the study is complete, the leftover tumor and blood samples, as well as an additional saliva sample (CRC participants only), will be stored in the OCCPI biorepository indefinitely. The biorepository will also contain saliva samples from the FDRs of the CRC participants and saliva and blood samples from the at-risk relatives of the participants with LS. The biorepository will be used for various future studies about the molecular epidemiology and treatment and outcomes of CRC. Focusing on identifying the etiology of CRC and gene-environment interactions will allow for more accurate risk prediction, focused intervention strategies, and enhanced early detection strategies.

Not only will the OCCPI be meeting a community and patient need, the project also aligns with OSU-CCC’s strategic goals of being a national leader in cancer care delivery and being recognized as a national authority on cancer. With the successful implementation of the OCCPI, knowledge will be gained that will aide in the development of a CRC research infrastructure within the state of Ohio that could be used for additional studies on cancer risks, prevention, screening, treatment and survivorship. Upon written request and subject to availability and approval by the OCCPI Steering Committee, data and biospecimens from this study can be shared with appropriately qualified investigators from contributing institutions.

2. Background and Rationale

The majority of CRC’s in the general population are sporadic occurrences, meaning that the cancer arises due to the normal aging process, lifestyle and environmental factors, or due to unexplained factors/chance. In families, CRC occurs as either a hereditary predisposition or a familial occurrence. Even though no universal definition exists, hereditary cancers are those in which the predisposition suggests a Mendelian inheritance pattern. In familial cancer, several cases of cancer occur in a family but there is no evidence of Mendelian inheritance. Familial cancers are thought to be due to a combination of minor genetic influences and environmental factors that cause one family to have a higher risk for a particular cancer than another. Most of these minor genetic influences and environmental causes are yet to be discovered and this will be an area of interest for the OCCPI biorepository.

Lynch syndrome (LS), previously known as “hereditary non-polyposis colorectal cancer”, is a hereditary cancer syndrome that causes the majority of hereditary CRC and approximately 3% of all CRC [3]. LS is inherited in an autosomal dominant pattern. Mutations in DNA mismatch repair (MMR) genes MLH1 (32%), MSH2 (38%), MSH6 (14%), and PMS2 (15%) lead to LS [3]. Deletions in the 3’ end of EPCAM, a gene responsible for cell adhesion, have been implicated in approximately 1% of LS cases because these deletions can disrupt the MMR pathway by causing methylation of the MSH2 gene [4]. MMR genes act as “spell-checkers” and are critical for the maintenance of genomic stability. When one or more MMR genes are not working properly due to a germline mutation or disruption in the pathway, additional mutations may accumulate in cells and initiate cancer.
The primary clinical feature associated with LS is CRC, which is often early-onset and right-sided\[5\]. For individuals with LS, the average lifetime risk for CRC is 54-74% for men and 30-52% for women, and the average age of diagnosis ranges between 42-61 years\[6-8\]. Comparatively, the lifetime risk for CRC for individuals in the general population is much lower at 5-6%, and the average age of diagnosis is increased to 65 years\[9\]. Individuals with LS also have an increased risk to develop extracolonic cancers, including endometrial (28-60%\[6-8\]), gastric (5-8%\[10\]), ovarian (4-11%\[8\]), upper urinary tract (8.4%\[11\]), small bowel (3-6%\[9\]), biliary tract (2-18%\[8\]), CNS (4%\[9\]), and certain types of skin cancer (1-9%\[9\]).

There are several different methods that can be used to screen an individual for LS. The Amsterdam I\[12\] and II\[13\] criteria, as well as the revised Bethesda guidelines\[14\], use family history information to determine if LS may be present and further evaluations are indicated. Tumor studies, including microsatellite instability (MSI) testing and immunohistochemical (IHC) analysis, provide information regarding characteristic features of LS-associated tumors. MSI, a form of genomic instability, is present in approximately 90% of LS-associated tumors\[15\]. This instability is due to mistakes that occur in repetitive segments of DNA during replication and failure of the MMR genes to “spell-check” and correct the errors\[16\]. This leads to a shortening or lengthening of the DNA repeat in the tumors of individuals with defective mismatch repair. IHC analysis can help to screen for loss of one or more of the MMR proteins in the tumor compared with normal tissue, and can help to target molecular testing\[3\]. IHC, when used in conjunction with MSI testing, may accurately identify close to 100% of LS-related CRC\[2, 17\]. Based on research efforts, the Evaluation of Genomic Applications in Practice and Prevention working group of the CDC found that tumor-based screening protocols to identify CRC patients with LS, rather than methods using family history, produced more consistent results and identified a higher percentage of patients\[3, 18-20\].

Molecular testing for LS involves DNA sequencing and gene rearrangement testing to identify point mutations, deletions, duplications and insertions within the MLH1, MSH2, MSH6, PMS2 and EPCAM genes\[3, 9, 18, 19\]. The accuracy of molecular testing varies depending on the laboratory and technique used; however, the identification of an MMR gene mutation after a positive screen test confirms the diagnosis of LS\[3, 9, 18, 19\].

While LS is the most common cause of hereditary CRC, there are additional less-common autosomal dominant cancer syndromes that also increase the risk for CRC. Familial Adenomatous Polyposis (FAP) is caused by mutations in the APC gene and can increase lifetime CRC risk up to 100%\[21\]. Peutz-Jeghers syndrome, caused by mutations in the STK11 gene, increases the lifetime risk for CRC to 39%\[22\]. Cowden syndrome (caused by mutations in the PTEN gene), Li Fraumeni syndrome (caused by mutations in the TP53 gene), and CDH1 gene mutations (which most notably increases the risk for Hereditary Diffuse Gastric Cancer), can also increase the lifetime risk for CRC\[23-25\]. SMAD4 and BMPR1A gene mutations cause Juvenile Polyposis. Lastly, MYH-Associated Polyposis (MAP) is an autosomal recessive
hereditary cancer syndrome that is caused by biallelic MUTYH mutations and can increase the lifetime risk of CRC to 28% [26]. Clinical screening tests for CRC, most notably colonoscopy, can not only detect cancerous lesions early, but can also remove pre-cancerous lesions. Moreover, among persons with a genetic predisposition (like individuals with LS), cancer screening has even higher benefit and is of public health importance because of the early-onset of cancer, as well as the high lifetime risk to develop cancer. Järvinen et al. conducted one of the first studies that showed clinical screening by colonoscopy significantly reduces the mortality of CRC in LS individuals[27]. Based on research efforts, the Evaluation of Genomic Applications in Practice and Prevention working group of the CDC (EGAPP) reported that more than 90% of at-risk relatives of patients with LS would have molecular testing, and more than half of those individuals who were found to have LS would begin CRC screening at 20-25 years of age[3, 18-20]. Compliance with these recommendations has been shown to reduce cancer morbidity and mortality associated with LS [3, 18-20, 28]. Today, the National Comprehensive Cancer Network (NCCN) has released strong recommendations for increased cancer surveillance for individuals with LS and other hereditary cancer syndromes, as well as their at-risk relatives[28].

The Ohio State University Comprehensive Cancer Center (OSU-CCC) conducted a study between 1999 and 2008 that evaluated the feasibility of testing for LS gene mutations among all newly diagnosed colorectal and endometrial cancer patients in the Columbus-area[2]. This study was funded by an R01 grant from the National Cancer Institute, and it included 1,566 CRC patients and 562 endometrial cancer patients. The results of The Columbus-Area Lynch Syndrome Study are visually depicted below:

The Columbus-Area Lynch Syndrome Study proved that a large-scale screening program would be conceptually and technically feasible, desirable and not harmful [29]. Based largely on the findings from this research, the EGAPP indicated that large-scale screening for LS is justified and recommended that all newly diagnosed CRC patients be screened for LS[2, 18, 29]. Unfortunately, many institutions have not yet implemented the screening protocol due to a variety of factors including, but not limited to, a lack of readily available genetic counseling. There are hospitals in the U.S. and Europe that have begun to utilize the LS screening protocol; however, there is protocol variation among institutions.

Given the hereditary nature of this syndrome, screening all patients who are newly diagnosed with CRC for LS can identify additional individuals who are at high risk of
developing cancer. If consistently implemented in the U.S, a universal screening protocol could result in more than 20,000 individuals being diagnosed with LS per year. Of the 6,370 colorectal cancers diagnosed annually in Ohio, 3% will have LS (n=191). On average, 3 additional relatives of each of these patients will be found to also have LS (n=573), for a total of 764 individuals who could be diagnosed with LS annually in Ohio through a universal screening protocol.

A universal screening protocol for LS will reduce morbidity and mortality from colorectal and other cancers in the patients themselves and their at-risk relatives and has been shown to be cost-effective[3]. Underutilization of universal screening for LS is a public health issue as many lives could be saved through early cancer surveillance and prevention options targeted at those diagnosed with LS.

3. Specific Aims and Objective

The overall objective of the OCCPI is to reduce morbidity and mortality due to CRC in the state of Ohio. The USLS arm of the OCCPI will reach this goal by achieving the following specific aims:

1. Establish and implement a statewide universal screening protocol for LS.
2. Elucidate the prevalence of hereditary CRC in Ohio.
3. Provide screening recommendations for high-risk individuals with CRC and their families, as well as local access to genetic counseling.
4. Create a CRC biorepository for future research on the etiology of CRC from the leftover samples of the CRC patients, as well as samples from their relatives.
5. The Ohio State University will be the only site that will also include all newly diagnosed endometrial cancer patients in the USLS arm of the OCCPI and the biorepository.

4. Methods

Research design

The USLS arm of the OCCPI will be a prospective, population-based multi-center study.

Sample size

Assuming incomplete accrual at the highest volume Ohio hospitals (and their affiliates) over a 3 year period, we intend to accrue 4,000 newly diagnosed CRC patients for this study. Approximately 400 newly diagnosed EC patients (from OSU only) will also be accrued for this study. In addition, the first-degree relatives (FDRs; parents, siblings and adult children) of the 4,000 CRC patients will be invited to join this study. While it is hard to anticipate how many FDRs will join the study, we are
estimating that an additional 8,000 individuals will be accrued. We expect that around 768 at-risk relatives of the patients found to have LS will be invited to participate in genetic counseling and testing and the biorepository. Therefore, the total number of participants in the OCCPI is estimated to be 13,068.

**Inclusion criteria**

Individuals will be eligible to participate in the USLS arm of the OCCPI if they meet any of the following criteria between 1/1/2013 and 12/31/2016:

- Newly diagnosed with a primary invasive colorectal adenocarcinoma (all stages) and have a resection at any hospital in Ohio between 1/1/2013 and 12/31/2016.
  - For individuals who have neoadjuvant treatment and show a complete response at resection, the tumor screening will be attempted on their original biopsy (even if it occurred in 2012) as long as their resection occurred between 1/1/2013 and 12/31/2016.
  - Many individuals with stage IV CRC will not have a resection; therefore, the tumor screening will be attempted on their original biopsy as long as their primary diagnosis occurred between 1/1/2013 and 12/31/2016. If only metastatic CRC is available on a biopsy, tumor screening will be attempted on the metastatic tissue.
- Newly diagnosed with a primary invasive endometrial cancer (any histology except sarcoma) and have a resection between 1/1/2013 and 12/31/2016 exclusively at OSU.
  - For individuals who have neoadjuvant treatment and show a complete response at resection, the tumor screening will be attempted on their original biopsy (even if it occurred in 2012) as long as their resection occurred between 1/1/2013 and 12/31/2016.
- All at-risk relatives of the participants found to have LS.
- First-degree relatives (parents, siblings and adult children ≥ 25 years of age) of the CRC participants who do not have LS.

Individuals who are cognitively impaired are eligible for the study and consent for participation must be given by a legal authorized representative or parent. Pregnant women are eligible for the study.

**Exclusion criteria**

Prisoners and individuals who are under the age of 18 will be specifically excluded from participation in the study. Individuals must have a primary colorectal or endometrial cancer, not a recurrence of a previous colorectal or endometrial cancer.
**Removal criteria**

Participants can be removed from the study if they meet any of the following criteria:

- During the course of pathology confirmation, the tumor is determined to be anything other than a primary colorectal adenocarcinoma or endometrial cancer (any histology eligible except sarcoma).
- During the course of pathology confirmation, the colorectal tumor is deemed too small to be used for *at least one* of the tumor screen tests (MSI or IHC).
- During the course of pathology confirmation, the endometrial tumor is deemed too small to be used for *at least one* of the tumor screen tests (MSI and IHC).
- We do not receive a blood sample to obtain DNA for genetic testing.

The participant is free to withdraw from the study at any time and no reason needs to be given.

**Incentives**

The only incentive for the participants will be MSI and IHC at no cost. Depending on their results, some patients will also receive *MLH1* promoter hypermethylation testing, genetic testing and genetic counseling at no cost.

There are some hospitals that already perform some or all of the tumor tests (MSI, IHC, methylation) required for this study as part of their patients’ regular clinical care. If a hospital performs all tumor tests required for the study, the participant’s tumor testing will be billed to their insurance company as part of their clinical care. If a hospital performs some (but not all) tumor tests required for the study, the testing performed by the hospital will be billed to the patient’s insurance company as part of their clinical care. The remaining tumor test(s) not performed by their hospital will be done at OSU for free as part of the study. If a hospital does not perform any tumor tests required for the study, the testing will be done at OSU for free.

For all CRC/EC participants, there are no costs associated with the genetic testing and genetic counseling provided in the study. The family members of participants found to have LS will have the opportunity to have genetic counseling and testing at no cost to them.

**Recruitment procedures for the CRC patients**

In order to facilitate the adoption of a universal screening protocol for LS and the creation of a statewide CRC biorepository, the OCCPI invited the top 25 Ohio hospitals with the greatest reported volume of patients diagnosed with CRC annually, as well as their affiliate hospitals, to participate in the USLS arm of the
study. The majority of the hospitals are located in the major metropolitan areas including Columbus, Cleveland, Cincinnati, Dayton, Akron/Canton and Toledo. However, patients from all 88 counties in Ohio will most likely be represented because they can have their surgery anywhere in Ohio, not just at the participating hospitals.

Appendix 1 lists all of the hospitals that are officially participating in the USLS arm of the OCCPI. OSU will serve as the lead institution for this study. Participating hospitals were invited to join the study after the initial approval from the OSU IRB. In order to participate, invited hospitals had to obtain either IRB approval from their institution (or community oncology program), reliant review from a participating institution, or cede review to OSU’s IRB.

The participating hospital will designate their own “on-site study personnel” (clinical trials nurse/genetic counselor/etc) and OSU will provide compensation to the institution for each case accrued. If necessary, OSU will hire regional study personnel for accrual (clinical trials nurse/genetic counselor/etc). Each participating hospital or community oncology program will have its own “site-PI” (usually GI surgeon or oncologist) who is the primary communicator between the study personnel at OSU and their own site.

At each participating site, designated on-site study personnel will scan the operating room schedules for CRC surgeries; receive notification of recent CRC diagnoses and upcoming operations from treating GI surgeons, oncologists, or the site-PI; and screen recent pathology reports from CRC surgeries for eligible participants. A Partial Waiver of HIPAA Research Authorization allows designated accrual personnel to access and record the personal health information needed for accrual. On-site study personnel will obtain permission (verbal or written) from the treating physician or site-PI before approaching the patient when possible. If possible, the treating physician or site-PI will introduce the study to the patient before on-site study personnel approaches them. Once appropriate permission has been obtained, on-site study personnel will meet face-to-face with the patient before or after their operation to discuss the study and ask if they would like to participate. A Full Waiver of HIPAA Research Authorization allows accrual personnel to keep a running list of patients who have been approached for the study but declined participation in order to prevent them from being approached again (Appendix 2). If a patient declines participation, the reason for decline will be collected (but not associated with any identifying information) and stored on a separate tab of the Decline list document. These lists will be destroyed at the completion of the study.

Additional recruitment strategies include a flyer (Appendix 3) and recruitment letter (Appendix 4) that can be personalized for each site, websites such as StudySearch, The James (cancer.osu.edu) and Clinicaltrials.gov, and the use of ResearchMatch.org (see Appendix 5 for a general description of ResearchMatch).

Recruitment procedures for the EC patients
The USLS arm of the OCCPI will only accrue EC patients that are newly diagnosed and have their resection at OSU. Designated study personnel will scan the operating room schedules for EC surgeries; receive notification of recent EC diagnoses and upcoming operations from treating gynecologist/oncologists; and screen recent pathology reports from EC surgeries for eligible participants. On-site study personnel will obtain permission (verbal or written) from the treating physician before approaching the patient when possible. If possible, the treating physician will introduce the study to the patient before OCCPI study personnel approaches them. Once appropriate permission has been obtained, OCCPI study personnel will meet face-to-face with the patient before or after their operation to discuss the study and ask if they would like to participate. A template was created to facilitate a running list of patients who have been approached for the study but declined participation in order to prevent them from being approached again (Appendix 2). If a patient declines participation, the reason for decline will be collected (but not associated with any identifying information) and stored on a separate tab of the Decline list document. These lists will be destroyed at the completion of the study.

Additional recruitment strategies include a recruitment letter (Appendix 4), websites such as StudySearch, The James (cancer.osu.edu) and Clinicaltrials.gov, and the use of ResearchMatch.org.

Informed consent process for the CRC/EC patients

During the accrual process, on-site study personnel will describe the USLS protocol and provide verbal and written information (factsheet) about the OCCPI (Appendix 6 for CRC patients, Appendix 7 for EC patients). In addition, they will discuss the risks, benefits, and limitations of genetic testing and the possible results of genetic testing (positive, negative, uncertain). If the patient expresses interest in the study, they will be asked to sign the consent form (Appendix 8 for CRC, Appendix 9 for EC) and Medical Records Release form (Appendix 10). The CRC participants will be asked to provide three 10ml samples of blood drawn by a trained healthcare professional. The EC participants will be asked to provide two 10ml samples of blood drawn by a trained healthcare professional. If the participant consents to the OCCPI biorepository, a saliva sample will also be collected (CRC patients only, EC patients will not contribute saliva samples to the biorepository). After the sample collection, the on-site study personnel will complete the Teleform (Appendix 11, 12 or 13) and all forms and collected samples will be mailed together to the OCCPI study personnel located in the Clinical Cancer Genetics department (CCG) at the OSU Polaris Innovation Centre. After the participant’s operation, either their entire paraffin-embedded tumor block or fifteen unstained slides will also be sent to the study personnel at the OSU Polaris Innovation Centre.

It is important to inform the participant that the consent process for the ACCS arm of the OCCPI is completely independent of the consent process for the USLS arm of the OCCPI. While the two arms are under the same “umbrella study”, participants
have the option to participate in the USLS arm of the OCCPI without participating in the ACCS arm. However, participants cannot participate in the ACCS arm without participating in the USLS arm. **If USLS participants indicate that they would like to be contacted about other studies on their consent form, ACCS study personnel will contact them a few months after their enrollment in the USLS arm and offer them participation in the ACCS arm.**

The consenting process for the USLS arm will take as much time as the participant needs in order to fully understand the study and its procedures; however, the estimated total time needed to participate in the initial portion of the study is approximately 15 minutes.

**Recruitment procedures and informed consent process for the FDRs of the CRC participants without LS**

The FDRs of the CRC study participants without LS will be given the opportunity to contribute to the biorepository for future research. There are three potential ways these FDRs can be enrolled in the biorepository.

If the CRC participant consents to participating in the ACCS arm OR if the CRC participant is not eligible for ACCS (due to age >75) or is in poor health and does not want to participate in ACCS, ACCS study personnel will ask them to provide contact information for their FDRs. If contact information is provided, ACCS study personnel will contact the FDRs and offer them participation in both the USLS biorepository and ACCS arms of the OCCPI. The FDR has the option to decline either or both invitations. If they express interest in contributing to the USLS biorepository, study personnel will mail them the biorepository consent form (Appendix 16), relative teleform (Appendix 17), Medical Records Release form (Appendix 10) and saliva kit to return to the OCCPI biorepository in the Human Genetics Sample Bank. They will also be invited to complete the baseline questionnaire. Details pertaining to the consent process and study procedures of ACCS can be found in the ACCS protocol (OSU IRB# 2013C0022).

If the CRC participant does not want to be contacted regarding future studies or declines participation in the ACCS arm, they will be asked to provide their FDRs with a Family Member Consent for Contact form (Appendix 18). If the FDR is interested in obtaining additional information about enrollment in the USLS arm, they will complete and mail the Consent for Contact form back to USLS study personnel (providing permission to be contacted). Once the form is received, USLS study personnel will contact them and offer them the opportunity to contribute to the biorepository. If the FDR expresses interest in contributing to the biorepository, study personnel will mail them the biorepository consent form (Appendix 16), relative teleform (Appendix 17), Medical Records Release form (Appendix 10) and saliva kit to return to the OCCPI biorepository in the Human Genetics Sample Bank. They will also be invited to complete the baseline questionnaire.
For the FDRs of OSU CRC participants only: Occasionally, a FDR will be present at the time a CRC participant is initially accrued to the USLS arm of the OCCPI. In this situation, accrual personnel have the opportunity to consent the FDR to the biorepository. The FDR will be asked to sign a Family Member Consent for Contact form (Appendix 18) or they will be provided with a pre-paid pre-addressed IRB approved (OSU IRB# 2013C0022) postcard to complete and mail to OSU (or turn in directly to their accrual nurse) if they are interested in obtaining additional information about enrollment in the ACCS arm of the OCCPI. Additionally, if the FDR consents to the biorepository and their relative (the CRC participant) is found to have LS, the FDR will be given the opportunity to be consented as an “at-risk relative” for the USLS arm of the study at that time and will be eligible for free genetic testing and genetic counseling (Appendix 19).

Recruitment procedures and informed consent process for the at-risk relatives of the participants with LS

The CRC/EC participants with LS will be asked to notify their at-risk relatives to let them know that they are eligible to enroll in the USLS arm of the OCCPI and receive free genetic counseling and genetic testing. The relatives can contact study personnel directly to schedule an appointment for genetic counseling or they can complete a Family Member Consent for Contact form (Appendix 18), which will allow us to contact them to schedule an appointment for genetic counseling. At their counseling appointment, they will be given the option to consent to the USLS arm of the study (Appendix 19), which includes completing the relative teleform (Appendix 17), Medical Records Release form (Appendix 10), single site mutation testing and the opportunity to contribute to the biorepository (optional). The LS Fact Sheet (Appendix 7) will be provided. If the at-risk relative elects to pursue genetic testing, free follow-up genetic counseling and appropriate cancer screening recommendations and referrals will be provided. The FDRs of the CRC participants with LS will also be provided with a pre-paid pre-addressed IRB approved (OSU IRB# 2013C0022) postcard to complete and mail to OSU (or turn in directly to their genetic counselor) if they are interested in obtaining additional information about enrollment in the ACCS arm of the OCCPI.

Relatives of participants found to have a hereditary cancer syndrome other than LS will be offered genetic counseling and testing at their own expense since these syndromes are not the main aim of this study. Additionally, relatives of participants found to have a hereditary cancer syndrome other than LS will be eligible to participate in the biorepository, but they will not be eligible for the ACCS arm of the OCCPI.

Study procedures for the CRC/EC participants

No drug, supplement or device will be used for this study. A Standard Operating Procedures (SOP) guide is available (Appendix 14).
A baseline questionnaire (estimated to take approximately 1 hour from start to finish) (Appendix 15) should be completed by each participant. The participant will complete the questionnaire in their own home at their convenience. In order to make the questionnaire as participant-friendly as possible (as well as maintain a high response rate), participants will have the option of completing it one of two ways. **Option 1:** For those with Internet access (the majority), the participant can complete the questionnaire themselves using their home Internet. Participants who choose Option 1 will need to provide their email address and will have 2-4 weeks from the time they are accrued at their hospital to complete the questionnaire themselves. If it is not completed by the end of the initial 2-4 week period, the participant may automatically be reverted to Option two. **Option 2:** For those without Internet access or those who prefer not to self-administer the questionnaire, designated study personnel will call the participant on the telephone and will verbally administer the questionnaire. If a participant has not completed the questionnaire after ten attempts by study personnel (sending the email invitation or calling them on the telephone), it will be assumed that the participant declined to complete the questionnaire. If ten attempts have been made by study personnel without a response from the participant, they will no longer attempt to contact the participant regarding the questionnaire. IRB approved letters may also be sent to the participants to remind them to complete the questionnaire. If the participant contacts study personnel after the ten attempts and expresses interest in completing the questionnaire, they will be permitted to do so at that time.

Study participant’s CRC/EC tumor samples will be studied for MSI, IHC and methylation (if applicable). Tumor screening will be performed on all participants’ tumor tissue if it was not already performed clinically at the time of the patient’s diagnosis.

The following study participants will have genetic testing:
- CRC and EC study participants with unmethylated MSI-high (MSI-H) tumors or unmethylated tumors with abnormal IHC
- CRC study participants diagnosed with CRC <50 years, regardless of tumor studies or family history
- CRC study participants diagnosed with CRC ≥ 50 years with normal tumor studies AND a FDR with CRC or EC OR a history of synchronous or metachronous CRC or EC

**Microsatellite instability testing**

MSI testing will be done using the Promega MSI Analysis System (Version 1.2), which is a fluorescent PCR-based assay for detection of MSI\cite{16}. Typically, MSI analysis involves comparing allelic profiles of microsatellite markers generated by amplification of DNA from matching pairs of test samples consisting of “normal” tissue and “test” tissue (MMR-deficient). Alleles that are present in the “test” sample but not found in the corresponding “normal” samples indicate MSI.
The MSI Analysis System includes fluorescently labeled primers for co-amplification of seven markers including five mononucleotide repeat markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27) and two pentanucleotide repeat markers (Penta C and Penta D). The mononucleotide markers are used for MSI determination. The standard size of these repetitive sequences is known and the number of repeats in the tumor DNA are counted and compared to the expected. For example, tumor DNA is studied for BAT-26 allele size. Tumors showing the regular \((A)_{26}\) pattern or a pattern deviating in Adenine number by one or two \((A)_{25}\) or \((A)_{24}\) are classified as MSI-L at this marker. DNA from the blood sample of the participant is studied to determine if the BAT-26 allele in the tumor is different from that of the constitutional one. The pentanucleotide markers are used to detect potential sample mix-ups and/or contamination. Internal lane size standards are added to the PCR samples to assure accurate sizing of alleles and to adjust for run-to-run variation. The PCR products are separated by capillary electrophoresis using an ABI PRISM® 310, 3100 or 3100-Avant Genetic Analyzer or Applied Biosystems 3130 or 3130xl Genetic Analyzer. The output data maybe analyzed with GeneMapper® Analysis Software to determine MSI status.

Tumors showing MSI at none of the markers are classified as MSS. Tumors showing MSI at a single repeat marker are classified as being MSI-L. Tumors showing MSI at more than one repeat marker are classified as being MSI-H. MSI-L tumors are handled the same way that MSS tumors are in this study since it has been shown that it is rare for individuals with MSI-L tumors to have LS.

All participants will have MSI testing using the Promega MSI Analysis System (Version 1.2) unless it was already done as part of their routine clinical care.

Immunohistochemical analysis

Traditionally, IHC analysis examines antibody staining for MLH1, MSH2, MSH6, and PMS2 proteins. More recent research suggests that it may be economically sound to initially stain for secondary proteins, MSH6 and PMS2\(^{30}\). This suggestion is based on the fact that the MMR proteins form heterodimers\(^{31-34}\). MSH2 partners with MSH6\(^{34}\), and MLH1 partners with PMS2\(^{33, 35}\). MSH2 and MLH1 are “primary proteins”, meaning if there is a mutation in \(MSH2\), it will cause concurrent loss of MSH6 and if there is a mutation in \(MLH1\), it will cause concurrent loss of PMS2. Because MSH6 and PMS2 are secondary proteins, mutations in those genes will not cause obligatory loss of the primary proteins\(^{30}\). Therefore, the initial “alternative protocol” IHC analysis for MSH6 and PMS2 can help guide further testing and possibly eliminate the need to stain for all four proteins. Tumors missing MSH6 will undergo subsequent staining for MSH2 and tumors missing PMS2 will undergo subsequent staining for MLH1 to determine whether the secondary proteins are the sole missing protein or if both of the partner proteins are missing.
All participants will have IHC analysis following the alternative protocol unless it was already done as part of their routine clinical care. If MSI cannot be done, staining for all four proteins will be attempted, if possible. The OCCPI will not repeat the IHC analysis done at outside hospitals unless IHC and MSI results are discrepant.

**Methylation analysis of MLH1 promoter**

In order to rule out cases of sporadic CRC and EC for this study, the 5’ part of the promoter region of MLH1 will be assessed using Pyrosequencing, a method of quantitative analysis that detects epigenetic changes (methylation)\[^{36, 37}\]. In humans, DNA methylation consists of the addition of a methyl group to the fifth-carbon position of the cytosine pyrimidine ring via a methyltransferase enzyme. Tumors displaying methylation of the promoter region of MLH1 are more often sporadic colon cancers and not inherited colon cancers (like LS). In order to test for methylation, DNA is modified with sodium bisulfite which causes unmethylated cytosines to be converted into uracil while methylated cytosines remain unchanged. The bisulfite treated DNA is amplified by Pyrosequencing. Based on Pyrosequencing technology’s quantitative properties, assessment of DNA (CpG) methylation is more accurate, sensitive and reproducible than by any other technique.

Occasionally, methylation will need to be done (the participant was MSI-H and/or absent MLH1/PMS2) and there will be insufficient tumor for this test to be completed. When this instance occurs, a similar screening test (BRAF IHC stain) will be substituted for methylation analysis (colon tumors only) because it requires much less tumor and can help to determine if methylation is present or absent.

All participants whose tumors are MSI-H and/or absent MLH1 and PMS2 on IHC will be studied for methylation of the MLH1 promoter region using Pyrosequencing unless it was already done as part of their routine clinical care.

**Germline genetic testing for participants with abnormal tumor screenings**

For the study participants with abnormal tumor screenings not explained by MLH1 promoter methylation (regardless of age at diagnosis or family history), the ColoSeq™ - Lynch and Polyposis Syndrome Panel will be administered. The assay, offered by the University of Washington, utilizes Next Generation Sequencing and will sequence all exons, introns, and flanking sequences of several genes including (but not limited to) MLH1, MSH2, MSH6, PMS2, EPCAM, MUTYH, APC, CDH1, PTEN, TP53, SMAD4, BMPR1A and STK11. Large deletions and duplications are also detected by the assay and will be reported. As stated previously, LS causes the majority of hereditary CRC\[^{2}\], however, there are additional cancer syndromes that can increase the risk for CRC as well. This panel includes several additional hereditary cancer genes; however, we are not expecting a high yield from these additional genes.
Participant blood samples will be sent in batches from the OSU Polaris Innovation Centre to the University of Washington once a month. A total of 345 kb will be sequenced and the average coverage ranges from 320 to >1,000 sequencing reads per bp. Genomic regions will be captured using biotinylated RNA oligonucleotides (SureSelect), prepared in paired-end libraries with ~200 bp insert size, and sequenced on an Illumina HiSeq2000 instrument with 100 bp read lengths, in a modification of a procedure described by Pritchard et al. 2012[38]. Large deletions and duplications are detected using methods described by Nord et al. 2011[39]. The molecular testing is expected to take approximately 12 weeks and results will be faxed to designated study personnel at OSUMC. The blood samples will be labeled with identifying information in order to be able to report the results on a clinical level.

**Somatic tumor genetic testing for participants with unexplained abnormal tumor screenings**

For the study participants with abnormal tumor screenings not explained by MLH1 promoter methylation or a pathogenic germline mutation, the OncoPlex Cancer Gene Panel will be administered. The assay, offered by the University of Washington, utilizes next-generation "deep" sequencing on an illumina instrument to detect most classes of mutations, including single nucleotide variants, small insertions and deletions (indels), gene amplifications, and selected gene-fusions in 194 cancer-related genes. The purpose of this tumor testing is to look specifically for somatic mutations in the MMR genes so results will typically only be reported for the following genes: MLH1, MSH2, MSH6, PMS2, EPCAM, POLE, POLD1, BRAF.

Extracted DNA from participant tumor samples will be sent in batches from the OSU Polaris Innovation Centre to the University of Washington once a month and tested as described above.

**Somatic tumor genetic testing for all CRC participants**

For a subset of CRC study participants with sufficient tumor, tumor sequencing (using the University of Washington’s assay as described above) will be done on leftover tumor in parallel with the tumor screening tests (MSI, IHC, methylation) for the final year of the study. This testing will be to compare the sensitivity/specificity/cost-effectiveness of current standard-or-care practice (step-wise MSI, IHC, methylation, germline genetic testing, somatic testing; which is already being done for this study) to upfront tumor sequencing. Extracted DNA from participant tumor samples will be sent in batches from the OSU Polaris Innovation Centre to the University of Washington once a month and tested as described above.

**Germline genetic testing for CRC participants with normal tumor studies diagnosed <50 years or ≥ 50 years a FDR with CRC or EC OR a history of synchronous or metachronous CRC or EC**

For the CRC study participants with normal tumor studies but diagnosed <50 years of age or have a FDR with CRC or EC or have synchronous or metachronous CRC/EC, Myriad Genetics Laboratories will perform Next Generation Sequencing of several genes that
increase the risk for hereditary cancer including (but not limited to) MLH1, MSH2, MSH6, PMS2, BRCA1, BRCA2, PALB2, CDK2NA, CDK4, ATM, CHEK2, RAD51C, RAD51D, BRIP1, BARD1, NBN, EPCAM, MUTYH, APC, CDH1, PTEN, TP53, SMAD4, BMPR1A and STK11. Large deletions and duplications are also detected by the assay and will be reported.

Frozen blood samples will be sent in batches from the OSU Polaris Innovation Centre to Myriad once a week to once a month (depending on volume). Technical specifications include ultra-deep targeted sequencing using Raindance ThunderStorm platform for DNA amplification and Illumina MiSeq or Hiseq next generation sequencing technology. The molecular testing is expected to take approximately 2-4 weeks and results will be securely emailed or mailed to designated study personnel at OSUMC. The blood samples will be labeled with identifying information in order to be able to report the results on a clinical level.

Additional testing

Sometimes a different test may need to be substituted for a planned test due to insufficient tumor quantity or other technical issues. In addition, an additional test(s) may sometimes need to be added to help clarify the rest of the results. In all cases, these tests will be to help determine whether or not the tumor was due to LS or another hereditary cancer susceptibility syndrome.

Result procedures for the CRC/EC participants

When a participant’s tumor screening is complete, their pathology department will receive the results by secure fax so it can be added to their medical record. The participant’s accrual nurse and physician will receive written documentation of the participant’s tumor screening results and genetic testing results (if applicable). If the participant has genetic counseling, the physician will also receive written documentation of the visit.

The CRC/EC study participants who do not qualify for genetic testing will receive written documentation explaining that they are unlikely to have LS and will not proceed to the genetic testing portion of the study.

The CRC study participants who have normal tumor screenings and qualify for genetic testing will have germline genetic testing of several genes that increase the risk for hereditary cancer including (but not limited to) MLH1, MSH2, MSH6, PMS2, EPCAM, MUTYH and APC. Since these participants were unlikely to have LS in the first place based on their tumor screening, they will receive notification by letter if their gene test does not reveal any pathogenic mutations.

The CRC/EC study participants with abnormal tumor screenings not explained by MLH1 promoter methylation will have germline genetic testing of several genes that increase the risk for hereditary cancer including (but not limited to) MLH1, MSH2,
MSH6, PMS2, EPCAM, MUTYH, APC, PTEN, TP53, CDH1, SMAD4, BMPR1A and STK11.

In some cases, the CRC/EC study participants with unexplained abnormal tumor screenings (no MLH1 promoter methylation or pathogenic germline mutation) will have additional somatic genetic testing using tumor DNA. Somatic mutations occur only in the tumor tissue and could help clarify if the participant’s tumor is sporadic (biallelic somatic mutations present or a somatic mutation present plus loss of heterozygosity) or more likely hereditary (somatic mutations not found, abnormal tumor screening unexplained, possible undetected germline mutation). If the participant is found to have somatic mutations in their tumor and the abnormal tumor screening is explained, a letter will be mailed to them detailing their results. If the participant is concerned about their results or personal/family history of cancer, they can call the telephone number listed on the letter to schedule an appointment with a genetic counselor in their area (at their expense).

Participants with a pathogenic germline mutation or unexplained abnormal tumor screenings will need to have genetic counseling to receive their results. The participant will be contacted to let them know their results are available and they will be given the option of scheduling a genetic counseling appointment at a convenient location or they may be provided with the option to be counseled over the telephone. During the counseling session, the participant’s results will be discussed with them and appropriate cancer surveillance recommendations and referrals will be provided. When the participant is contacted, they will also be given the option to opt out of receiving their genetic test results. If the participant does not want to know their test results, they can choose not have genetic counseling.

Some participants may have an unclear genetic test result (also known as a variant of unknown significance), meaning a change in a gene was found but it is unclear if that change increases the risk for cancer or if the change is a normal variation that is not frequently seen. For participants with normal tumor screenings found to have a variant, a letter will be mailed to them detailing their tumor screenings and genetic test result. If the participant is concerned about their results or personal/family history of cancer, they can call the telephone number listed on the letter to schedule an appointment with a genetic counselor in their area (at their expense if the variant is in any gene other than a LS gene).

Result procedures for the at-risk relatives of the participants with LS

The at-risk relatives of participants with LS will undergo single-site genetic testing through OSUMC Molecular Pathology lab or the University of Washington (depending on the type of mutation present in the family). Results will be provided in-person or by telephone by the genetic counselor and appropriate cancer screening recommendations and referrals will be provided.  
Communication Oversight Plan
There are several ways that communication will be facilitated between the lead PI and project manager at OSU with accrual nurses and study personnel at outside hospitals.

- The PI and project manager will have a standing monthly conference call with the accrual nurses from the participating hospitals. These scheduled calls will include updates on accrual numbers, discussion of any subject complaints, as well as any issues the nurses have come across during accrual. If some nurses are not able to join the conference call, they will receive the meeting minutes.
- The SOP guide is available at all times for OCCPI study personnel to reference (Appendix 14).
- There is a taped training session for nurses who may benefit from a "refresher course" or new nurses beginning to accrue to the study. The training session is available at http://panopto.con.ohio-state.edu/Panopto/Pages/Viewer/Default.aspx?id=b46d9cbd-03ee-464f-902e-4cbad4ab1c89.
- Accrual nurses are always able to contact the project manager should immediate issues or questions arise.

5. Methods of data collection

Teleform

The teleform is an important part of the accrual process. There are four teleforms for the study: OSU CRC patients (appendix 11), other CRC patients (appendix 12), EC patients (appendix 13) and relatives (appendix 17). The completed teleform will contain demographic information, preferred method of contact and information on current and past cancers (if applicable). The teleform will also gather information on the participant’s family history (FDRs, specifically) including life status, current age or age of death, cancer history and optional names. One important use of the family history information is to help determine the type of genetic testing the participant may be eligible to receive.

Baseline questionnaire

The baseline questionnaire (Appendix 15) includes questions concerning participant demographics, cancer/medical history, family history, lifestyle factors and environmental factors. Participants can skip the questions they would prefer not to answer. The baseline questionnaire will be completed using REDCap, a secure, web-based application designed to support data capture for research studies by building and managing online surveys and databases.

After the participant is consented to the study, study personnel will enter them into REDCap and will indicate the participant’s preference for completing the
questionnaire (Internet or telephone). For the individuals completing the questionnaire on the Internet, they will be sent an invitation via email that will provide them with the link to their own baseline questionnaire, as well as a validation code that will allow them to access their questionnaire anytime. Once the participant begins their questionnaire, they will have the freedom to complete it at their leisure (taking breaks, leaving the REDCap website, etc) as long as they continue to enter their validation code each time they want to enter the questionnaire. For the individuals completing the questionnaire by telephone, designated study personnel will attempt to contact the participant using the phone number they provided within 2-4 weeks of enrolling in the study.

**Biospecimens**

*For all CRC study participants:* The three tubes containing 10ml of blood will be transferred from the participant’s hospital to the Human Genetics Sample Bank. One tube will be frozen and the other tubes will be processed so that DNA and plasma will be extracted and a Trizol cell suspension will be created and stored. The frozen blood (4ml) will be used for mutation detection for all cases that proceed to gene testing at Myriad. The processed DNA will be used for mutation detection for all cases that proceed to gene testing at the University of Washington, as well as the “normal” DNA to complete the MSI testing at OSU in cases that do not have enough normal tissue on their tumor slides.

*For OSU CRC study participants:* The OSU pathology department will confirm the tumor as colorectal adenocarcinoma and will select a representative tumor tissue block and normal tissue block (with corresponding H&E stained slides) and will give the H&E slides to the pathologist to mark an area on the tumor block containing as high a proportion of cancer cells as possible. Fresh and/or frozen tissue may also be used for OSU CRC patients only. The CLIA-approved molecular lab at Polaris Innovation Centre will then core the tumor and/or cut eleven 10 micron unstained slides and one or two 4 micron H&E slides (per block). The slides or cores will then undergo DNA extraction for the MSI test (performed following the instructions in the Promega kit) and methylation (if applicable).

*For Cleveland Clinic CRC participants:* The Cleveland Clinic pathology department will confirm the tumor as colorectal adenocarcinoma. The Cleveland Clinic already routinely performs MSI and IHC for the four mismatch repair proteins as part of the clinical care for their patients, therefore, the OCCPI will not repeat the tests already performed on the tumor tissue. CCF will send one H&E slide along with 10-20 four micron unstained slides from a block that contains both tumor and normal tissue for all the cases that are MSI-H and/or absent MLH1/PMS2 proteins on IHC so that OSU can do the methylation test. The OSU lab will perform the methylation test for these cases and will provide the CLIA-approved result to the Cleveland Clinic Pathology Department for inclusion in their medical record. If a participant has methylation testing at OSU and they consented to the biorepository, their remaining tumor and normal DNA will be kept in the OCCPI biorepository. Additionally, CCF
will send one H&E slide along with 10-20 four micron unstained slides from a block that contains both tumor and normal tissue for all the cases that did not have methylation testing at OSU but elected to participate in the OCCPI biorepository.

For CRC participants from all other participating hospitals: The outside pathology department will confirm the tumor as colorectal adenocarcinoma and depending on their preference, will select EITHER one representative block with tumor and normal tissue OR eleven 10 micron unstained slides, four 4 micron unstained slides and one or two 4 micron H&E stained slides and send them to study personnel at the OSU Polaris Innovation Centre. The H&E slides will be given to the pathologist to mark an area containing as high a proportion of cancer cells as possible. If blocks were sent, the CLIA-approved molecular lab at Polaris will then core the tumor and/or cut eleven 10 micron unstained slides and one or two 4 micron H&E slides. The slides or cores will then undergo DNA extraction for the MSI test (performed following the instructions in the Promega kit) and methylation (if applicable). Two of the four 4 micron unstained slides will be used for MSH6 and PMS2 IHC, if IHC was not already performed at the outside hospital. The extra 4 micron slides will be used as needed to repeat stains that fail and/or to reflex to MSH2 or MLH1 IHC if MSH6 or PMS2 are absent, respectively.

For OSU EC study participants: The two tubes containing 10ml of blood will be transferred to the Human Genetics Sample Bank. The tubes will be processed so that DNA and plasma will be extracted and a Trizol cell suspension will be created and stored. The processed DNA will be used for mutation detection for all cases that proceed to gene testing at the University of Washington, as well as the "normal" DNA to complete the MSI testing at OSU in cases that do not have enough normal tissue on their tumor slides. The OSU pathology department will confirm the tumor as endometrial cancer (any histology other than sarcoma) and will select a representative tumor tissue block and normal tissue block (with corresponding H&E stained slides) and will give the H&E slides to the pathologist to mark an area containing as high a proportion of cancer cells as possible. The CLIA-approved molecular lab at Polaris Innovation Centre will then core the tumor and/or cut eight 10 micron unstained slides and one or two 4 micron H&E slides (per block). The cores or slides will then undergo DNA extraction for the MSI test (performed following the instructions in the Promega kit) and methylation (if applicable).

For the at-risk relatives of the participants with LS: Three tubes containing 10mL of blood will be transferred from the participant’s hospital to the Human Genetics Sample Bank. One tube of blood will be used for single site testing at the Molecular Pathology Laboratory at OSU or University of Washington and the remaining blood will be processed so that DNA and plasma will be extracted and a Trizol cell suspension will be created and stored. Some participants will provide a saliva sample for the genetic testing in addition to or in place of blood.

For all participants consenting to the biorepository: Saliva samples will be collected at the time of enrollment for CRC participants and transferred directly from the
participant’s hospital to the Human Genetics Sample Bank. Once received, it will be separated into two aliquots and spun down into a cell pellet and frozen for future use. Relatives will return saliva samples to the Human Genetics Sample Bank where they will be separated into two aliquots and spun down into a cell pellet and frozen for future use.

6. Data management

The study database will be managed by study personnel using the infrastructure provided by the Division of Human Genetics Data Management Platform (DHGDMP). The core of the DHGDMP is a division-owned server housed at the Ohio Supercomputer Center (OSC) that runs the BC|Enterprise research data management and laboratory information management software system from BC Platforms Ltd. The DHGDMP also includes leased storage on OSC’s IBM General Parallel Filesystem (GPFS). Clinical data are stored and managed on the server using the BC|Enterprise interface to an IBM DB2 database management system back end. Individuals’ genomic data files, which are stored outside of the server in an access-controlled area of OSC’s GPFS, are also managed using the BC|Enterprise interface and can be linked to clinical data. DHGDMP users will have OSC user accounts managed by DHGDMP administrators using OSC’s project management portal. Users will access the platform to manage databases through an encrypted web browser connection. At the discretion of the DHGDMP administrators, users performing genomic analyses may also be authorized to access the platform through an encrypted secure shell connection. Using these interfaces, users may query or manipulate databases, submit analysis jobs to the server or OSC high-performance computing clusters, or view analysis job results. The back end may also be accessed directly by DHGDMP administrators or other authorized applications via the open/Java database connectivity (O/JDBC) interfaces.

DHGDMP administrators, OSC staff, and BC Platforms staff have collaborated to develop a comprehensive platform-level security plan that satisfies the requirements of The Ohio State University Wexner Medical Center Information Security (OSUWMC IS), which oversees information technology compliance with the Health Insurance Portability and Accountability Act (HIPAA) for OSUWMC. This plan is designed to (1) prevent unauthorized access to human subject data and (2) reduce the probability and impact of unintentional data loss or system failure. Based on this plan, risk acceptance for the DHGDMP has been obtained from OSUWMC IS. OSUWMC IS will provide continuing oversight of platform security, and the DHGDMP administrators will work with OSC and BC Platforms staff to ensure and document compliance with all OSUWMC IS requirements going forward.

An additional layer of security is provided at the study database level. In order for a DHGDMP user to access the study database, the designated database owner, who is a DHGDMP user affiliated with this protocol, must explicitly grant access. Different levels of access can be granted depending on each user’s role on the study. The
database owner may also revoke a user’s access to the study database at any time. To enable smooth operation of the platform, these restrictions will not apply to certain administrative accounts belonging to DHGDMP administrators, BC Platforms support staff, and OSC systems administrators. These accounts will be able to invoke elevated privileges and to access any data in the platform when necessary to complete a legitimate systems administration task. Such tasks could include upgrading software, applying security patches, configuring hardware, migrating data, or changing database ownership. These accounts will be used only when absolutely necessary to complete administrative tasks (DHGDMP administrators who are also affiliated with this protocol will have separate user accounts for non-administrative work). Moreover, data access will be limited to the minimum necessary to complete a particular administrative task. To ensure appropriate use and data integrity, actions performed by both administrative and non-administrative users are logged to the extent required by OSUWMC IS. Should unauthorized or inappropriate access to data be suspected, the audit trail in these logs could be used to investigate the incident.

Some key personnel on the current protocol may also be key personnel on other research protocols using the DHGDMP. Because each non-administrative DHGDMP user has only one DHGDMP user account, these individuals may have full access to data belonging to the current protocol as well as data belonging to other research protocols through the same account. Such individuals will access only the data belonging to the current protocol in the context of conducting research under this protocol. Note that this does not preclude accessing data from other protocols in this context when there is an IRB-approved data sharing plan covering this access. Also note that this should not be construed as precluding access to the data belonging to the other protocols in the context of executing duties as key personnel on those protocols.

REDCap, used to complete the baseline questionnaire, works directly with the OSU CCTS Research Informatics Services Core and will be used as a central location for data processing and management. Vanderbilt University, with collaboration from a consortium of institutional partners (including OSU) and the NIH National Center for Research Resources, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the CCTS Research Informatics Services Core. As part of the data dictionary development process, individual fields can be denoted as “identifiers”. When exporting a de-identified dataset, these variables are omitted. Additionally, the data export tool also allows for the shifted of dates for a limited data set export. REDCap provides a secure, web-based application that is flexible enough to be used for a variety of types of research, provides an intuitive interface for users to enter data and has real time validation rules (with automated data type and range checks) at the time of entry. It offers easy data manipulation with audit trails and ad hoc reporting functionality for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical
packages (SPSS, SAS, Stata, R/S-Plus). REDCap is 21 CRF Part 11 capable. Currently, REDCap installations support electronic signatures by positively identifying the user through a unique username and password combination. The provisioning of accounts and user access to specific database(s) is integrated with the OSU Medical Center LDAP authentication service, and the provisioning of access and specific user rights are managed by CCTS staff.

Each participant will be assigned a unique participant identification number (individual ID) that will follow their electronic information in REDCap and the DHGDMP database, as well as their biospecimens, throughout the study. After the participant is consented to the study and their teleform and biospecimen samples are received by study personnel at OSU Polaris Innovation Centre, the Human Genetics Sample Bank managers will enter the participant’s information into the database and will assign them a unique ID. At that time, any identifying information from the physical biospecimen samples will be removed and replaced with the unique ID and a sample ID. Tumor samples will be linked to each participant in the database by the pathology number located on the teleform and/or unique ID. Study personnel will hand-enter the information from the teleform into the database. That information will be double checked for accuracy by different study personnel. Although each participant’s ID will be the same in REDCap and the database, information stored in REDCap will not be accessible to the sample bank.

Each participant will have their own folder that will contain identifiable data including a copy of their consent form, teleform, medical records release form, pathology report, test results and any letters sent to the participant. Protected health information gathered for this study will be stored at The Ohio State University Wexner Medical Center (OSUWMC). Identifiable data will be kept in participant folders (under lock and key in the PI’s office building and/or in locked locations under the direction of the Division of Human Genetics at OSUWMC in compliance with university policies), in the secure DHGDMP database, and in REDCap (the online data capture system used for the baseline questionnaire). Biological samples will be coded and stored in the OCCPI Biorepository in the Human Genetics Sample Bank.

In order to facilitate communication between the pathology department and study personnel, a secure excel spreadsheet will be kept for the duration of the study because the pathology department does not have access to the database. The secure excel spreadsheet will primarily facilitate the transfer of the tumor screening results into the database, but it will also contain clinical information, genetic test results and follow-up information. Only IRB approved key personnel can access this spreadsheet. The spreadsheet is password protected, it is behind the OSU firewall, and it will be destroyed at the completion of the study.

No identifying information about a study participant will be given to third parties, including family members, unless that subject has given written (Appendix 22), witnessed or verbal consent to do so. Participant data (both electronic and physical biospecimen samples) will be coded. If the participant consents to the biorepository, their leftover samples will remain coded and will become part of a biorepository that
will be available indefinitely for analysis/future research studies pertaining to cancer research, including the genetics of CRC. Participant data will remain coded, rather than de-identified, so that results can be provided to the participants if future research studies ever reveal anything clinically relevant and if the participant has indicated that they would like to receive any clinically relevant results. If the participant does not consent to the biorepository, their leftover samples will be destroyed when the study (including data analysis) is complete.

It is possible that data gained through this research may be shared with collaborators from both non-profit and for-profit organizations external to OSUMC. If samples or data from the biorepository are requested (Request for Samples, Appendix 21) by collaborators for secondary research purposes, the initial requests will be reviewed and approved by the OCCPI steering committee. Collaborators may be PIs, co-Is, or key personnel on protocols approved by the OSUMC IRB or on protocols approved by IRBs at other institutions. All outside collaborators must have IRB approval for the research they propose using the OCCPI samples and/or data. Once the samples/data leave the OCCPI biorepository after the initial approval, the OCCPI steering committee may defer subsequent research approvals to the approved requester.

It is possible that genomic information gained through this research will be submitted in restricted access public databases such as the National Institutes of Health (NIH) database of Geneotypes and Phenotypes (dbGaP). For all public database submissions, only data from participants who consented to participation in the biorepository will be included. The PI and/or authorized study personnel will create a spreadsheet for the electronic data requested and that person will ensure that only authorized data is included for the transfer. As previously described, a unique numerical code generated by the research database will supplied. The DNA samples are coded with a unique “individual ID” and a unique “sample ID”, there is no identifying information on the tubes. Electronic data will be coded with the “individual ID”. Genotypic data that may be shared would include Lynch syndrome status (Yes/No), if known. Phenotypic data that may be shared would include gender, race, age at diagnosis, tumor location, tumor histology, MSI status and data from the baseline questionnaire (including medical history, family history, lifestyle factors, environmental exposures). Any data that is included in the baseline questionnaire that is one of the 18 HIPAA identifiers will be omitted from any data transfer. Any transferred data will be submitted for restricted use access. Data will be available only to those researchers granted access for cancer research, as per our protocol and consent forms.

Participating institutions can only request to use samples that they contributed to the biorepository. For example, if an institution only contributes blood samples and not tumor or saliva samples, they can only use blood samples for future research. If participating institutions decide not to contribute samples to the biorepository, those institutions will not be eligible for consideration to use the samples for future research.
If a participant contacts study personnel and asks to withdraw, a Change in Status form (Appendix 20) will be completed to help the study personnel clarify exactly in which study activities the participant no longer wants to be involved. Participant clarifications could include determining if they want to withdraw from the entire study, they do not want to receive their results but we can continue to do research on their samples, they do not want to complete the questionnaire but they still want their results, etc.

7. Risks and benefits

All risks (physical, financial, psychological, insurance, privacy) related to participation in the OCCPI are minimal.

The physical risks foreseen with the study involves the blood draw. Discomforts and risks of the blood draw that occur most often are temporary discomfort with the needle stick, bruising, and minimal bleeding. Less frequent risks of the blood draw are prolonged bleeding and/or discomfort, infection, possible fainting, or collection of blood in the tissues of the arm (hematoma).

There should not be any financial risks foreseen with the study. For all CRC/EC participants, there are no costs associated with the tumor screenings, genetic testing and genetic counseling provided by the study. There will be no cost for the genetic testing for the at-risk relatives of the participants found to have LS. We will attempt to pay the local hospitals to provide the genetic counseling at no charge for the at-risk relatives of the participants found to have LS. If this is not possible, we will offer the at-risk relatives two options; 1) free telephone genetic counseling, or 2) clinical genetic counseling at their local hospital which will be billed to their insurance.

Some participants may experience psychological discomfort stemming from thinking about their cancer risk, the possible hereditary nature of CRC and their genetic status. Participants will be provided with information regarding additional counseling services if they feel they may benefit from further psychosocial counseling anytime during the study.

Insurance risks foreseen with the study are minimized by a federal law called the Genetic Information Nondiscrimination Act (GINA). All health insurance companies and group health plans must follow this federal law. GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against individuals based on genetic information. GINA does not protect against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under Ohio law, health insurance companies cannot ask about the results of a genetic test or use any information obtained from genetic testing to make decisions about providing coverage or benefits for health care services.
Managing the study database in the DHGDM does not pose additional risks to subjects beyond those inherent in receiving medical care or enrolling in a research study. In particular, because the DHGDM has a HIPAA-compliant platform-level security plan supervised by OSUWMC IS, storage of a subject’s data in the platform poses no greater risk than entry of his or her data into other HIPAA-compliant OSUWMC information systems. The DHGDM also has additional internal controls described above to prevent unauthorized access to the study database by DHGDM users not affiliated with this protocol. Because of these stringent controls, the probability of a data breach is likely lower for this platform than for most study databases currently used for research.

This study has both benefits to the participant, as well as benefits to society. The primary benefit to the participants will be the knowledge of their future cancer risk (increased or general population risk), their relatives future cancer risks, and in some cases the experience of having genetic counseling and receiving cancer surveillance recommendations that can help to reduce risk for future cancers. The participant may also benefit from knowing that their participation has helped researchers try to prevent new individuals from being diagnosed with CRC in Ohio, as well as increase survival for individuals with CRC in Ohio.

8. Statistical analysis

To determine the incidence of hereditary CRC among all CRC cases, we will divide the total number of mutation positive individuals by the total number of individuals tested. Assuming that the incidence of mutation positive status is binomially distributed, we will also generate a corresponding 95% binomial confidence interval around this incidence estimate. Based on the literature, we expect that approximately 3% of all subjects screened here will be classified as mutation positive (i.e. testing positive for LS). Based on screening at least 4,000 subjects for LS, an incidence rate of 3% (i.e. 120 identified with LS out of 4,000 CRC subjects screened) would have a corresponding exact 95% binomial confidence interval of 2.49% to 3.58%.

In addition, we will further characterize those with vs. without LS subjects in terms of the demographic, lifestyle, and clinical characteristics that we are collecting. In particular, we will evaluate and summarize familial incidence information that is reported and collected. We can explore potential associations of or differences in these factors in those with vs. without mutation positive results using a logistic regression model on incidence of LS. With an estimated 120 CRC patients with LS in this model, we would be able to explore multivariable models as well with up to 10 covariates. Differences in these various factors between those with vs. without LS will also be explored graphically and quantitatively evaluated in a bivariate manner.

9. Timeline
### Study Preparation

<table>
<thead>
<tr>
<th>Months 0 - 8</th>
<th>Months 9 - 26</th>
<th>Months 27-38</th>
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<tbody>
<tr>
<td><strong>Study Preparation</strong></td>
<td><strong>Accrual Period</strong></td>
<td><strong>Finalize Study</strong></td>
</tr>
<tr>
<td>• IRB approval of protocol at all sites</td>
<td>• Accrual period for 4,000 colorectal cancer patients</td>
<td>• Testing finishes</td>
</tr>
<tr>
<td>• Training of accrual staff</td>
<td>• Testing occurs</td>
<td>• Genetic counseling and testing of individuals with Lynch syndrome occurs</td>
</tr>
<tr>
<td>• Preparation for sample receipt</td>
<td>• Genetic counseling and testing of individuals with Lynch syndrome occurs</td>
<td>• Publication</td>
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### 10. Appendix

1. List of participating hospitals
2. Patient decline list
3. Study flyer
4. Recruitment letters
5. ResearchMatch information
6. OCCPI Fact Sheet
7. LS Fact Sheet
8. CRC consent form
9. EC consent form
10. Medical Records Release form
11. OSU CRC Teleform
12. CRC Teleform
13. EC Teleform
14. Standard Operating Procedures
15. Baseline questionnaire
16. Biorepository (FDR without LS) consent form
17. Relative Teleform
18. Family Member Consent for Contact form
19. LS relatives consent form
20. Change in Status form
21. Request for Samples form
22. Record Release to Family Members form

### 11. References