

Consent to Participate in a Research Study
Pulmonary Vascular Disease Phenomics Program (PVDOMICS) Consent
May 12, 2016

Study title: Pulmonary Vascular Disease Phenomics Program (**PVDOMICS**)

Sponsor: National Institutes of Health (NIH), Heart, Lung and Blood Institute, (NHLBI)

PI: XXX

Study Coordinator: XXX

You are being asked to join in a research study on pulmonary hypertension. Being in a research study is different from being a patient. The purpose of this consent form is to provide a written review of the discussion of research information you had with the research team. It is also for use as a reference during the study.

Please note:

- **You are being asked to join in a research study**
- **You can ask as many questions as needed so you can make an informed decision.**
- **Carefully consider the risks and benefits of the research**
- **Your decision to join is completely voluntary and will have no effect on your medical care if you choose not to join. You can also stop doing the study at any time.**

INFORMATION ON THE RESEARCH

Why is the research study being done?

Doctors from medical centers across the U.S. have formed a research group to study pulmonary hypertension (high pressures in the blood tubes of the lungs). These medical centers are Mayo Clinic, Vanderbilt University, Johns Hopkins University, Columbia University, Cornell University, University of Arizona, Brigham and Women's Hospital (Boston) and Cleveland Clinic. The goal of this group is to gain a better understanding of this illness and problems in the right side of the heart, based on traits from the cells of the body and tests. The current classification system and treatments for pulmonary hypertension will be looked at to see if improvements can be made. This study also hopes to identify new ways to avoid, detect and treat pulmonary hypertension.

Why are you being asked to take part in this research?

You are being asked to take part in this study because you have been diagnosed with pulmonary hypertension, you are at risk for developing pulmonary hypertension, or you are being evaluated because your doctors suspect that you have pulmonary hypertension.

How many people will take part in the study?

About 1500 participants (including 100 healthy volunteers) will take part in this study at the centers listed above.

What is involved if you decide to take part in this research study?

This study will be done over 3 to 4 visits. The visits should be completed within 6 weeks. The tests listed below are part of the study, but some may be done as part of your routine care or are available from prior tests you had done.

During the course of the PVDOMICS Study, if the medical tests or other research analyses find an abnormality or a potential health problem, we will contact you. We can also contact your doctor, if you would like us to. The results of many of the medical tests you undergo for this study will be automatically put in your medical record which means they will be available to your healthcare providers.

Medical History:

We will ask you about your medical history including the medicines you are taking. We will also look at your medical record and gather results from other tests that you have had or will have done related to pulmonary hypertension, including medicines, blood test results, echocardiogram(s) (ultrasound of your heart), right heart catheterization(s) (pressure measurements in your heart and lung vessels), exercise and lung function tests, and radiology reports. If you had a medical test that is being done as part of this study at another hospital, we may be able to use the results from this test with your permission.

Physical Exam:

You will have a physical exam. This exam will include measuring your height, weight, and vital signs (heart rate, blood pressure, breaths per minute and oxygen saturation).

Questionnaire(s):

During the study you will be asked to fill out several forms regarding your pulmonary hypertension symptoms, health, and quality of life.

Echocardiogram:

An echocardiogram will be done to look at your heart function. This test is an ultrasound of your heart. It is done by a trained person by holding a device (shaped like a microphone) on the skin of your chest with some pressure to look at the heart and surrounding larger blood vessels. It will take about 30-45 minutes. An intravenous line may be placed in order to inject fluid containing tiny bubbles to improve the pictures and check for any abnormal connections between your heart chambers. This may be done as part of your routine care or just for this research study.

Electrocardiogram (ECG):

An ECG is a test that measures your heart's electrical activity. You will be asked to lie flat on a table and several small electrode pads (like stickers) will be placed on your body. These electrodes record the beats of your heart. This test takes about 10 minutes.

Waist to Hip Ratio and Bioelectrical Impedance Analysis:

Measurements will be taken of your waist and hips. An additional test will measure your body make up such as body fat. It is called Bioelectrical Impedance Analysis (BIA). This test is painless and should take less than 15 minutes.

Urine Testing:

We will collect urine to learn more about pulmonary hypertension. If you are a woman who could have a baby, urine samples will also be used for pregnancy testing. The pregnancy test results must be negative in order to continue to take part in the study. .

Blood Tests:

Blood will be collected two times during the study, once at the first research visit and then also during the right heart catheterization. Approximately 90 mls of blood (7.5 tablespoons) will be collected each time. Some of the blood will be used to check your general health. The rest of the blood will be stored and used for this study's research relating to pulmonary hypertension, including genes (DNA) that may be related to pulmonary hypertension and other diseases. Any blood not used in this study will be stored in a biobank for later, if you agree to this.

The research samples (including genetic samples) will be labeled with a study code and not your name or medical record number. Some of this blood will be sent to the Data Coordinating Center at the Cleveland Clinic for DNA storage, and genetic testing by researchers in this study.

Pulmonary Function Tests:

You are asked to complete several breathing tests for this study, if they are not already being done for your medical care. These tests involve taking in a deep breath and blowing out the air through a mouthpiece several times. We will also measure how well oxygen transfers between your lungs and blood. This is done by taking in a deep breath of a safe gas mixture, holding your breath for 10 seconds, and then exhaling rapidly. Again, this is repeated at least twice during the test. Finally, we will take pressure and air flow measurements while you sit inside a small airtight booth and breathe through a mouthpiece. These tests will take about 30 to 45 minutes.

Cardiopulmonary Exercise Test (CPET):

This heart and lung test is done to look at your ability to exercise on a stationary bike when you are giving the most effort you can. You will be asked about the symptoms that you experience during this exercise. During the exercise test you may be asked to breathe through a mouthpiece attached to a machine that will collect and analyze the breath you breathe out.

Cardiac Magnetic Resonance Imaging (MRI):

Even if a cardiac (heart) MRI is not necessary for your current care and treatment, one will be done for this study. MRI uses magnetic waves to take pictures of your heart. Please tell the study team if you have any metal implants, pacemaker or defibrillator, as you may not be able to have an MRI. You cannot have a MRI if your heart rate is more than 120 beats per minute. This procedure involves having an IV tube inserted into your vein for a contrast material called gadolinium to be given. If you have moderate or severe chronic kidney disease, you can have a non-contrast MRI. You will spend about 60 minutes in the MRI scanner while pictures of your heart and major blood vessels are taken.

Right Heart Catheterization (RHC) Procedure:

During a RHC, a very thin plastic tube, called a catheter, is placed in a large blood vessel in your leg, neck or arm. The doctor will move the catheter through your body while looking at an X-ray (a technique called fluoroscopy) until it is in the main blood vessel going into your lungs called

your pulmonary artery. The catheter measures the amount of blood the heart pumps and how hard it is to push the blood through the lungs and heart. You may be given drug(s) during this procedure that will make you feel sleepy, so you will need to have someone with you to drive you home after the test. The RHC will take about 1-2 hours. During the procedure, you may be given nitric oxide (a substance that makes blood vessels open) to inhale by mask, fluid through the catheter, and a medicine called nitroprusside that causes blood vessels to open through the catheter. After these are given, the pressures in your heart and lungs will be measured again. Some people may be asked to perform their cardiopulmonary exercise test (CPET) with the catheter in place during the RHC. If this is the case, you will have another catheter placed in your arm and blood will be drawn from this catheter while you exercise to measure the levels of gases in your blood.

CT Scan of Chest:

You will be asked to complete a CT scan of the chest for the study. These are specialized x-rays of the lungs. For this test you will lie down on a table that moves into a large-tunnel shaped CT scanner. You will be asked to hold your breath for about 5-6 seconds while pictures are taken. This test will take about 10-15 minutes.

Lung Scan:

You will also be asked to have a ventilation/perfusion (VQ) scan if one has not been done in the past year. During this test you breathe in small amounts of radioactive tracers (these emit rays that are detected by a special camera) that enter your lungs. You will also receive an injection of another tracer into your vein (blood tubes) that flows with your blood into your lungs. The special camera's pictures of the tracers so doctors can see where air and blood flow in your lungs.

Overnight Sleep Study:

You will have an overnight sleep monitoring test. You will be given a small device to take home, and at bedtime you will wear straps around your chest and abdomen, a small clip on your finger and small plastic prongs in your nose. These will monitor your breathing and oxygen levels while you sleep. The information that you need to write down during this time will be explained by a study coordinator. The following morning you will remove the equipment and return it to the study team.

Six Minute Walk Test:

You will be asked to walk as far as possible in six minutes. You may self-pace and rest as needed as you walk back and forth along a marked walkway.

Follow-Up

We may look at your medical records at any time during the study. You may be contacted by the study team by phone and/or mail during the study. You may be asked to have one more visit if you are having another right heart catheterization for medical reasons during the next five years. We may contact you in the future, if another study arises that you may be a candidate for.

RISKS

What are the possible risks or discomforts from being in this research study?

Blood Draw Risks:

The risks of drawing blood are small and may include pain, bruising, dizziness, and/or passing out, or infection at the site of the blood draw.

Genetic Research:

These studies might uncover a genetic or inborn abnormality that you did not previously know about. Some genetic changes may be clinically relevant, meaning they could affect your risks for future health related problems and change the recommendations for your health care. They might also show that you have a genetic risk factor for pulmonary hypertension that could be shared by other members of your family.

You can decide whether or not you want to be told about this type of genetic result. This information may cause you and family members to be worried and have many questions. Therefore, if you choose to be told about these results, you will be recommended to talk to a genetic counselor who can explain the meaning of the results. The central core laboratory that is doing genetic testing is a research facility and does not have the ability to provide genetic test results directly to you. Therefore, the study investigator at your site will send the information to the genetic counselor and the results will need to be confirmed in a clinical testing laboratory before they are given to you. The cost of genetic counseling and clinical genetic testing is not covered under this research protocol.

To help prevent disclosure, the results of the genetic research will not be placed in your medical record. While every effort will be made to protect the privacy of your results, this cannot be certain. Because your genetic information is unique to you, there is a chance that someone could trace it back to you even without having your name or other personal information in the study database. The risk of this happening is very small.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, makes it against the law for health insurance companies, group health plans, and most employers to discriminate against you based on genetic information. This law will protect you by: (1) Health insurance companies and group health plans may not ask for your genetic information that we get from this research. (2) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums. (3) 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 terms of your employment. This federal law does not apply to companies that sell life insurance, disability insurance, or long-term care insurance and does not protect you against use of this information for an already diagnosed genetic condition or disease.

Please initial below to indicate whether or not you would like to be notified about clinically relevant genetic results.

_____ (initials) I would like to be contacted if clinically relevant genetic results become available during this study. I would like to receive results related to (initial one option below):

_____ (initials) ONLY results related to pulmonary hypertension risk

_____ (initials) ONLY results related to risks for other serious health conditions

_____ (initials) ANY results related to pulmonary hypertension or other diseases

OR

_____ (initials) I do not want to be contacted about any abnormal genetic results.

Confidentiality Risk:

The information and samples that researchers are going to collect includes your DNA and information on your medical history. Before your information is sent to the study database, your name and other identifiers will be removed and replaced with a study code. We will keep your identity private but there is a small risk that someone could identify you from the information in the study database.

Tests performed at your center, such as laboratory tests, electrocardiogram, pulmonary function tests, sleep studies and imaging, are likely to be placed into your medical record which can be accessed by healthcare providers other than study physicians.

At the conclusion of this study your medical information collected during the study will be transferred to a biobank at the National, Heart, Lung and Blood Institute. Your name and other identifiers will be removed before the transfer. A biobank is a database that has medical information available to researchers so that more can be learned about this disease. **We cannot include you in this study without your permission to have your information transferred to the biobank. You do not have to give us this permission. If you do not, then you may not join this study.**

Quality of Life Questionnaire Discomforts:

It may be uncomfortable for you to answer personal or difficult questions about your pulmonary hypertension and how it affects your activities of daily living but there is no pain expected with completing the forms.

Echocardiogram:

This test uses sound waves to look at your heart. The person doing the test will press on your chest with a machine to obtain the pictures. The pressure may be uncomfortable.

Pulmonary Function Testing:

These lung tests may make your chest tight or make you short of breath. You might also have coughing or lightheadedness with the tests. These feelings are temporary and should be gone within minutes after the tests are over.

CPET:

While exercise testing is generally safe, there is a chance of heart attack, stroke, or dangerous arrhythmias (irregular heartbeats) occurring during this testing. We take precautions to prevent these risks during the test.

Cardiac MRI:

During the cardiac MRI, you will lie on a narrow table, which slides into a large tunnel-shaped scanner. An MRI exam causes no pain, but you may have difficulty keeping still or may become nervous in the scanner. The sound of the MRI scanner can be loud; you may be given special ear plugs to minimize the noise. You may be able to discuss with your doctor if you can be given medication if needed to help with this.

The cardiac MRI may involve the use of a contrast agent containing gadolinium. This agent is frequently used, and is non-radioactive. The gadolinium agent will be injected by needle into a vein in your body and the injection itself may be hurt, may bruise, and there is risk of infection at the injection site. The most common side effects of gadolinium are mild headache, nausea or burning at the injection site. It is rare to have an allergic reaction to gadolinium. If you have had an allergic reaction to gadolinium, the contrast portion of the cardiac MRI will not be done. Recent information shows that the gadolinium used for the cardiac MRI studies may pose additional risk to the kidneys in patients with kidney problems. Your doctor will evaluate your kidney function during the study with blood tests. If the blood test shows significantly reduced kidney function, the contrast portion of the cardiac MRI will not be done. If you have a pacemaker or defibrillator that is not MRI compatible, the cardiac MRI will not be done, unless your center has a system in place to do such scans safely.

CT Scan:

The primary risk of the chest CT is exposure to radiation. If your scan is being performed for purposes of this research study and not as part of your clinical evaluation, then the radiation exposure is not necessary for your medical care and is for research purposes only. While the amount of radiation is small, there is no known threshold of radiation exposure. For each CT scan, you would be exposed to the amount of radiation that you are naturally exposed to while living in the US for about 12-18 months. Although there are no proven harmful effects from this small amount of radiation, repeated episodes of radiation exposure may increase your chances of developing cancer in the future. However, it is believed that the risk related to the radiation you will receive in this study is low.

Lung Scan:

Lung scanning involves little risk for most people. The agent that contains the radioisotopes used for both parts of the test exposes you to a small amount of radiation. The amount of radiation in the gas and injection together are about the same as the amount a person is naturally exposed to in 1 year. Although rare, the radioisotopes may cause an allergic reaction.

6-Minute Walk Test Risk:

During the 6-minute walk test you may feel short of breath, dizzy or tired.

Right Heart Catheterization Risk (RHC):

There are risks associated with the RHC procedure. Complications can include:

- Bleeding, infection, bruising, and pain where the catheter is inserted into your body
- Damage to blood vessels; this is a very rare complication caused by the catheter scraping or poking a hole in a blood vessel as it is threaded to the heart
- Abnormal heartbeat, which often goes away on its own but may need treatment if it persists
- Blood clots that can trigger strokes, heart attacks, or other serious problems
- Low blood pressure
- A buildup of blood or fluid in the sac that surrounds the heart. This fluid can prevent the heart from beating properly
- Air leaking into the heart or chest area
- Exposure to radiation during the right heart catheterization. The amount of radiation that you will receive has a low risk of harmful effects.

BENEFITS

What are possible benefits of participating in the research?

There is no direct benefit for your participation in this study. Your participation in this study may provide information that may help other people who have a similar medical problem in the future.

COSTS

Are there any costs to you if you participate in this study?

The study related tests, procedures, and visits will be provided at no cost to you. The cost for routine tests and services that would normally be performed even if you don't participate in the study will be billed to you or your insurance provider. You will be responsible for your usual co-pays and deductibles that you would pay when you have a medical test or see your doctors for a regularly scheduled visit.

Will I be paid for taking part in this study?

You will receive \$XXX to cover costs and time related to the study. By law, payments to subjects may be considered taxable income. You will not receive any financial benefits from future use of your samples or information.

RESEARCH RELATED INJURY

What will happen if you are injured as a result of taking part in the research?

In the event you are injured as a result of participation in this research, medical care is available to you. The costs of such medical care will be billed to you or your insurance company. There are no plans to provide compensation for lost wages, direct or indirect losses. The XXX will not voluntarily provide compensation for research related injury. You are not waiving any legal rights by signing this form. Further information about research related injury is available by contacting the Institutional Review Board at XXX.

PRIVACY AND CONFIDENTIALITY

Your name and participation in these studies will be held strictly confidential. Your research samples will be identified only by an ID number (not your name). Any identifying data will be kept in a locked drawer or in a password protected computer file. Only the Principal Investigator, XXX, of this study and his or her study coordinator will have access to the numeric

code, which identifies you by name. No group health companies or insurance companies will ever be allowed to access to the genetic results. These are some things to remember:

Although the genetic information about you is shared with other investigators in the study, the information will be anonymous: other investigators will be unable to link the results with you.

Results from the research using your samples may be presented in publications and meetings but individual names will not be identified. As part of the publication process, genetic results may be placed in databases that are available to other researchers outside the study, but no personal identifying information will be included.

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.

Also, your study data may be reviewed by the following groups (as applicable to the research):

- The U.S. Department of Health and Human Services
- The XXX Institutional Review Board or Human Subjects Protection Program
- The National Institutes of Health (NIH), their agents or study monitors

Tests, such as laboratory tests, electrocardiograms, pulmonary function tests, sleep studies and imaging tests, are likely to be placed into your medical record at the site of your testing. Placement into your medical record means that healthcare providers outside of the PVDOMICS Study, and insurers, will have access to those test results. Placement in medical records also means that any abnormal findings from those tests can be seen by your healthcare providers.

Protected Health Information

The XXX has rules to protect information about you. Federal and state laws also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it. Generally, only people on the research team will know that you are in the research study and will see your information. However, there are a few exceptions that are listed in this section of the consent form.

The people working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may collect other information including your name, address, date of birth, and other details.

Health information may be collected about you from:

- Your medical record, including the management of your pulmonary hypertension.
- Research procedures including interviews, questionnaires, lab results, and other exams explained above.

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

- To do the research
- To report the results

- To see if the research was done correctly
- To create a National Institutes of Health Global Unique Identifier (GUID) to be able to identify a person who participates in more than one research study. Your GUID will be a random number and does not include any of your protected health information.

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

Who may use or share your health information?

- XXX research staff involved in this study
- The XXX Institutional Review Board that oversees the research.
- Researchers involved in this study at other institutions
- The National Institutes of Health (NIH)
- The Data Coordinating Center (at the Cleveland Clinic) and the Observational Safety Monitoring Board (OSMB) for this study
- Future researchers may request study data from the National Heart, Lung and Blood Institute Biological Specimen and Data Repository Information Coordinating Center (BioLINCC) repository where the study data will be stored when the study is over.

We cannot include you in this study without your permission to use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form; however, people outside the XXX who receive your information may not be covered by this promise. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee this.

The use and disclosure of your information has no time limit.

QUESTIONS

Who do you call if you have any questions or problems?

- XXX contact information for PI (required) and primary SC (optional) which must be 24/7 number(s)
- XXX If the study involves the Clinical Research Unit (CRU),
- XXX IRB Contact Information

VOLUNTARY PARTICIPATION

What Are Your Rights As A Participant?

Taking part in this study is voluntary. You will be told of any new, relevant information from the research that may affect your health, welfare, or willingness to continue in this study. You may choose not to take part or may leave the study at any time. Withdrawing from the study will not result in any penalty or loss of benefits to which you are entitled. Your samples and any study data collected will be destroyed at the time, if you decide to withdraw consent. If you decide to withdraw, contact the study PI, XXX at XXX.

There are certain circumstances that would result in your early withdrawal from the study without your approval. You will be withdrawn from the study if you develop conditions that might make continued participation harmful.

SIGNATURES

Statement of Participant

I have read and have had verbally explained to me the above information and have had all my questions answered to my satisfaction. I understand that my participation is voluntary and that I may stop my participation in the study at any time. Signing this form does not waive any of my legal rights. I understand that a copy of this consent will be provided to me. By signing below, I agree to take part in this research study.

Printed name of Participant

Participant Signature

Date

Statement of Person Conducting Informed Consent Discussion

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

Printed name of person obtaining consent

Signature of person obtaining consent

Date

CONSENT FOR SUBJECTS WHO CANNOT READ

The study subject has indicated that he/she is unable to read. The consent document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

Printed Name of Impartial Witness

Signature of Impartial Witness*

Date

*Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject.

Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance