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Dear ClinSeq Participant,

Welcome to the first edition of the ClinSeq Newsletter! You are part of a study that is both groundbreaking and exciting. This research study will push forward into a future where we can begin to envision personalized medicine – that is, the approach by which we hope to be able to customize a person’s health care by knowing all about their genes and DNA. Many of you may have read about how genetics and the Human Genome Project are going to change medicine and health care, and you are helping to make that happen.

We plan on sending newsletters, such as this one, periodically so that you are up-to-date on the study and aware of key findings that may come up in the future. Please note that you can find an electronic version of this newsletter on our website at:

[www.genome.gov/clinseq](http://www.genome.gov/clinseq)

I would like to take this opportunity to thank you for your participation in the ClinSeq study! Your involvement and enthusiasm are very important to the success of our study.

Thank you again for your participation in this groundbreaking study,



Leslie Biesecker, M.D.  
 Principal Investigator  
 Chief, Genetic Disease Research Branch  
 NHGRI



**Featured Story:**

**Trans-NIH Study Explores Medical Role for Genome Sequencing**

**Patients with Cardiovascular Disease to Participate in Genetic Sequencing Study**

National Institutes of Health (NIH) researchers have begun a pioneering new study that will use high-throughput genome sequencing technology for personalized health benefits. This trans-NIH effort, called ClinSeq, will explore the fundamental medical, molecular and bioinformatic challenges facing individualized gene sequencing in a clinical research setting.

Over the next two years, the ClinSeq research team will enroll 1,000 people with the warning signs and symptoms - also known as phenotypes - of coronary heart disease. Researchers will use large-scale medical sequencing to gather detailed data about each participant’s genetic makeup, and then analyze that data to see how individual genetic variations relate to the risk of coronary heart disease.

The participants, some of whom will be followed for up to 10 years, will include 45- to 65-year-old men and women. In addition to having their DNA sequenced, participants will be evaluated for coronary heart disease, which is a common condition with major public health implications. Researchers hope the individualized data generated by ClinSeq will help to better inform treatment approaches in the future.

**“ClinSeq is the first study in which results from high-throughput DNA sequencing will be communicated back to individual patients,”** -Leslie Biesecker, M.D.,

“Science is advancing another step towards the age of genomic medicine,” said Eric Green, M.D., Ph.D., National Human Genome Research Institute (NHGRI) scientific director and director of the NIH Intramural Sequencing Center (NISC), which will perform the sequencing for ClinSeq. “Sequencing has the potential to guide researchers investigating better strategies for disease diagnosis, treatment and prevention. As sequencing capabilities improve, including how we process the information, sequencing for medical purposes will have a role beyond being a research tool - it will help guide the delivery of care to patients.”

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"ClinSeq is the first study in which results from high-throughput DNA sequencing will be communicated back to individual patients," said Les Biesecker, M.D., chief of the NHGRI Genetic Disease Research Branch. The term "high-throughput" refers to the data-generating capacity required to sort through the 3 billion base pairs of information in the human genome. As principal investigator for ClinSeq, Dr. Biesecker heads a team of collaborating researchers from NHGRI; the National Heart, Lung, and Blood Institute; NIH Clinical Center; NISC; and NIH Heart Center at Suburban Hospital, near NIH in Bethesda, Md.

This sequencing-based approach is particularly attractive because it can reveal not only common variants, which usually confer only a modest degree of susceptibility to disease, but also rare variants, which confer a greater risk of susceptibility to disease. ClinSeq researchers are interested in learning more about the relative contributions of common and rare variants to the development of common disease. Initially, ClinSeq will focus on some 200 to 400 genes that prior research suggests may be implicated in coronary heart disease. Genes for additional diseases will be analyzed later in the study.

Considering that each person's genome contains as many as 20,000 genes, just locating gene variants associated with coronary heart disease is a major challenge and an ongoing pursuit for genomics researchers. Still, looking ahead, ClinSeq eventually plans to employ recent advances in genomics that will push the envelope even further. In fact, ClinSeq participants will be the first among a number of heart study populations to consent to have their entire genomes sequenced if such comprehensive analysis becomes feasible and economical.

Flavia Facio, M.S., a genetic counselor and the lead associate investigator for the study, said, "The study has several goals, including detecting genetic changes that increase the risk for cardiovascular disease, developing the process by which genome sequencing can be used as part of medical care, and assessing if participants want to acquire genetic information about themselves and how they respond to such information."

Participants in the ClinSeq project undergo an initial clinical evaluation that includes an electrocardiogram and an echocardiogram at the NIH Clinical Center. They also undergo CT scan of their coronary arteries at the NIH Heart Center at Suburban Hospital, an NHLBI-affiliated center, to obtain a coronary calcium score. These tests provide a description of each subject's cardiovascular signs and symptoms, or phenotype. A small amount of blood is drawn during the patient's first visit. Some of the blood is used to purify genomic DNA, which is sent to NISC for high-throughput sequencing. Ultimately, the characteristics of the disease, or phenotypes, will be correlated with the genetic variants found by sequencing.

In addition to providing a personal medical history, each participant creates a profile of their family health history. Many diseases, such as cancer, diabetes and heart disease, can run in families. Family health data will be analyzed to identify disorders for which participants may be at risk and to guide discussion with participants about strategies for disease prevention.

"My family has lost some to heart attacks," said Alan L. Freeman, a 48-year-old electric utility company employee from Silver Spring, Md., who enrolled in January as ClinSeq's first participant. Freeman was told about the ClinSeq project by his cardiologist, whom he was seeing for a heart checkup prompted by some undiagnosed chest pains.

"From what I know, it sounds absolutely fascinating to me," said Freeman, whose hobbies include golf, scuba diving and working around the house. "Just the thought of being a part of this study is too much to believe. You never know who this research might benefit."



All of the DNA sequence data generated by ClinSeq will be organized by gene and by patient. Sequence variants will then be profiled and differentiated: those mutations likely to trigger disease versus innocent variations not involved in coronary heart disease. Only if the researchers have a strong measure of confidence in what the data reveals will they convey these results to the participants.

The researchers also will explain to participants how to interpret any individual genetic test results. "We will be making judgments about what information should and should not be returned to the participants," Dr. Biesecker said. "The right way to do this is to involve the patients in the process in a controlled, realistic environment. We will inform them about what we understand about their genes, and interact with them as the results become available."

How often participants return for further tests will depend on how many significant variants are detected. Each patient will receive a letter with the results of standard clinical laboratory analysis and evaluations, as well as recommendations for follow-up with their physicians.

Freeman's enthusiasm about study participation extends to the people he's met at NIH and the project they have described to him. In the week following his initial visit to the NIH Clinical Center, he spoke of the staff as "some of the nicest people I've ever met." They spelled out clearly what they wanted - blood and not tissue. You get thoroughly checked out.

"I am by nature curious," he continued. "I have been following human genome research because of my coronary problems and heart. Just the fact that they can look at a gene, and perhaps even treat you before a problem occurs - just the fact they are headed that way - fascinates me."

Of the goals of the ClinSeq researchers, Freeman reflects, "I may have a longer or better life with what they see. Hopefully, they will get as much or more out of it. You can never tell what they're going to discover."



## Genetics 101

**By Flavia M Facio, M.S.  
Certified Genetic Counselor**

For most ClinSeq participants, the first person you met with was me. When I meet with participants, I explain that the goal of the ClinSeq study is to look at your genes by a process called DNA sequencing. I thought it would be helpful to take this opportunity and review with you what genes are and what DNA sequencing can reveal.

### What are genes and sequencing?

ClinSeq is all about genes and genes are made up of DNA. So let's start by talking about genes. We have two copies of each gene, one inherited from our mother and one from our father. But not all copies of a person's pair of genes are exactly the same and these variations in genes can affect our health. These variations in genes are due to differences in their DNA sequence. So now we need to talk about DNA. DNA stands for **d**eoxyribon**u**cleic **a**cid. DNA is the material that makes up each gene. The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). So A, G, C, and T make up the DNA alphabet. These bases are arranged in a certain order or sequence to form a gene, much like letters of the alphabet appear in a certain order to form words or sentences. Currently, it is estimated

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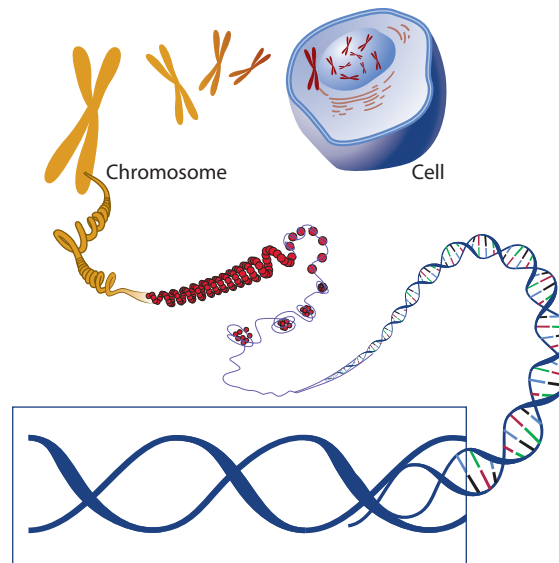
***“Eventually, we hope to sequence most or all of your genes.”***

***-Flavia M Facio, M.S.***

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that humans have about 25,000 genes. The differences in genes are called gene variants or mutations. I prefer the term “gene variant”. While some gene variants do not affect a person's health, others may cause or contribute to disease. This is because some gene variants may affect the function of a gene. In order to find gene variants, we are using a method called DNA sequencing. This method allows us to “read” the DNA sequence of a gene and detect many (but not all) gene variants. In the beginning of the ClinSeq

study, we will sequence genes that we suspect to play a role in heart function. As the study progresses, we hope to sequence other genes related to other conditions. Eventually, we hope to sequence most or all of your genes. This is the remarkable part of the study – you are one of a very few people in the world who will undergo this kind of gene sequencing and there is a lot that we hope to learn from you! Anytime we come across a gene variant that is believed to cause or contribute to disease, I will contact you to let you know



of this finding in our research lab. At that time, you will be given the opportunity to come in and learn about that result. You may also choose not to learn of this result. Your decision to learn or not learn the result will not change your participation in the study. Either way, we hope you will share your thoughts about this process with us – it is one of the key things that we want to learn from the study participants. It may take months or even years before you hear back from us. That is because using DNA sequencing to look at hundreds of genes takes a lot of time. Furthermore, it can take a long time to interpret the meaning of some gene variants.

I hope you found this helpful. We will talk more about genetics on our next newsletter!

## ClinSeq News

### What is the latest on the ClinSeq project?

Currently, we are focusing our research on genes related to heart disease. We have selected about 200 genes for our “gene list” up until now. More genes will continue to be added to our “gene list”. At this point, we are selecting genes that play a role in heart function and disease. In the future, we will select other genes related to other conditions. We will keep you informed about future genes and conditions.

### Have there been any results yet?

We are grateful to tell you that we have already identified gene change in three participants who have very high levels of cholesterol. These gene changes are in a gene named LDLR (low density lipoprotein receptor) that is important for moving cholesterol out of the blood and getting it into the liver. The variations in the LDLR gene in these participants gives them a disorder called Familial

Hypercholesterolemia (FH). It is important that patients with FH take aggressive treatment to lower their cholesterol because they have a much higher than average rate of heart attacks. This is a great example of personalized medicine. While we all know that lowering cholesterol is important for heart health, it is even more important for patients with FH to do this. We are very grateful to know that we are already making a difference in the lives of some of the study participants and their families.



## Current Enrollment

**By Stephanie Brooks, B.S.**  
**ClinSeq Research Assistant**

We currently have more than 300 participants enrolled in the ClinSeq study. Many of our recent participants heard about ClinSeq through word of mouth, from participants who had enrolled in the past. Thank you for speaking so highly of your experiences and for referring others!

We are still enrolling participants, so if you have friends or spouses who are interested in participating, and meet the criteria below, please ask them to call (301)443-6160. Also, please note that those who have coronary artery disease (including individuals who have had a heart attack, bypass surgery, and stents placed) are eligible for the study and are encouraged to enroll. We are looking for participants that meet the following criteria:

- Are between 45 and 65 years of age
- Have not smoked regularly in the past year
- Live in the Metropolitan DC, Baltimore, or Northern Virginia areas
- Have a primary care physician
- Do not have a first-degree family member (such as a brother or sister) participating in the ClinSeq study.



*Aerial photograph of the NIH Clinical Center*

### Is your phone number changing?

#### Are you relocating?

If your phone number(s) or address changes, please let us know. You can call (301) 443-6160 or e-mail [clinseq@mail.nih.gov](mailto:clinseq@mail.nih.gov). We need to have your up-to-date contact information so that we can share the latest ClinSeq information with you and let you know when genetic results become available for you.

## Featured ClinSeq Associate Investigator

### Q & A with Richard Cannon, M.D.

#### 1) What is your position at NIH?

I am clinical director of the Division of Intramural Research, National Heart, Lung, and Blood Institute. I am a cardiologist, and head of the Clinical Cardiology Section in the Translational Medicine Branch.



#### 2) What motivated you to become involved in the ClinSeq study?

I am intrigued by the potential of “personalized medicine”, that by knowing your (or your patient’s) gene profile, important decisions

***“I am intrigued by the potential of  
“personalized medicine,” -Richard Cannon, M.D.***

can be made that may prevent disease or guide disease treatment. This information may also benefit children of persons who know their gene profile, through better understanding of potential inheritable disease risk (what we now think of as “family history”).

#### 3) What are your other research interests?

For many years I have performed studies of the endothelium of arteries. These are cells that line blood vessels and play a major role in arterial function, largely through the release of an important molecule, nitric oxide. For many years I, and most others, thought that nitric oxide’s biological functions was restricted to cells in the immediate vicinity of its endothelial synthesis and release, and that its activity was brief. We now know that nitric oxide can be transported around the bloodstream for activation at sites distant from its synthesis. More recently I have been interested in bone marrow-derived cells that appear to play a role in maintaining proper endothelial function, and how exercise may mobilize these cells into the circulation. I have been fortunate to work with many talented collaborators throughout the Clinical Center in conducting these studies.

### Do you have questions or need to contact us?

- If you have questions about the study, need to update your contact information, or would like to refer a participant, please call Stephanie Brooks (Research Assistant) at (301) 443-6160.
- If you have questions about your clinical test results (including your echocardiogram, ECG, CT scan, and lab results), please contact Paul Gobourne (Nurse Practitioner) at (301) 594-6341.

For more information about the ClinSeq project, visit

[www.genome.gov/ClinSeq](http://www.genome.gov/ClinSeq)

