The ClinSeq™ Newsletter

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Inside this issue:

Dear ClinSeq™ Participant,

I am very excited to see this third edition of our ClinSeq™ newsletter as we have a lot to report and update. As some of you may know, the technology of sequencing is advancing very rapidly and our ability to sequence genes has advanced faster than many people thought would be possible. Later this year we expect to have news regarding full genome sequencing of ClinSeq™ participants. We continue to enroll and accrue new subjects to the protocol, and we are especially eager to recruit persons who have had cardiovascular disease (bypass, stents, significant narrowing on catheterization). If you know a person in this situation, please do pass our information along so they may consider enrolling.

Since our last newsletter, we have published a major scientific paper on the design and initial efforts of the project. This paper was published in the journal "Genome Research" (Biesecker et al, 2009 19(9):1665-74). For those of you with access to scientific journals, you can review it at the Genome Research website. It is also available to all, free of charge, at the PubMed Central web site (PMCID: PMC2752125). We expect several additional papers to be published later this year, as we have made a lot of progress and are eager to share it with the scientific community.

Thank you again for your ongoing participation in the study; without you, we could not create the new field of medical genomics!

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

Featured Story:

A Participant's Perspective on Receiving Genetic Results from ClinSeq™

Every participant who enrolls in ClinSeq™ hears about the potential to learn genetic results over the course of their participation in the ClinSeq™ study. For a few participants this potential has become a reality. One such participant, Ken B., shared his experience with us in a recent interview.

Ken is 62 and is enjoying retired life after what he describes as a full, 36-year career with the federal government. He enrolled in ClinSeq™ in 2008, along with his wife, after hearing about the study from his cardiologist at the NIH. Participating in ClinSeq™, as Ken put it, "was an opportunity to learn about cutting-edge health research and to provide valuable information to my family and others."

Ken entered the study knowing more about his cardiac health than many participants. While in his 30s, his doctors had detected his unusually high cholesterol levels, and he received a clinical diagnosis of familial hypercholesterolemia in 1981. Patients with familial hypercholesterolemia have cholesterol levels that can be elevated as much as three times above normal and have a much higher incidence of heart attack than members of the general population. His family history was striking; his mother had a history of high cholesterol, and two of Ken's three siblings were diagnosed with high cholesterol and coronary artery disease at early ages. These two siblings passed away in their 40s and 60s because of their coronary artery disease.

After receiving the clinical diagnosis, Ken's cardiologist at the NIH began aggressive treatment with many medications to help lower his cholesterol levels and monitor his cardiac health. He credits being alive today to his doctors' careful monitoring. "I owe very much to the NIH and to all of the doctors I've seen over these past years. They've probably saved my life."

Though Ken knew his diagnosis entering the ClinSeq™ study, he had never been tested for genetic variants linked to the disorder, so had never received a genetic diagnosis. But as a result of the gene sequencing in the ClinSeq™ study, we detected a variant in Ken's DNA, within the low density lipoprotein receptor (LDLR) gene. The LDLR moves LDL cholesterol (so-called 'bad

continued...

cholesterol') out of the blood and into the cell, where it can be used, stored, or removed from the body. Variants in this gene have been shown to cause familial hypercholesterolemia.

Ken first heard about the availability of a genetic result when he was contacted by the ClinSeq™ genetic counselor by phone and informed that a genetic variant had been found by sequencing of his DNA in the research laboratory. "The result call... was a little bit of a shock because I really wasn't expecting to hear anything about it right away," he said. During that initial call, Ken was simply told that the genetic variant was of medical significance to him and his family. He was provided the choice of learning more, in which case the result would be confirmed in a laboratory with clinical certification prior to his return visit. "The initial call was very serious and very persuasive," Ken said. He decided to return to NIH for an explanation of this result.

> ***"I think genetic testing is kind of like peering into the future a little."***
> ***-Ken B.***

Ken learned that this genetic variant confirmed his clinical diagnosis and underscored the importance of the strict medication regimen he had been on for many years. "The study is going to cover a whole lot of other issues, and I don't know what the impact is going to be for the rest of it," Ken said. "But in this particular case, it did confirm something that I suspected and that the doctors suspected for a long time in the clinical tests." He was relatively well prepared for such a confirmation of his clinical diagnosis. Yet, he was impressed with his face-to-face visit at the NIH. He met with an interdisciplinary group that included a senior clinical geneticist, a genetic counselor, a molecular genetics fellow, and a cardiologist. "So many people there were ready and able to answer any possible question I could have."

Identifying the specific variant was also significant for Ken's family members, who might carry the same genetic variant and be affected with FH. Aggressive treatment, especially if started at an earlier age, has the potential to significantly improve the lifespan of individuals with FH. Upon learning the result, Ken initiated conversations with his family about the study and his result. He emphasized how this information could impact their future and some options available to them.

Ken is pleased with his family's response and already several of his family members have decided to be tested for the LDLR gene variant. "So far everybody was receptive to the news that I participated and that I got the results." Not only his family, but others he has told have been interested in his experience. "I've told various friends about the study, to see if anybody else was interested," he said. "It's noteworthy and newsworthy that the study is taking place!" As with many of his fellow ClinSeq™ participants, Ken also expressed hope that his results would have an impact beyond his immediate family and contribute to future research.

"I see no negative aspects to it," Ken said, reflecting on his decision to learn this genetic result. "I think genetic testing is kind of like peering into the future a little. It gives a person an opportunity to prepare and combat future problems. It's telling you what might be lurking in the shadows."

Ken is aware that in the future he may learn other genetic results from the ClinSeq™ study. While he might not look forward to learning about other diseases risks, he is resolved that "not knowing about it isn't going to make it go away." Knowledge is power, he says. "Knowing [about a health concern] beforehand can help you better prepare for dealing with it." For now, he plans to continue enjoying golfing, boating, home construction projects, and motorcycle riding.

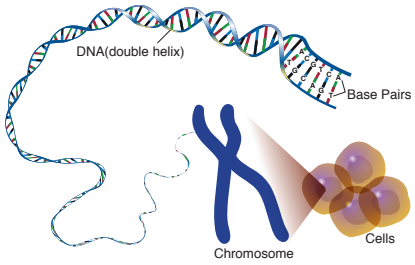
"The study has really been great," Ken said. "We really have a better understanding of what our hereditary issues are, and I'm just encouraged by the whole thing!"

If you have a story that you would like to share with us, please email Flavia M. Facio at Clinseq@mail.nih.gov. We will consider featuring your story in future editions of our newsletter.

ClinSeq™ News

What is the latest on the ClinSeq™ project?

Up until recently, our focus was on genes related to coronary heart disease. We had selected about 220 genes that were being sequenced by our research laboratory. However, we are about to embark on an exciting phase of the study during which we will be sequencing most or all of your genes! This has always been the goal of the study, as you probably recall based on the discussions we had with you during your initial visit to the NIH. But we never thought it would happen as quickly as it is happening. This is being made possible now because new technologies are available that allow us to sequence genes faster and cheaper than before.



What does this mean to you? It means that in the next few years it is very possible that most of your genes will be sequenced as part of this study. Consequently, there is a good chance we will find gene variants for you that may cause or contribute to a disease. These include:

1. Gene variants that do not affect your health, but that may be important to the health of other relatives, such as your children. For example, you could learn that you have a variant in the gene that causes cystic fibrosis.
2. Gene variants that predispose you to a disease that can be prevented or treated. For example, you could learn that you have a gene variant that means you are more likely to develop colon cancer.
3. And, gene variants that predispose you to a disease that cannot be prevented or treated. For example, you could learn that you have a gene variant that means you are more likely to develop Alzheimer disease.

It is important to remember that you have a choice in all of this. Anytime that we come across a gene variant for you that is

believed to cause or contribute to disease, we will contact you to let you know about this finding in our research laboratory. At that time, you will be given the choice to come in to learn about that result. You may also choose not to learn the result. It in entirely up to you! Your decision to learn or not learn the result will not change your participation in the study. In fact, we are interested in your decisions about the genetic information that may be available to you along the course of the study. We want to find out why some people want the information, while others don't. For this reason, we may ask you questions about your decisions in the future.

It may take months or even years before you hear about a genetic result from this study. That is because using DNA sequencing to look at thousands of genes in 1,000 participants takes a lot of time. But, perhaps, more importantly, it may take a long time to interpret the meaning of the genetic variants we encounter. In the meantime, we ask that you please stay tuned and let us know if your contact information changes, so that we have a way of reaching you.

Have there been any results yet?
Some people have been asked to make the choice to come in or not because they received a phone call notifying them that a variant had been found. A total of eight individuals have received such a phone call. All of them were found to carry mutations in one of two genes (LDLR or APOB) that are important in cholesterol metabolism. The gene variants found for these individuals are responsible for a disorder called Familial Hypercholesterolemia. Individuals with familial hypercholesterolemia have total cholesterol levels much higher than normal. As a result, they are at a higher risk to have heart attacks. It is very important that they take medications to lower their cholesterol. This is a great example of personalized medicine. While lowering cholesterol is important for everyone's general health, it is even more important for individuals with familial hypercholesterolemia to do this. All eight of these individuals with gene variants that cause familial hypercholesterolemia have chosen to return to the NIH to learn their results. Additionally, many of their family members have decided to meet with us and be tested for the familial gene variant, so that they can learn whether or not they carry this variant. See our Featured Story to learn more about one of these families.

"This is a great example of personalized medicine."
-Flavia M Facio, M.S.

ClinSeq™ Scientific Updates

As a ClinSeq™ participant, you may be interested to know that the study has been the subject of scientific publications and presentations since the last newsletter.

Publications
In September 2009, Dr. Biesecker along with other authors published a landmark paper on ClinSeq™ in a scientific journal called "Genome Research". This paper describes the many facets of the ClinSeq™ study including the process of enrolling and consenting participants into the study, the pipeline necessary to generate and analyze the gene sequencing data, and the implications of this type of research for the future. One of these implications is the ability to detect individuals who may have a higher risk to develop a certain disease, and who may benefit from early intervention or aggressive treatment. Although this type of personalized or individualized medicine is still in its early stages, we hope that ClinSeq™ can pilot this approach to medical care. We are very excited about this potential and grateful that individuals like you are stepping forward to participate in this new type of research!

American Society of Human Genetics
The leading international society of human genetics researchers accepted two applications for platform presentations on ClinSeq™. These presentation slots are prestigious in that fewer than 5% submitted applications are presented in this forum. First, Dr. Clesson Turner presented preliminary results that support the use of a project like ClinSeq™ to identify individuals affected with or at risk for a genetic disease. Specifically, Dr. Turner discussed that the ClinSeq™ study had identified eight participants with Familial Hypercholesterolemia, which is described in the article above. Dr. Turner explained our efforts to identify and test family members who might also be afflicted with familial hypercholesterolemia to determine if they have it and to help them institute effective treatment for their condition. Dr. Turner's presentation was received with great enthusiasm, as the human genetics community is very interested in the prospect of using gene sequencing technologies to identify individuals at risk for common heritable conditions. Ms. Flavia Facio presented the second platform presentation. She presented the results of a family history study based on the family histories provided by 150 of our participants. We compared the family history given to us by these 150 individuals to the same family history after it was reviewed and revised by the genetic counselor. We learned that the family history provided by the participants using the online family history tool (My Family Health Portrait, MFHP) was quite accurate for four diseases – diabetes, breast, colon, and ovarian cancer. The tool did not perform as well for stroke and coronary heart disease. We concluded that MFHP is a valid tool for the initial collection of family health history, but that it should be improved to better capture information for stroke and heart disease. Ms. Facio's presentation was well attended and generated a lot of discussion because the genetics community is very interested in promoting the use of family history as a screening tool for common heritable conditions, like coronary heart disease and diabetes. This work has also been accepted for publication and is currently in press in the journal "Genetics in Medicine".

Advances in Genome Biology and Technology
This is an annual meeting that includes leading researchers and companies that are focused on developing and applying sequencing technology to advance biology and medicine. At this year's meeting, Dr. Shurjo Sen was invited to present his work showing how we are using new sequencing instruments to study the levels and forms of messenger RNA that are present in blood cells of ClinSeq™ participants. Messenger RNA is the genetic messenger that carries information from your DNA to the part of the cell that converts that information into proteins, which can be thought of as the machines that do the work in the cell that the DNA tells them to do. Dr. Sen's work is showing promise in our ability to precisely measure the levels of these messenger RNA molecules as well as the variations in the structure of the molecules, which is new and exciting. Dr. Sen is working now to correlate changes in the level and structure of these molecules with the health and various results from the clinical studies that the ClinSeq™ volunteers have undergone.

Current Enrollment

By Riley Cooper-McCann, BS
ClinSeq™ Research Assistant

Our current enrollment is over 800 and we are looking to enroll 1,000 participants. We are still recruiting participants with a history of heart disease (including heart attacks, stents, and bypass surgery). These individuals must be between the ages of 45 and 65, live in the metropolitan DC or Baltimore area, be a non-smoker for the last year, have a primary care physician, and not have a first degree relative already participating in the study.

If you have friends or spouses who meet the criteria above and are interested in participating, please ask them to call (301) 443-6160. You can also direct them to the ClinSeq™ website, www.genome.gov/clinseq.

Featured ClinSeq™ Associate Investigator

Q & A with Andrew Arai, M.D.

1) What is your position at NIH?

I am a senior investigator in NHLBI [National Heart, Lung and Blood Institute]. I completed training in internal medicine and cardiology. I came to the NIH as a special volunteer around 1993, and in 1999 I converted to a tenure track position. While my early work at the NIH included both imaging and biochemistry experiments, the imaging experiments made the most progress and highest impact. I set up a clinical cardiovascular MRI research program at Suburban Hospital at a time when cardiac MRI was quite novel and not available at most medical centers around the country, let alone community hospitals. My tenure track project focused on the use of MRI to detect myocardial ischemia and myocardial infarction (heart attack). In particular, we ran a landmark study using MRI to diagnose patients with chest pain in the emergency department. The MRI scan had substantially higher diagnostic accuracy than conventional tests used at that time.

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

Cardiovascular disease, broadly defined, remains the leading cause of death in developed nations and is increasing in epidemic proportions in the industrialized third world. Despite enormous epidemiological efforts to define risk factors, our ability to predict who is at risk for heart disease remains poor. Furthermore, 50% of patients die of heart disease as their first recognized symptom. We need to find ways of identifying these patients before it is too late.

Genetics offers novel ways of risk stratifying patients with cardiovascular diseases. More importantly, genetics has the potential to define specific variations at the gene level that lead to increased risk of heart disease. Pinpointing underlying genetic variations that cause or contribute to disease could be used to target new treatments.

I think ClinSeq™ is a fantastic opportunity for patients and volunteers to help us learn what genetic variants are important. The combination of characterizing subjects with imaging and sequencing their genome may allow us to refine prediction of heart disease in a way that goes well beyond traditional risk factors described in the 20th century.

3) What are your other research interests?

For the past 10 years I have focused my attention on better characterization of cardiovascular disease through advanced cardiac imaging. Much of this work centers around developing new imaging methods and validating them in research studies prior to the technology being available commercially. For example, we recently developed and validated a new MRI method for identifying what part of the heart was at risk during a heart attack. Combined with other MRI methods, we can now determine how much heart muscle was at jeopardy, how much was permanently damaged, and how much was salvaged or saved. This can be detected even days after the heart attack. Our team of cardiologists, engineers, and physicists was able to take this finding and develop ways of programming cardiac MRI for this specific purpose. This is just one example of the interplay between technical developments and clinical research that remains the focus of our laboratory. 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.

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. 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.

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 Flavia Facio (Associate Investigator) at (301) 443-6160.

- If you have questions about your clinical test results (including your echocardiogram, EKG, CT scan, and laboratory results), please contact David Ng (Associate Investigator) at (301) 594-6341.

For more information about the ClinSeq™ project, visit www.genome.gov/ClinSeq