Dear ClinSeq™ Participant,

We are very excited to be entering a new phase of the ClinSeq™ project. Our primary recruitment is coming to a close as we have recruited 958 of our original goal of 1000 participants, and we have begun our “Phase 2” recruitment, which is specifically directed at enrolling African Americans to increase the diversity of our cohort. We are still recruiting individuals with heart disease of all ethnic groups in order to reach our final goal. Additionally, we are now increasing our efforts to interpret and return results, so more of you will begin hearing from us soon. As always, we are terribly grateful to you for your participation and welcome your input. Thank you for taking the time to look at this update from our work together.

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

Contact Information Updates

Are you relocating or changing your phone number? 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 about the study or want to refer a participant? If you need information or have questions about your clinical tests (such as your echocardiogram, EKG, CT scan, or blood work) or the study in general, please contact our research assistant at (301) 443-6160.
Where Are My Results? A Summary of Progress on Returning Results

Many of our participants have been wondering when they can expect to be contacted with the results of their genetic sequencing, and what type of results we have been sharing with participants so far. We are excited to report that we have been steadily analyzing sequence data and are continuing to return results to a growing number of our participants. Thus far, 28 of our 900+ participants have been called back to receive a genetic result. You may ask why the vast majority of people have not gotten information back yet, and the answer lies in the interpretation of the sequence data that we have. As part of the ClinSeq™ project, we have spent several years developing computer programs that can help us analyze the data that we generate through genetic sequencing, and integrate it with information from other databases of genetic information. In addition, it takes a highly skilled staff member to combine your sequence information with data from your personal and family histories and other research studies before we can share a result with you.

Many people have also asked how we decide which results to return first. The answer is that we have begun with the results that have the most serious health implications and those that we feel most confident in—that is, the genetic variations that have been seen previously and have a well-established connection to a disease. To give you a sense of the wide variation in the types of results that we have returned, please see the table on the right. Keep in mind that this is only a fraction of what we intend to return in the coming years, and that we expect that all participants may be that your material has not yet been sequenced or variations that have been seen previously and have a well-established connection to a disease. To give you a sense of the wide variation in the types of results that we have returned, please see the table on the right. Keep in mind that this is only a fraction of what we intend to return in the coming years, and that we expect that all participants have been steady analyzing sequence data and are continuing to return results to a growing number of our participants.

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Now that our primary recruitment efforts are slowing down, we have started to shift our emphasis towards interpreting and returning results. This should result in a drastic increase in the number of participants who are contacted with the option of receiving results in the next 1-2 years.

Analyzing Your Genetic Data

Recent advances in DNA sequencing technology have resulted in dramatically decreased costs for sequencing a human genome, as we are doing for all of our ClinSeq™ participants. While this process cost $75 million dollars per person ten years ago, it now costs $7,500. However, this lower cost presents a surprising challenge to researchers: the huge amount of information that can now be easily generated is challenging to analyze and interpret.

We use several different approaches to analyze and understand this information so that we can generate results to share with you. First, your genetic sequence is processed on computers to identify the positions where your genetic material differs from that of others in the study. We expect that most genetic material (about 99.9%) will be the same across all of our participants. Part of the ClinSeq™ study is to determine how the 0.1% of the genome that is different from one person to the next results in the large variety amongst the health of our participants. This process results in about 100,000 interesting genetic changes for each individual in ClinSeq™. Then, the computers are used to pull together information about each of those genetic changes from databases throughout the world, and summarize that information in one file.

Once we have the file, the final challenge is to allow ClinSeq™ investigators to easily search and analyze these genetic differences so that they can determine which changes are truly important to your health, and share those with you. To make this calculation, our researchers may take into account as many as 50 different pieces of information for each variant across hundreds of participants. In order to do this more efficiently, we needed a user-friendly program that could handle lots of data and make complex calculations. In response to this need, the ClinSeq™ group developed a graphical desktop software tool called VarSifter that allows researchers and clinicians to search, sort, and filter the genetic differences on their desktop computers in many different ways without having to learn computer programming. This allows them to answer many different research questions.
very quickly. For example, when a researcher wants to identify any differences in the LDLR gene (which encodes a protein critical for controlling the levels of LDL, or bad cholesterol) he or she can type in the name of the gene, sort and filter the differences based on whether they are known to cause high cholesterol levels, and then identify the individuals who may have these differences. This has been used to identify and then return this information to study participants.

Tools like VarSifter allow researchers to better understand and interpret the vast amount of genetic information new technologies are able to provide. These tools are primarily designed for research use, but may one day serve as a prototype for software programs, allowing individuals to look at and understand their own genetic information.

**Review of Ancillary Studies**

Now that ClinSeq™ has enrolled a large number of participants, we have begun to develop many new and exciting research questions that are connected to the original goals of the project, but not central to that mission. We call these “spinoff studies”, and their goals range from learning more about whether a specific genetic finding causes disease to surveying participants about gastrointestinal problems to asking about the value of the informed consent process. Here, we profile one such study that we completed recently with the help of our ClinSeq™ participants.

This spinoff project centered around understanding the role of a particular gene, called GCKR, in causing diabetes. Several ClinSeq™ participants were found to have variations in their GCKR gene invited to come back to the National Institutes of Health Clinical Center (NIHCC) for some additional testing. The study found that variations in the GCKR gene did have a significant impact on total cholesterol, LDL cholesterol and triglyceride levels. Some of those changes were found to increase cholesterol and triglyceride levels, whereas others decreased those levels. This increase was subtle (small in degree) and was not sufficiently significant to be useful on a clinical level for individual testing or adjustment of treatment. That is, changes in the GCKR gene cause a statistically significant effect at the population, but not individual, level.

This study did not find a definitive link between variations in the GCKR gene and Type 2 Diabetes in the patients clinically, but did show that these changes have a subtle effect on the protein is located within cells. Participants in the study were not given their specific GCKR testing results, but did receive a summary of the results and the journal article that was published about the findings. One participant in the study said, “[Participating in the study] was fascinating for me because there were lots of tests going on and the NIH is a premier place. I’m a science person so [joining the study] was a no brainer for me.”

New spinoff studies are starting all the time, and we may be contacting you about one in the near future. It’s important for you to know that your participation in those studies is optional and does not affect your participation in ClinSeq™ in any way. We hope that you’ll consider participating the next time we contact you about a spinoff study!

**ClinSeq™ Scientific Updates**

Publications: This year, we have published five new articles that relate to ClinSeq™ and either directly or indirectly use our data.


- Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: Lessons from the ClinSeq™ project Genet Med 2012 14:393-398


- Sloan JL, Johnston JJ, Manoli I, Chandler RJ, Krause C, Carrillo-Carrasco N, Chandrasekaran SD, O’Brien K,

Presentations: We've also had the opportunity to give 10 presentations on our study and data in the last year including:

- “Transcriptome Profiling of Cardiovascular Disease by Massively Parallel Short-Read DNA Sequencing.” NIH Research Festival. Bethesda, 2011
- “Transcriptome Profiling of ClinSeq™ Project Participants by Massively Parallel Short-Read DNA Sequencing.” Advances in Genome Biology and Technology 201. Marco Island, 2011
- “Detecting and interpreting human genome variation: From populations to the individual.” Human Genomics: The next 10 years. La Jolla, February 2011.

Website Updates

In response to suggestions we have received from you, we have begun the process of updating the ClinSeq™ website in order to make it a helpful resource that you can come back to anytime for updates on the project. While the revisions are still a work in progress, we intend to modify the content in the coming months to include all previous ClinSeq™ newsletters, links to our publications and presentations, and any new information about ClinSeq™ in the media. If you have any suggestions or feedback on how we can make the ClinSeq™ website more easily accessible or useful, let us know by calling (301) 443-6160 or e-mailing clinseq@mail.nih.gov.

Featured Associate Investigator: Katie Lewis

1. What is your position at NIH?
I am the newly hired genetic counselor working on the ClinSeq™ project. I know that many of you worked closely with Flavia Facio, the study’s previous genetic counselor, prior to her departure last year, and I look forward to getting to know you in the coming months and years!

2. What motivated you to become involved in the ClinSeq™ Study?
I was initially exposed to ClinSeq™ when I was still in my training to become a genetic counselor. I attended the training program that is housed here at the NIH, and clearly remember the day that Flavia came to give a seminar on this exciting, new project called ClinSeq™. At that time, the project was still being conceptualized, but I was fascinated by the complex set of challenges that the study team was dealing with, and the prospect that the project would make a huge impact on the world of genetics. Years later, when I had the opportunity to be directly involved with the project, it was an easy decision for me to make! I love that the project balances research with clinical interactions and care, and am enjoying being a part of a project that is still on the cutting edge of genetics.

3. What are your other research interests?
One of my main research interests is in the social and behavioral aspects of genetic counseling and testing. This is what I call the “human” piece of our project. I’m particularly interested in learning more from each of you about what motivates you to join a project like ClinSeq™, and how the results we share with you (including what we share and how we share it) affects you and your family.