

INSTITUTE: National Human Genome Research Institute

STUDY NUMBER: 07-HG-0002 PRINCIPAL INVESTIGATOR: Leslie G Biesecker, M.D.

STUDY TITLE: *ClinSeq* : A Large-Scale Medical Sequencing Clinical Research Pilot Study

Continuing Review Approved by the IRB on 11/13/14

Amendment Approved by the IRB on 5/27/15 (BB)

Date Posted to Web: 05/30/15

Standard – Group A1 and subset of Group A2

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends, or your personal physician or other health professional.

WHY IS THIS STUDY BEING DONE?

The goal of this study is to learn how to do genome sequencing in clinical research. Genome sequencing is a technology that allows us to analyze (or sequence) part or all of the genome from a single person. The human genome is the material in our cells that includes thousands of genes. Genes carry the instructions that our bodies need to develop and function. Genes are passed on from one generation to the next. Genome sequencing allows us to find gene alterations, which are also known as “gene variants”. These gene variants may be important to your health or the health of your relatives.

In the beginning of this study, we focused our efforts on heart disease and sequenced several genes thought to be involved with heart disease. But we have expanded the focus of the study to other genes and conditions. We are now able to sequence most of your genes as part of the ClinSeq™ study. If you decide to join this study, you may learn about your chance of having a hereditary condition, and/or of passing on a condition to your offspring.

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This study is not for everyone. We are looking for participants who are:

1. Comfortable with the idea of having many or all of their genes sequenced.
2. Willing to interact with us over a period of years.
3. Open to coming back to the NIH for more detailed clinical research in the future. These studies will be based on gene variants that we may find.

Society and medical research benefit from sharing cells and information among many researchers and institutions. The cells and medical information from participants in this study will be made available to researchers at universities, private companies, and other institutions in the United States and internationally. We may share your cells with our own research collaborators. Your samples will be used for research, and they may also be used to make commercial products and treatments, meaning that they can be bought and sold in order to treat other people. The research done with your samples may help to develop new products in the future. You will not receive any financial compensation, should this occur.

WHAT IS INVOLVED IN THE STUDY?

If you join this study, you will come for an initial visit at the NIH Clinical Research Center. This visit will take about half a day. In this visit, you will have a blood draw for your fasting (before eating) labs. Then you will take a survey. After that you will meet with the genetic counselor to learn more about the study. If you join the study, the following will take place:

- You will provide a family history (if you have not done so prior to this visit) and a medical history. We will check some basic things, like height, weight and blood pressure. You will also have some non-invasive heart tests, including an echocardiogram and an EKG.
- About 2.5 ounces of blood (just over 5 tablespoons) will be drawn by standard procedures. Part of your blood sample will be used for research and part of it will be used for clinical testing. One of the research procedures is the creation of a cell line from one of your blood samples.
- You may have a test called multidetector computed tomography (MDCT) to measure the calcium in your coronary arteries. If you have a stent or bypass surgery, you will not have this test.
- You will be asked to answer questions about your participation at different times during the course of the study.

After the clinical tests (echocardiogram, EKG, MDCT, and labs) are done, you will get a letter from us with the results of your clinical test results and evaluations. This letter will contain recommendations for follow-up with your doctor(s). Depending on the results of your clinical evaluations, we may call you and also ask to speak with your doctor.

The sample you provide for genome sequencing will be analyzed at our laboratories. Our plan is to sequence most of your genes. This analysis will take months or years to complete. This is because genome sequencing is difficult to do. It is also because we have much to learn about the genes we will be sequencing and the gene variants we find.

Genome sequencing is a research test that can provide various types of results. For example:

- We can find gene variants that are known to cause or contribute to disease;
- We can find gene variants that are known NOT to cause or contribute to disease, meaning they are normal variations of the genome;

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- We can find gene variants that are novel and of uncertain clinical importance, meaning that we do not know if they cause/ contribute to disease or if they are normal variations of the genome.

Most of the results that are important to your health and/or the health of your relatives fall in the first category – gene variants that are known to cause or contribute to disease. If we find one or more of these gene variants in your sample, it could be that:

- The gene variant has already caused you to have signs and symptoms of a disorder;
- The gene variant may cause you to have signs and symptoms of a disorder in the future;
- The gene variant may be important to the health of your offspring.

If we find a gene variant that has health implications, we will repeat the test for that specific gene variant in a clinical laboratory. We will **only** give you results about specific abnormal gene variants that we think are important to your health and/or the health of your relatives, and that have been confirmed in a clinical laboratory.

It is important that you know the limits of the test we are doing:

- First, at this point will be testing **most, but not all** of your genes.
- Second, if we do not find a gene variant, we will **not discuss** that result with you. The absence of a result does not mean that your gene is “normal”. This is because we can miss some gene variants by the test we are offering. Also, we will **not report** a gene variant that is known to be a normal variation.
- Third, as mentioned above, we may find gene variants that are novel and of uncertain clinical importance. In some cases, by studying this type of gene variant in more depth, we may learn that it can cause or contribute to disease. We will **only** report this type of gene variant to you if we can learn enough about it to make us believe that it can cause or contribute to disease.
- Fourth, as mentioned above, we will report gene variants that are known to cause or contribute to disease. **But**, most of the gene variants we find will not fall in this category. Additionally, there is much to be learned about genes and variations in them. For these reasons, most participants will not hear from us about this kind of result for months or even years.

In the future, we may contact you by mail or phone to find out if you are interested in learning about your results or gene variants that are important to your health and/or the health of your relatives. We may also contact you to find out if you are interested in having additional clinical tests and evaluations at the NIH Clinical Research Center.

You will be given a choice **to learn or not to learn** the results of your genome sequencing. You may “opt out” of learning any of your genome sequencing results, and still be in the study. (The only exception to opting-out is if we find a result that has **urgent** importance to your health. We plan to share this type of result with you or, if you prefer with your physician. However, you should know that this type of result will be found rarely, and most people in this study will not have a result like this).

If you choose to learn the results of your genome sequencing, you will be asked to return to the NIH Clinical Research Center. You will meet with the genetic counselor who will explain the results and what they mean to your health. She or he may also make recommendations for follow-up with your physician or with a specialist. For example, if you are found to have a gene variant that causes high cholesterol, you may be recommended to discuss this with your doctor so that he/she can monitor your cholesterol closely.

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At your follow-up visit, the genetic counselor will also discuss what the results mean for your relatives' health. This will be explained to you in detail so you understand the risks. We may or may not offer testing to your relatives as part of this protocol or another protocol at the NIH. If we cannot enroll them in a protocol at the NIH, we will make referrals for them to be seen by local genetic groups if they wish.

Because the science changes quickly, we will likely learn more about the human genome after you get your initial results. If we think this new information is important to your health and/or the health of your relatives, we may re-contact you. For us to do this, you have to keep us up to date with your current address and phone number.

It is important that you understand that we hope to sequence most, or in the future perhaps all of your genes. For this reason we are looking for participants who are comfortable with the idea of having many or all of their genes sequenced and who are also willing to interact with us over a period of years.

If at any time, you request to access all of the sequence data we have for you (including gene variants that are or novel or uncertain clinical significance, which we would typically not share with you as described above), we will withdraw you from our study. This is because you will no longer need the results we could provide to you through our analysis. It is also because any results we return to you will no longer be novel to you, which makes you ineligible for many side projects that aim to understand your reactions.

For a quick reference of what is involved in this study, please refer to the **diagram that the genetic counselor will give you (Appendix S)**.

WHAT ARE THE RISKS OF THE STUDY?

There are different kinds of risk that you may face if you join this study.

The physical risks are very minor or very rare:

- There is usually brief discomfort or pain and bruises where the needle enters for blood drawing.
- There is a small risk of an infection, excess bleeding or fainting from the blood drawing.
- CT scan:

This research study involves exposure to radiation from one CT scan of your heart. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.27 rem (for the CT scan at the NIH), which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please go to <http://www.genome.gov/Pages/Research/Intramural/IRB/ResearchPatientBrochure.pdf> for a copy of the pamphlet, *An Introduction to Radiation for NIH Research Subjects*, or ask the investigator to provide you a copy.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

MEDICAL RECORD**CONTINUATION SHEET for either:**

NIH 2514-1, Consent to Participate in A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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If you are pregnant you will not be permitted to participate in this research study. If you are breast-feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Beta-blocker:

If your resting heart rate is greater than 80 beats per minute, your heart CT images may be blurred. A beta-blocker medication (as a pill and/or in your vein) may be given to slow your heart rate for the purpose of getting clearer pictures of your heart. It might result in excessive slowing of your heart rate, lowering of your blood pressure, an allergic reaction or narrowing of your airways. These events may happen in small number of people who have lung conditions (e.g. asthma or chronic obstructive airway disease). However, you will not be given this medication if you have any of the conditions which might cause such a risk. Before and after you receive beta-blocker medications, we will monitor your heart rate and blood pressure. This is an off-label use of an FDA approved medication.

Echocardiogram:

There are no known risks to the ultrasound exam itself. Most people undergoing an ultrasound do not require contrast; however, some (about 1/4) do require contrast so that the sonographer can better visualize any changes in the heart. The contrast agents used are approved by the FDA. Side effects of these contrasts are usually minor and do not require any intervention. The most frequently reported adverse events are headache, nausea and/or vomiting, warm sensation or flushing, dizziness, back or renal pain, chest pain and dizziness. If you need contrast, the sonographer will go over these risks in more detail. Also, if you need contrast, an IV will be placed in your vein so that the agent can be given to you.

Other:

Some of the tests that are done as part of this study are not part of routine health care. Obtaining these results and sharing them with your doctor may affect your health care outside of this study. The clinicians involved with ClinSeq™ will share these with you and possibly with your doctor. They will also talk with your about further testing or follow-up that may be recommended. The cost of the recommended testing or follow-up will not be paid for by the NIH, so you may to pay for this additional care yourself.

Emotional and psychological risks are also possible:

- It is possible that learning that you have a gene variant that causes or contributes to a disorder could lead to emotional or psychological harm. Counseling will be provided to you in the event that you experience any emotional or psychological distress as a result of participating in the study. A referral will be provided if you wish to pursue long-term counseling.
- It is possible that learning that you could pass on a gene variant for a disorder could cause emotional or psychological harm. As above, counseling will be available to you.
- It is possible that your relatives would be upset to learn that they may be at risk for a disorder because of your participation in this research study.

PATIENT IDENTIFICATION**CONTINUATION SHEET for either:**

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 09-25-0099

MEDICAL RECORD**CONTINUATION SHEET for either:**

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NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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- If we don't find any gene variants in your sample, you may still have gene variants that we missed or did not check for. It is possible that you will feel falsely reassured if we do not report specific gene(s) variant(s) to you.
- If we find that you have a gene variant that causes or contributes to disease and return that result to you, that result will become part of your medical records at the NIH. This result will be released as part of your medical records if you sign a release of information to a third party, such as your insurance company. There may be a risk that genetic information obtained as a result of participation in research could be misused for discriminatory purposes. However, state and federal laws provide some protections against genetic discrimination. Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your genetic information.
- Family information such as parentage and adoption may be found in this research project. It is **not** our practice to disclose this type of information unless it has direct medical implications for your family, which is unlikely.
- We may publish results of this research study, including your family history and other medical information. It is unlikely that you and/or a family member could be recognized because of such publications. This is because most of the diseases we will be investigating are common, such as heart disease.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. Possible benefits to you include:

- Free clinical testing for cholesterol and other lipids, diabetes, etc.
- Free CAT scan to detect coronary artery disease (MDCT).
- If we find gene variant(s) that are important to your health and/or the health of your relatives, you and your family may benefit from knowing that information.

It is possible that you may not learn anything from the genome sequencing part of the study.

The results from this study will benefit the public in the future by improving our knowledge of the relationship between gene variants and health.

WHAT ARE MY OTHER OPTIONS?

You do not have to join this study if you do not want to. Alternatives to having some of the evaluations you would have in this study include: (1) having a check up for heart disease with your doctor, and (2) having genetic counseling to assess your family history for heart disease and other conditions. Other research studies for heart disease are available at the NIH and at regional centers (see www.clinicaltrials.gov).

WHAT IF I CHANGE MY MIND?

You may quit this study at any time. If you do wish to quit the study, we need to talk with you about how to do this. There are several parts of the study and we need to know what to do about each part. We need to know if you want to stop future interactions with us, whether we can keep using your samples, what to do about samples that may have been shared with other researchers, etc. We will make reasonable efforts to comply with your wishes. If you don't tell us how to do this, we will stop our future contacts with you, remove personally identifying information from the research samples and data, and we may or may not keep using your samples and data. It is important for you to know that once we have

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deposited your sequence data into public databases, those deposits cannot be removed or retrieved (see next section). Also, we cannot promise that samples we have shared with other researchers can be retrieved, but we will make reasonable efforts to do so if you request that.

WHO ELSE WILL KNOW THAT I AM IN THIS STUDY?

Data from this study will be identified with a code number instead of your name. The key for this code will be stored in a locked file cabinet or in a password protected computer. Only the investigators and support staff helping carry out this project will have access to this key.

We may publish data from this study in a paper or book chapter, but we will not use your name. Therefore, others will not recognize you as a research participant.

The blood sample and information that we collect from you may be shared with other qualified researchers looking to answer important medical questions. When we share such information with these researchers, we will NOT give information that can identify you, such as your name, address, or phone number. There will be a code to link your sample with your name and other personal information. Only the investigators and support staff helping to carry out this project will have access to this code. Additionally, these researchers will need to get approval for their projects from committees that are set up to protect you as a research participant.

The results of the analysis of your genes will be available in public databases that store information about the human genome. First, you should know that this information is stored in such a way that it is NOT possible to know which result belongs to which individual. Secondly, you should know that only people with expertise are able to interpret this information. Additionally, the results of the analysis of your genes, the results of your clinical tests and basic information, such as age and gender, will be available in databases monitored by the NIH. You should know that this information will NOT contain identifiers, such as your name or medical record number. One database that we may use is called dbGap, and access to this database is tightly controlled by the NIH. It is, however, possible that someone with a high level of expertise could link anonymous data stored in such a database with an individual person.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project. The researchers do not intend to make voluntary disclosures unless there are extenuating circumstances. For example, in the event someone intends to hurt him/herself or others, disclosure may be necessary.

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WILL I RECEIVE PAYMENT FOR BEING IN THIS STUDY?

You will not receive payment for the time you spend in clinical visits and receiving clinical information.

CONFLICT OF INTEREST

The National Institutes of Health reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process <http://ethics.od.nih.gov/forms/Protocol-Review-Guide.pdf>. You may ask your research team for additional information or a copy of the Protocol Review Guide

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