The ClinSeq® Newsletter

Volume 6, Summer 2013

Inside this issue:

Dear ClinSeq® Participant,

The ClinSeq® study is beginning to have a real impact on the practice of medicine. With your continued support, we have pioneered a way to return genome sequencing results for serious health problems. We first wrote about our approach in a paper we published on the return of results related to cancer risks. We hope to soon have similar papers published on results related to a serious surgical complication called malignant hyperthermia and heart rhythm/muscle problems. Our experience allowed me to co-chair a working group of the American College of Medical Genetics and Genomics on returning results from sequencing. This group put together a new policy that guides the analysis of genetic sequences for all patients who have testing through their doctor. The policy says that all sequences should be analyzed for a certain list of genetic changes that are known to cause health problems regardless of the reason the sequence was originally ordered. This list spans 57 genes for 24 disorders. In general, the list includes conditions that an individual or family would get medical benefit from knowing about, and genes that have been clearly linked to those health conditions. If any of the disease-causing changes is found in a person, those results would be shared with their doctor, and in early all cases are recommended for returned to the patient.

This policy is part of a sea change in medicine. We can now see that genomics is entering the mainstream of medicine. Genomic testing can start to be treated like other medical tests, instead of something that is special. This change in policy has not been without debate. Regardless of any conflict, what is clear is that our ClinSeq® participants were a major part of that change. Your willingness to join this study, allow us to explore your genomes, and share your experiences with receiving results have supported this new approach to medicine. I hope that you all share my excitement and are proud of your participation in this study. It is not every day that a person has the chance to change how medicine is practiced.

We look forward to continuing to work with you on this important project!

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

ClinSeq® Research: Focus Groups on Return of Genetic Results

In spring 2012, we held a series of focus groups with several ClinSeq® participants in an effort to better understand how they intend to use their genetic results, and their practical preferences for getting those genetic results back. In total, 39 ClinSeq® patients, divided into six focus groups participated in 90-minute guided discussions. The individuals in one of the groups had received at least one genetic result from ClinSeq®; the rest had not yet received a result. Researchers analyzed these discussions to identify recurring themes and attitudes across groups. We recently submitted a paper entitled, "Preferences for results delivery from Whole Exome Sequencing/Whole Genome Sequencing," which explores the results of these focus groups, to Genetics in Medicine. Here, we summarize the findings of the paper.

Participants expressed a general desire to learn most of their results, though some admitted to mixed feelings about learning results for conditions without clear treatments or preventions. They identified being able to take steps to prevent disease, future/financial planning, alerting family members, and contributing to medical science as some of the chief benefits conveyed by genetic sequence information. For example, one participant said, "[A result for an untreatable condition] is something I really want to know about because that's a different life expectancy and a different plan for your life, very much." When asked about the deeper value of the information, many participants said they anticipated feeling an increased sense of control over their health and future and acquiring "peace of mind." Some participants also expressed drawbacks to learning genetic results, such as one participant who said, "I'm still not really sure if I want to know all that's out there. I'm still kind of on the fence." The concerns about getting results that were most commonly expressed were that genetic information might be a source of distress or fear, or might be difficult to share with family members, especially if it pertained to incurable or untreatable conditions.

We also asked the focus group participants for their reactions

"I'm still not really sure if I want to know all that's out there. I'm still kind of on the fence."
-Focus Group Participant

to our intended procedure for sharing their genetic results. This procedure would offer results to our participants as soon as they are generated. However, because we query one gene at a time across all participants (instead of querying one individual's entire genome at a time), a given participant will receive his or her results over an extended period of time.

Focus group participants generally liked that this method both minimized the time delay between generating their results and delivering them and broke their potentially large set of results into manageable bites. They also expressed support for receiving the results through multiple forms of media; they especially liked having a meeting where they could ask questions and a written report that they could take to their physician.

"[A result for an untreatable condition] is something I really want to know about because that's a different life expectancy and a different plan for your life, very much."
- Focus Group Participant

Understanding the expectations and preferences of patients who undergo whole genome sequencing will become increasingly important as genome sequencing becomes more prevalent in routine care. Our results emphasize the need for healthcare professionals to develop a framework for results return that makes results comprehensible and manageable for patients, gives them choices about what to learn, limits the delay between finding results and reporting them, and includes optional psychosocial support. We would like to thank all of our focus group participants for taking the time to participate in this important research, and for sharing their thoughts with us.

Return of Results Update: How we Analyze and Share Your Results

As we have for the past several editions of this newsletter, we are including a table of the genetic results that we have returned to ClinSeq® participants so far here. While 45 people in the ClinSeq® cohort have received at least one genetic testing result, the majority of our participants have yet to hear from us with their results. This wait time is because the system that we use to analyze your genes is designed so that we can learn the maximum amount of information, but is quite time consuming. Using this system, we do not look at all of your genes start to finish, but rather, we look at one gene at a time across all of the participants in our study. This allows us to answer specific research questions as we review your genetic information. Of course the goal is to fully analyze most of your genes by the end of the project.

So what does it mean to analyze your genes? First, we extract your genes (or DNA) from some of the blood you gave when you joined the study. Those genes are then sent to be

Results Returned to ClinSeq® Participants

Gene with Variation	Number of Participants with Results Returned	Health Implications
LDLR or APOB	14	High cholesterol at a young age that may require medication
KCNE1, KCNH2, SCN3B, MYH7, PLN , MYBPC3	11	Variants associated with heart problems, including abnormalities in heart rhythm and structure
BRCA1 or BRCA2	9	Increased risk for cancers including: breast, ovarian, prostate and others
PMP22	3	Numbness or weakness in the limbs
RYR1	2	Malignant hyperthermia, which causes a fast rise in body temperature and severe muscle contractions after a person is given anesthesia
CCR5Delta32	1	Decreased susceptibility to HIV infection, possibly increase susceptibility to West Nile Virus
LRRK2	1	Predispositi on to Parkinson Disease
MSH6	1	Increased risk for cancers including: colon, endometrial, ovarian, stomach and others
PKD1	1	Polycystic kidney disease, which causes cysts in the kidney that can lead to high blood pressure and kidney failure
PPARG	1	Predisposition to abnormal patterns of muscle and fat distribution in the body, abnormal lab values, such as high triglycerides
SDHC	1	Increased chances for benign tumors of the nervous system and gastrointestinal tumors

sequenced in a laboratory. If you think of your genes as a set of instructions that tell your body how to grow, develop and function, the sequencing gives us a written version of those instructions. Then, your gene sequence is compared with a reference or standard sequence to look for differences between your sequence and the standard.

If we look at the data for everyone in ClinSeq® as of this report, there are many differences between the sequence of someone in our study and the reference. Next we have to look at these differences to find out which ones might have an impact on your health. In order to do this, we look to see if other researchers have reported on each of these differences in the past. We begin by looking at online databases to see if the difference has been seen before and whether it caused health problems. Then, we read scientific papers to learn more about the research that was done in the past. In ClinSeq® we report variants understood to have a potential effect on health either for the participant or their children. Across your entire genetic sequence, this process will begin with thousands of variants, and will be reduced down to a handful of results that could impact your health (or your children's health), which we will share with you

The most important thing to understand about the results from ClinSeq® is that you cannot make any conclusions based on the lack of information.

Knowing that some people in our study have received results back, such as finding out about an increased risk for cancer, the next question might be what it means if you did not receive a result? The most important thing to understand about the results from ClinSeq® is that you cannot make any conclusions based on the lack of information. This is true for a variety of reasons. First, it could be that your genes have not been sequenced yet. Even if your genes have been sequenced, the completeness of the data varies from individual to individual and real variants can be missed by the analysis. Finally, even though gene sequencing is allowing us to learn more about an individual's genes, we still have much more to learn. We understand new things every day about genetic variation and how it relates to disease so a variant without a known clinical significance today may have one tomorrow.

In short, you can expect that you will receive a handful of genetic results that are important to your health returned to you as we find them in the coming months and years. We encourage you to continue following our reports of the results we are returning to other participants in this newsletter so that you can be more aware of the range of results you might receive in the future, and can begin to think about what information you want to receive and what you will do with that information.

Smithsonian's Genome Exhibit

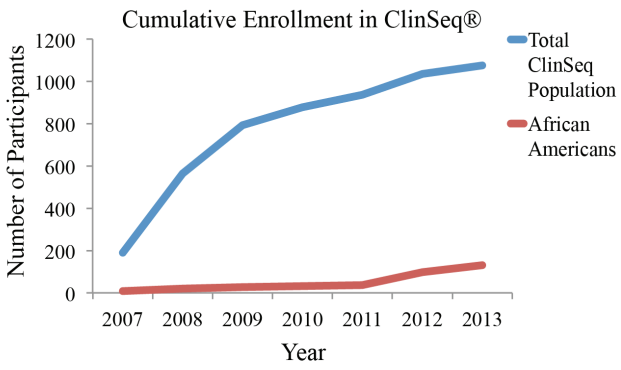
GENOME UNLOCKING LIFE'S CODE

In April of 2003, the Human Genome Project succeeded in sequencing the entire human genome. This year marks the 10-year anniversary of this achievement, and to celebrate, the National Human Genome Research Institute (NHGRI) and Smithsonian's National Museum of Natural History (NMNH) are partnering to create a temporary exhibit entitled "Genome: Unlocking Life's Code". The exhibit will have information on recent advances in genomics, personalized medicine, genetic testing, cancer, diversity, and evolution. There will also be segments of the exhibit devoted to the ethical and social implications of these advances in technology, such as genetic information and privacy or the impacts of genetic testing on individuals. These topics will serve as an interactive way for people of all ages to learn how their genetic code affects not only their own health, but also the health of their families. Additionally, there will be a hands-on activity center with fun crafts and activities to encourage both kids and adults to think about genetics in new and different ways. The exhibit is scheduled to open on June 14, 2013 on the 2nd floor of the NMNH in Washington DC. For more information, you can go to the NMNH website (www.mnh.si.edu) and look under "Exhibitions".

Enrollment Update

There are currently over 1,050 participants enrolled in the ClinSeq® study, which is an increase of over 50 participants since our last newsletter. As we mentioned in our last newsletter, we are working to enroll a total of 500 African Americans into our project. As of the time of publication, we have enrolled approximately 130 African Americans enrolled, with another 40 scheduled for visits in the coming months. We owe much of our success to those of you who have spread the word about our project to others, and for that we are very grateful. Thank you for bringing your enthusiasm to the ClinSeq® project!

We are continuing to recruit African American participants, as well as people of all races who have heart disease. If you know someone who may be interested in ClinSeq® or who is hosting a community event where we could recruit, please contact Sandra at 301-402-0020.



Featured Associate Investigator: David Ng, MD

1. ***What is your position at NIH?***
   I am a clinical specialty consultant and associate investigator with the ClinSeq® study. My role in ClinSeq® is to discover novel disease-susceptibility genes, provide clinical evaluations, identify medically relevant gene variants and to return genetic results to research participants in a clinically sensitive manner.

2. ***What motivated you to become involved in the ClinSeq™ Study?***
   As an Internist and Clinical Geneticist, the ClinSeq® study allows me to incorporate an individual's genomic data into a customized plan for health screening, preventative medicine and eventually for individualized treatment. This "personalized medicine" is no longer a hypothetical possibility, but it has become reality as we partner with our participants to explore the clinical relevance of their genetic profile. I feel fortunate to be a part of ClinSeq® as we bring exciting discoveries from the bench to the clinic with the hope of improving health care for each of our participants.

3. ***What are your other research interests?***
   I have an interest in studying families with genetic susceptibility to disease. The willingness and cooperation of entire families to be clinically evaluated and to have their DNA analyzed, enables us to do family studies. Family studies allow geneticists like myself to locate causative genes by looking for stretches of DNA that are shared by affected family members. Partnering with research participants and their relatives has been most gratifying for me and has made possible my identification of the causative gene for Lenz microphthalmia (an inherited eye condition) and familial chordoma (a rare cancer susceptibility syndrome). In the future, I hope to continue investigating the genetic susceptibilities to more common diseases in collaboration with our multidisciplinary ClinSeq® research team and study participants.

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.