VUMC Institutional Review Board
Informed Consent Document for Research

Study Title:	Integrating gene signatures to guide management of HR+ MBC in a diverse cohort (INSIGHT) NCT05693766
Version Date:	April 18, 2022
PI:	Sonya Reid, MD

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.

Key information about this study:

This study is looking to see if chemotherapy is better at preventing tumor growth than the usual endocrine-based therapy for the treatment of non-luminal A hormone receptor-positive (HR+) metastatic breast cancer. You will be asked to submit a sample of your tumor for testing to determine if your breast cancer is considered Non-Luminal A. In the future, we hope that this test will assist a doctor in picking the best treatment for a patient with your type of cancer.

If your tumor is Non-Luminal A type, then you will receive either the normal endocrine therapy chosen by your doctor or study chemotherapy (capecitabine). The chemotherapy being used in this study is approved by the FDA to treat your cancer but is usually given after tumors have grown on endocrine therapy.

You may experience side effects during your participation in this study. Common side effects from the normal endocrine-based therapy include hot flashes, flushing, headache, dizziness, mood disturbances, increased sweating, whole body pain, nausea, vomiting, constipation, cough and shortness of breath, swelling and water retention, tiredness, vaginal discharge and bleeding, and abnormal increase in cholesterol. Common side effects from chemotherapy include diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and yellow discoloration of the eyes and skin (jaundice).

This study will also collect several blood samples (up to 1.5 tablespoons each time) to look at potential cancer markers found in your blood. Potential side effects from the blood collection are minor pain, bruising, and/or infection at site of needle stick.

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Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

You are being asked to take part in this research study because you have metastatic breast cancer and would normally receive endocrine-based therapy to treat your cancer. You will either receive the normal endocrine-based therapy or chemotherapy (capecitabine). Capecitabine is FDA-approved to treat your type of cancer.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services, or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Side effects and risks that you can expect if you take part in this study:

As part of this study, you will either receive the normal endocrine-based therapy chosen by your doctor or receive the study chemotherapy (capecitabine). Your doctor will tell you which therapy you will be given.

If you end up receiving the normal endocrine-based therapy:
Common side effects from the normal endocrine-based therapy include hot flashes, flushing, headache, dizziness, mood disturbances, increased sweating, whole body pain, nausea, vomiting, constipation, cough and shortness of breath, swelling and water retention, tiredness, vaginal discharge and bleeding, and abnormal increase in cholesterol.

Please ask your study doctor for a list of possible side effects specific to the drug you are taking.

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If you end up receiving capecitabine: Possible side effects are listed below.

COMMON, SOME MAY BE SERIOUS In 100 people receiving capecitabine, more than 20 and up to 100 may have:
• Swelling of the body • Blisters on the skin • Redness, pain or peeling of palms and soles • Pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Anemia which may require blood transfusions • Infection, especially when white blood cell count is low • Bruising, bleeding • Feeling of "pins and needles" in arms and legs • Tiredness • Fever
OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving capecitabine, from 4 to 20 may have:
• Blurred vision, dry or itchy eyes • Muscle spasms, body aches • Abnormal heartbeat • Restlessness, irritability • Swelling of face, fingers and lower legs • Constipation • Difficulty with balancing
RARE AND SERIOUS In 100 people receiving capecitabine, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Other Risks:
Breach of confidentiality: As this study involves the use of your identifiable information, there is a potential for a breach of confidentiality.

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Good effects that might result from this study:
The benefits to science and humankind that might result from this study: This study will teach us if chemotherapy earlier is better at preventing tumor growth for a certain type of breast tumor compared to the standard endocrine treatment. This study will also teach us if the test to determine breast tumor type is helpful at choosing the best treatment options for future patients.

Procedures to be followed:
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the study. Some of these tests or procedures are part of your regular cancer care and will be done even if it turns out that you do not take part in this study.

- **A medical history**, which includes questions about your health, current medications, and any allergies.
- **Performance status,** which evaluates how you are able to carry on with your usual activities.
- **Tumor test**, to determine if your tumor is Luminal A or non-Luminal A. This is a research test that will be performed on tumor tissue collected from a prior biopsy. BluePrint® and MammoPrint® tests will be performed.

If your tumor is Luminal A, then you will be off study and receive the normal treatment for your cancer. Follow up contact will include looking at your medical record and possibly publicly available information to see how you are doing. This will be done every 6 months for the first 2 years and then annually for 3 years up to 5 years total.

If your tumor is non-Luminal A, then you will be randomly assigned ("randomized") into one of the study groups:

- Arm A: normal endocrine-based therapy chosen by your doctor
- Arm B: study chemotherapy (capecitabine)

Randomization means that you are put into a group by chance. You and your doctor will know what group you will be in. You will have a 50% chance of being placed in Arm A and a 50% chance of being placed in Arm B. You will stay on your assigned treatment for as long as you are tolerating it and your tumor isn't growing.

After the screening procedures confirm you are eligible to participate in the research study, you will begin study treatment:

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Arm A participants will receive endocrine-based therapy chosen by your doctor. This could be tamoxifen, an aromatase inhibitor, or fulvestrant. Your doctor will provide details on when and how the drug is given.

Arm B participants will receive chemotherapy (capecitabine). Capecitabine is an oral medication that you will take for 7 days straight followed by 7 days where you do not take the medication. In other words, you will take this medication every day for 1 week and then off 1 week, and repeat this pattern for as long as you are on the study.

Regardless of treatment arm, each treatment cycle is 4 weeks (28 days).

Before the treatment starts (Arm A or Arm B):
Many of the tests and procedures below are likely to be part of your regular cancer care. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **Clinical Exams:** During this visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An assessment of your tumor** by one or more of the following standard assessment tools: CT (Computerized Tomography) scan, Bone scan, or PET/CT
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.
- **Serum (blood) or urine pregnancy test** for women of child-bearing potential. About 1 to 2 teaspoons of blood is required for this test.
- **Research blood tests:** Blood samples will be collected to study cell-free DNA related to your cancer. DNA (deoxyribonucleic acid) is found in each cell of your body and cell-free DNA is DNA from the tumor that is released into the bloodstream. The blood samples will be approximately 1.5 tablespoons.
- **Patient survey**: You will rate on a scale from 0 (none at all) to 5 (very much) how bothered you are by side effects of treatment

The following will occur on Day 1 of Cycle 2:

- **Clinical Exams:** During this visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and you will be asked

questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.
- **Pill diary:** You will be asked to complete a daily pill diary to track when you took the oral medication. You will give the completed forms to the study nurse when you visit the clinic.

The following will occur on Day 1 of Cycle 3:

- **Clinical Exams:** During this visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.
- **Pill diary:** You will be asked to complete a daily pill diary to track when you took the oral medication. You will give the completed forms to the study nurse when you visit the clinic.

The following will occur on Day 28 of Cycle 3:

- **Research blood tests:** Blood samples will be collected to study cell-free DNA related to your cancer. DNA (deoxyribonucleic acid) is found in each cell of your body and cell-free DNA is DNA from the tumor that is released into the bloodstream. The blood samples will be approximately 1.5 tablespoons.

The following will occur every cycle while you are on treatment:

- **Clinical Exams:** During this visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.
- **Pill diary:** You will be asked to complete a daily pill diary to track when you took the oral medication. You will give the completed forms to the study nurse when you visit the clinic.

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The following will occur every 3 cycles while you are on treatment:

- **An assessment of your tumor** by one or more of the following standard assessment tools: CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging), bone scan, or PET/CT.
- **Patient survey**: You will rate on a scale from 0 (none at all) to 5 (very much) how bothered you are by side effects of treatment.

At the end of the study you will undergo:

- **Clinical Exams:** During this visit you will have a physical exam, which will include measuring your weight and vital signs (blood pressure, heart rate, and breathing rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood tests.** Blood will be drawn to measure blood counts, organ function and for other safety reasons.
- **Research blood tests:** Blood samples will be collected to study cell-free DNA related to your cancer. DNA (deoxyribonucleic acid) is found in each cell of your body and cell-free DNA is DNA from the tumor that is released into the bloodstream. The blood samples will be approximately 2 tablespoons.
- **Patient survey**: You will rate on a scale from 0 (none at all) to 5 (very much) how bothered you are by side effects of treatment

Planned Follow-up:

Every 6 months after you stop taking the treatment, a wellness check will occur to see how you are doing. This will last for 2 years. This wellness check will occur once a year after that for 3 years up to 5 years total.

Payments for your time spent taking part in this study or expenses:

There is no compensation for being in this study.

Costs to you if you take part in this study:

If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

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You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other treatment plans with you.

You will not have pay for the research only procedures (research blood tests and patient surveys) that will be performed in this study.

Payment in case you are injured because of this research study:

If it is determined by Vanderbilt and the Investigator that an injury occurred, then you and/or your insurance may be billed for the cost of medical care provided at Vanderbilt to treat the injury. You will be responsible for any copayments or deductibles associated with the treatment of that injury.

There are no plans for Vanderbilt to pay for the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

Who to call for any questions or in case you are injured:
If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact **Dr. Sonya Reid** at [redacted].

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time.

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Clinical Trials Reporting Program.
Vanderbilt's NCI-Designated Cancer Center or the Sponsor registers National Cancer Institute (NCI)-supported clinical trials with NCI though their Clinical Trials Reporting Program (CTRP) to provide study related information. The data provided will include the following identifiable information that may identify you: birth month/year and five-digit zip code. NCI uses the data to manage and enhance the nation's investment in cancer research.

Confidentiality:
If you join this study, some people and organizations might need to look at your medical or research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Institutional Review Boards (IRB), including the Vanderbilt University Medical Center IRB. An IRB is a group that reviews the study to protect your rights as a research participant.
- Vanderbilt University Medical Center
- Office for Human Research Protections

We will do our best to keep your personal information confidential. But we cannot guarantee total confidentiality. Your personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare. We will not use your personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see the medical record, they would see a copy of this consent form.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

Privacy:
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done

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on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Vanderbilt University, Vanderbilt University Medical Center, and/or others. If this happens, there are no plans to provide money to you. Future research could include whole genome sequencing (human germline or somatic).

At any time, you may ask to have your sample destroyed. You should contact Dr. Sonya Reid at [redacted] to have your sample destroyed and no longer used for research. We will not be able to destroy research data that has already been gathered using your sample. Also, if your identity was removed from the samples, we will not be able to locate and destroy them.

There will be no costs to you for any of the tests done on your samples.

Study Results:
You will be told whether or not your tumor is Luminal A or non-Luminal A. You will not be directly informed of the study results. At study completion, all results will be available on www.clinicaltrials.gov, as required by U.S. Law. Study results may also be presented in meetings or in publication.

Authorization to Use/Disclose Protected Health Information

What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical

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Center. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

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STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date _____ Signature of patient/volunteer _____

Consent obtained by:

Date _____ Signature _____

Printed Name and Title _____