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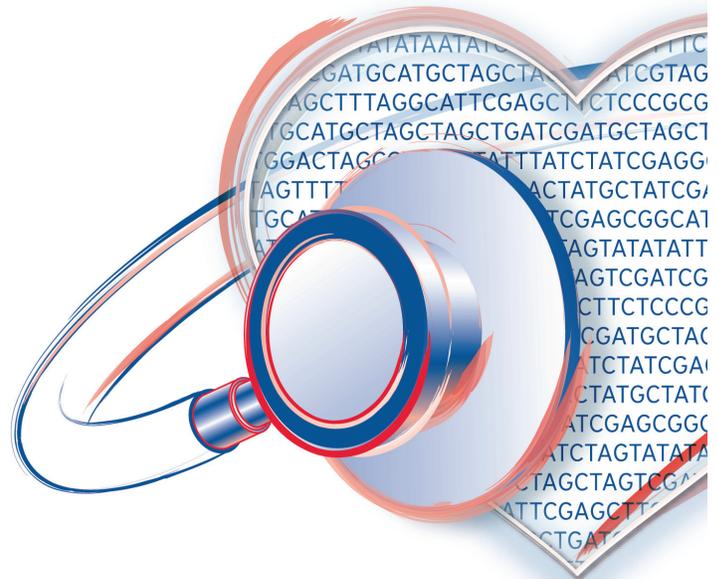
Dear ClinSeq™ Participant,

I hope that you are as pleased as I am to see this fourth edition of our ClinSeq™ newsletter. There is a lot going on with the project and the pace of activity is really picking up. As we reported in the last newsletter, the technology of sequencing is advancing rapidly and we have now completed gene sequencing on over 500 participants in the study. This means that we have genetic sequencing results on many of our participants and we are gearing up to offer to return those results to you, our participants. We will be doing this in novel ways and will be soliciting your input on the best ways to do this – keep a look out for a call or letter in the coming months soliciting this input from you.

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.

As before, we 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:

ClinSeq™ today and tomorrow: what it means for you

Since the start of the ClinSeq™ study we had known that eventually we would be sequencing most or all of your genes. You probably recall this discussion at the time you came to the NIH to enroll in the study. In the 2010 newsletter, we mentioned that we were about to embark on this new and exciting phase of the study, and we did! By the time this 2011 newsletter went to print, more than 500 participants had what we call “exome sequencing”.

What does exome sequencing mean? To understand this we need to discuss genes in more detail. A gene is the basic unit of heredity passed from parent to offspring. A gene is made of DNA and is arranged into different parts – called exons and introns.

“Sequencing the exome of one person generates about 30,000 to 50,000 gene variants that are different from the current human reference sequence.”

Exons are the parts of a gene that code for a protein. Introns are found in between exons, and correspond to parts of a gene that do not code for a protein. Exome sequencing allows us to sequence only the exon portions of the approximately 20,000 genes that make up the human genome. The current belief is that most gene mutations or variations that are highly predictive of disease risk or susceptibility occur in the exons. Additionally, the cost of whole exome sequencing is much less than the cost sequencing all of the DNA. Given that our goal is to enroll over 1,000 participants in ClinSeq™ and the fact that most disease predicting variations are found in exons, we are focusing our efforts on exome sequencing.

So far, we’ve been able to perform whole exome sequencing on over half of the participants’ samples. The speed at which technology is improving and cost is decreasing is surprising, even to us. The NIH Intramural Sequencing Center is able to generate whole exome data for 15-20 samples each week. Despite the tremendous progress in generating data for our participants, the bottleneck is interpreting

this sequencing data! Sequencing the exome of one person generates about 30,000 to 50,000 gene variants that are different from the current human reference sequence. Although most of these variants are unlikely to be involved in disease, a few of them predispose to or cause disease in the person carrying it or their descendants. Making the determination of which variants are implicated in disease is a labor-intensive process that can take a long time. For this reason, it might take months before you hear back from us about variants that we believe are important to your health or the health of your relatives.

You may recall the discussion in your initial visit about the different types of gene variants you could learn from this study.

These include:

- 1) 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 puts you at higher risk to develop colon cancer.
- 2) 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.
- 3) And, gene variants that do not affect your health but that may be important to the health of your descendants. For example, you could learn that you carry a gene variant for cystic fibrosis.

When we find gene variants for you that fall in any of these categories, we will call you. During this conversation, we can give you a general idea about which type of gene variant we have found for you, but we cannot tell you specific information about the variant due to US regulations. If you decide during the course of the phone call, or at a later time, that you want to learn about the variant(s) we have found for you, then we will send a sample to a certified clinical testing laboratory and a report will be generated. In most cases, we will ask you to return to the NIH for a visit with the team, and we will discuss the meaning of the variant(s) with you.

Since our knowledge about genetic variations is constantly changing, the results of whole exome sequencing are analyzed on an ongoing manner in the ClinSeq™ study. This means that you may be called multiple times to discuss the availability of research findings that may be important to your health and/or the health of your relatives. Through this process, we will want

to learn from you how best to return this information – smaller amounts on multiple visits or larger amounts in fewer visits. We may also try new ways to communicate results with you other than an in-person meeting. You may be hearing more about this in the coming months.

About 15 participants have already had the opportunity to make decisions about whether they were interested in learning more about their genetic results. This is currently done, as noted above, in a phone call where we give general information about the finding. Our experience so far shows that these phone calls can be difficult and frustrating since participants have to wait at least a couple of weeks for the confirmation test to take place before they return to the NIH for a consultation. We are sensitive to this issue, and take the input of our participants seriously in considering new ways to accomplish this. Because you are in the cutting-edge of genomic research, it is essential that we gather and document your preferences about learning feedback from whole exome sequencing!

It is important that you understand that the decision to learn or not learn about a genetic variant or group of variants is entirely up to you. You will remain part of the study independent of your decision (“yes” or “no”). There is only one exception to this approach and that is if we find a genetic variant that is implicated in a condition that could pose an immediate threat to your life, and for which there are screening tests or interventions that might minimize your risk. In this case, we will confirm the genetic variant in a clinical testing laboratory, and invite you to come in to discuss your result. We feel that our duty to warn you of such a finding comes first, and make the assumption that most or all of our participants would appreciate being told such result so that they can take the necessary precautions.

Your continuing participation in ClinSeq™ as we move forward into this very exciting phase of the project is vital to the goals of the study! Please stay tuned and let us know if your contact information changes.

What happens with the genetic results if a participant passes away?

In the past year it has come to our attention that a few of our participants have passed away. These are sad and unexpected news for us, and we express our sincere sympathy to the families of these individuals.



In the face of these events, we have worked with the NIH Clinical Bioethics department to determine if and how we will disclose genetic variant results in such cases. The decision is to first communicate with the executor of the estate or the next of kin to discuss the study and the family's preferences with regards to learning or not learning genetic results for their deceased relative. In essence, we will rely on the executor of the estate to be a liaison to other family members, and to indicate to us the preferences of the family. If the desire of the family, as relayed to us by the executor, is to learn individual genotype results, we will return genetic variants known to be disease causing or predisposing, as they become available. The finding of such results could take months or years, and we ask that the executor stay in touch with us and let us know of any changes to his/her contact information.

We urge you, current participants, to discuss your participation in ClinSeq™ with your family members. Please explain to them that they would have an opportunity to learn about your genetic variants, which would be of potential significance to them, in the event you were to pass away. Please also let them know that we count on the family members to reach out to us in these events. The study main phone line is (301) 443-6160, and email is clinseq@mail.nih.gov

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.

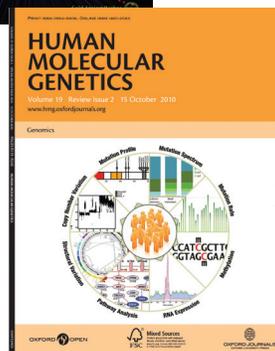
ClinSeq™ Scientific Updates

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

Several publications have highlighted the work being done in the ClinSeq™ project. These include two papers that describe some of the pros and cons of the technical methods that we are using (Teer and Mullikin, Human Molecular Genetics, volume 19, page R145, 2010 and Teer et al, Genome Research, Volume 20, page 1420, 2010). Also, it is becoming clear that your samples are extremely valuable

to researchers working on rare genetic diseases. Because these diseases are quite rare, other researchers can use the absence of variations in ClinSeq™ samples to show that the presence of mutations in their patients with rare diseases is important. An example of this is a paper by McLaughlin et al, American Journal of Human Genetics, volume 87, page 560, 2010). I am sure that we will have even more papers in our next newsletter, as the use of ClinSeq™ data is increasing rapidly.



Presentations

In May of 2011, Dr. Les Biesecker (ClinSeq™ Principal Investigator) and Ms. Flavia Facio (ClinSeq™ Lead Associate Investigator) gave a presentation through a webinar entitled "The ClinSeq™ Project: An Approach to Clinical Genomics Research". This webinar was sponsored by a company called Illumina, Inc. and can be found at www.illumina.com/events/webinars.ilmn

Dr. Biesecker also presented ClinSeq™ at the University of Maryland program for genomic medicine in May, at the National Meeting of the Society for Clinical and Translational Research in April, at the annual meeting of the Massachusetts Biotechnology Council meeting in March, and to the Royal Netherlands Academy of Sciences symposium in March.

We recently completed a study about your motivations to seek your own genomic

information through a study like ClinSeq™. You may recall that when you enrolled, we asked you a number of structured and open-ended questions about this. This is a cutting edge approach to personalized medicine and many researchers are interested to hear your perspective and expectations. For this reason, Ms. Flavia Facio had the opportunity to present these results at three conferences – the National Society of Genetic Counselors Annual Educational Conference in 2010, the National Conference on Genomics and Public Health in 2010, and the Ethical, Legal, and Social Implications of Genomics Congress in 2011. These results will be appearing soon in a scientific journal and we will alert you to that in a future newsletter.

Current Enrollment

*By Haley Eidem, BS
ClinSeq™ Research Assistant*

Our current enrollment is close to 900 individuals. At this time we are recruiting **only** participants with a history of coronary artery disease. This means individuals who have had 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. We still need more than 100 participants who meet these criteria.

If you have friends or spouses who are interested in participating and meet the criteria outlined above, please ask them to call Haley Eidem, ClinSeq™ Research Assistant at (301) 443-6160.



Farewell to ClinSeq™ participants from Flavia Facio

Dear ClinSeq™ Participants,

It is with much appreciation for your contribution to this study, that I bid you farewell. After being involved with this wonderful project from its inception, I've decided to leave so that I can devote more time to my daughter. As I reflect on the ClinSeq™ project, I can find many reasons for its successful trajectory including the tenacity of the principal investigator (Dr. Les Biesecker), the dedication of the research team, the talent of our many collaborators, and the enthusiasm of all of you – our research participants. Without your curiosity, participation, and contribution, ClinSeq™ would not be where it is today. I take this opportunity to thank each one of you not only for enrolling in the study, but also for sharing with me your family histories and your reasons for seeking more information about your genetic make- up. Although I only spent 60 to 90 minutes with most of you, I feel privileged to have heard your stories and motivations. Thank you!



Sincerely,

Flavia Malheiro Facio

Flavia M. Facio, MS, CGC
Associate Investigator
ClinSeq™ Study