The ClinSeq® Newsletter

Volume 8, Winter 2014

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Dear ClinSeq® Participant,

Greetings to you from the ClinSeq® study! We are pleased to update you with a lot of news from the study. Our work on so-called incidental findings continues to receive much attention and is really beginning to have an effect on clinical practice and policies for return of results from other research studies. As we have previously described to you, we have searched ClinSeq® sequence files for mutations that lead to inherited cancer susceptibility – we have now identified 12 of our ClinSeq® participants (1.2%) have a gene mutation that leads to a markedly increased risk of cancer. Upon returning these results to our participants, we have had a range of reactions, but most gratifying is that in one case, this return of results led to pre-emptive surgery that likely saved the life of a relative of a ClinSeq® participant. We have extended this approach to non-myocardial infarction heart disease and inherited heart rhythm disorders and identified another six participants who have a potentially serious (but in most cases treatable) disorder that causes overgrowth of the heart muscle or abnormal heart rhythms. Finally, we have studied a rare disorder called malignant hyperthermia susceptibility and identified several participants with this trait, which is a life-threatening reaction to anesthetics. When recognized and treated effectively, this condition can be avoided, again leading to major benefits for these participants. So although our numbers of returned results are not large, we started with the most serious, life threatening disorders and are now expanding that effort into less severe conditions.

The next big phase of the study will be to return carrier risk results to participants. These are disorders that are unlikely to affect you, but may be a risk for your descendants. This will be done in a way that allows us to learn about the best ways to return results to you and will hopefully make our health care system more efficient.

Thank you again for your participation – we remain terribly grateful to you and always solicit your advice and feedback.

Leslie G. 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.

## Return of Results Update

Though ClinSeq® began as a study of genes related to heart disease, it has since expanded well beyond that, and currently, we are looking through your genetic sequence for changes related to *any* health condition. Many participants who have received their genetic testing results have reported feeling surprised that their results did not pertain to heart disease. In addition, several of the people who have received results so far had no family history of the condition their result pertains to.

In order to prepare for receiving your results, we encourage you to review the list of results that we have returned so far (below) and to consider whether you want to receive similar results if they are offered to you in the future. It may help to imagine what it would be like to actually receive the result, as well as what you would do with the information and how it might impact you in the long-term. This exercise can help you clarify your values, make choices about the results you want to receive in the future, and help you prepare for receiving unexpected results.

Thus far, only a small number of ClinSeq® participants have received results from us, but we plan to begin returning results to participants in much larger numbers in the coming year (see "Update on ClinSeq® Social Science Studies" for more information).

## ClinSeq® Social Science Studies

As many of you know, the ClinSeq® study is designed to learn how to best implement the kind of large-scale genetic sequencing that you will all receive. While much of our research related to that aim takes place in the laboratory, and focuses on how to interpret your genetic sequence data, we are also doing what is known as social science research. We often refer to social science as the "human side" of our research because it focuses on how you relate to your participation in this study.

Thanks to ClinSeq® participants, we have been successful in conducting a series of social science studies to assess educational, psychological and practical aspects of learning

### Genetic Results Returned to ClinSeq® Participants

| Gene with Variation | Number of Participants with Results Returned | Health Implications |
|---|---|---|
| LDLR or APOB | 13 | High cholesterol at a young age that may require medication |
| KCNE1, KCNH2, SCN3B, MYH7, PLN | 9 | Variants associated with heart problems, including abnormalities in heart rhythm and structure |
| BRCA1 or BRCA2 | 8 | Increased risk for cancers including: breast, ovarian, prostate and others |
| RYR1 | 4 | Malignant hyperthermia, which causes a fast rise in body temperature and severe muscle contractions after a person is given anesthesia |
| PMP22 | 2 | Numbness or weakness in the limbs |
| LRRK2 | 2 | Susceptibility to Parkinson's disease |
| PKD1 | 1 | Polycystic kidney disease, which causes cysts in the kidney that can lead to high blood pressure and kidney failure |
| CCR5Delta32 | 1 | Decreased susceptibility to HIV infection, possibly increase susceptibility to West Nile Virus |
| PPARG | 1 | Predisposition to abnormal patterns of muscle and fat distribution in the body, abnormal lab values, such as high triglycerides |
| SDHC | 1 | Increased risk for cancers including: pheochromocytomas, paragangliomas and gastrointestinal |
| MSH6 | 1 | Increased risk for cancers including: colon, endometrial, stomach and others |
| *FLCN* | *2* | *Susceptibility to Birt-Hogg-Dube syndrome, which is a condition characterized by benign skin tumors, cancerous or non-cancerous kidney tumors and lung cysts* |
| *SGCE* | *1* | *Predisposition to myoclonus-dystonia, which is a condition that causes quick, involuntary muscle jerking or twitching and muscle cramping, such as writer's cramp* |
| *PROS1* | *1* | *Susceptibility to developing abnormal blood clots* |
| *MTND4* | *1* | *Susceptibility to an inherited form of vision loss* |

Results that are italicized have been returned in the last 6 months, and, therefore, were not included in this table for the last edition of the newsletter.

genetic results from this study. Many of you likely recall responding to a survey during your initial visit on your motivations for participating, or to a survey about the types of results you may want to learn from the study. Both of these surveys led to publications that have characterized ClinSeq® participants as highly motivated to learn many types of results from their sequencing. Last summer, a small number of you participated in focus groups about preferences for return of results, which were described in the Summer 2013 newsletter. survey on their perceptions and preferences about receiving results, as well as personality traits and other characteristics. Though the survey is quite long, it gives us critical information on the ClinSeq® population as a whole, and serves as the foundation for many planned research studies and publications. More than half of all eligible participants completed this survey in the last year, and the survey remains open to those who still want to participate.

***"Our next big social science project will be a randomized control trial of four different methods of returning results to participants. The goal of the study is to determine whether one mode of delivering results is more effective and acceptable to participants than another."***

Our next big social science project will be a randomized control trial of four different methods of returning results to participants. The goal of the study is to determine whether one mode of delivering results is more effective and acceptable to participants than another. This study will begin in early January and is expected to take one year to complete. We will begin by recruiting ClinSeq® participants who have completed their baseline survey, and hope to enroll at least 400 participants in the project. All of the results returned through this project will be inherited in an autosomal recessive pattern, and will not be expected to affect your health, but could be important for your family members. We often refer to social science as the "human side" of our research because it focuses on *your* thoughts and feelings about your results and the study.

*If you have not yet completed the baseline survey and would like to do so, please contact our research assistant, Willie, at (301) 443-6160. The survey can be completed electronically or on paper.*

## Cardiac Disease Genetic Variants in ClinSeq®

One goal of the ClinSeq® study is to identify gene variants (or changes) that lead to disease susceptibility. We often work through these genetic variants one condition at a time. This allows us to develop expertise with a specific gene or set of genes, and is an efficient way to review genetic changes. Recently, Dr. David Ng, who is one of the geneticists working on ClinSeq,® analyzed the genetic data to look for changes in genes associated with two heart conditions known as arrhythmias and cardiomyopathies.

Cardiac arrhythmias are a group of conditions that cause changes to the heart's regular rhythm. Someone with an arrhythmia could experience symptoms such as heart palpitations, rapid heart beat, fainting, and, in some cases, sudden death. Genetic susceptibility to these conditions is relatively uncommon, affecting 1/3,000 to 1/2000 people.

Cardiomyopathies are structural abnormalities of the heart. In this condition, the heart muscle cannot pump blood as efficiently as the body needs. This leads to symptoms including tiredness, shortness of breath, chest pain, heart palpitations and fainting. People with cardiomyopathy are also at risk for sudden death. Approximately 1/500 people have cardiomyopathy due to a genetic susceptibility.

Dr. Ng's project analyzed 870 ClinSeq® participants to look for variants in more than 60 genes that are related to either arrhythmia or cardiomyopathy. To determine whether each variant could impact someone's health, we ask 3 key questions. First, we need to know how whether the quality of the sequencing test is good for the variant? If not, we disregard the result and do not consider returning it to you. If the quality is good, we then ask how common the variant is in our study and other genetic databases? If the variant is very common, it's unlikely to cause these rare health conditions, so we do not return those to you, either. If the variant is not too common, we then ask how much data there is to suggest that the variant is associated with arrhythmia or cardiomyopathy? For some variants, there is research showing that they are not linked to these conditions—those variants would not be returned to you. Other variants have limited or no information to link them to these conditions. At this time we have not returned these variants to participants. This leaves us with those few changes that are known or highly likely to cause arrhythmia or cardiomyopathy, which we did return to participants if they wanted to receive them.

As you can see, Dr. Ng found 6 genetic variants that had evidence of causing increased risk for arrhythmia or cardiomyopathy. Four of these changes were reported to increase the risk for cardiomyopathy. All four of those participants received an echocardiogram (ECHO), which uses sound waves to look at the structure of the heart. Three out of the four participants had changes in the structure of their hearts on their ECHOs. The two remaining variants were associated with an arrhythmia called Long-QT syndrome. Fortunately, both people had no detectable signs of this condition when they were tested.

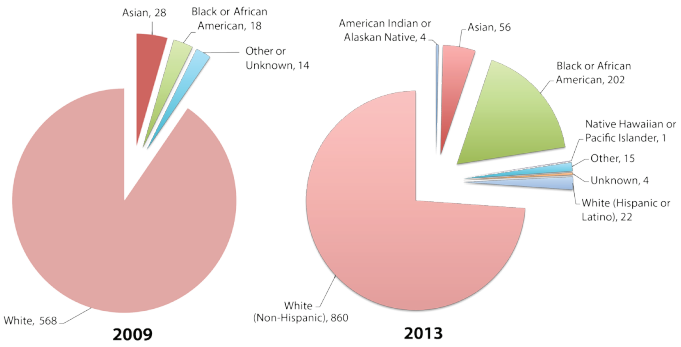
This study makes several important contributions to the research on genetic sequencing. First, it provides data on the yield of an analysis that aimed to identify genetic variants that might be returned to participants. There is currently a great deal of debate about whether it is necessary and feasible to undertake these analyses for research participants who receive genomic sequencing, in part because this is such a time-consuming process for researchers. As our data shows, the vast majority of variants that are reviewed do not have clear impacts on health; however, the impacts on participants who do receive results can be quite significant. Second, since our participants were not recruited based on a history or cardiomyopathy or arrhythmia, these findings show that healthy people in the general population may have genetic changes that put them at risk for these conditions. Finally, this data points to a possible change in the way medicine could be practiced in the future, with more focus on identifying and monitoring people who may have a genetic susceptibility before they show symptoms.

It is important to remember that you should not make any conclusions about your risk to develop any of these conditions if you have not received a result from us. It may be that your genes have not yet been sequenced, so you could not have received a result from us. Even if your genes have been sequenced, the completeness of the sequence data varies from person to person – so real variants can be missed by our analysis. The most important thing to understand about the results from ClinSeq® is that you cannot make any conclusions based on a lack of information or results.

*These findings were presented at the American Society of Human Genetics' Annual Meeting in 2012 and were recently published in the journal Circulation Cardiovascular Genetics.*

## Enrollment Update

ClinSeq® enrollment has grown steadily this season, in a large part due to the efforts of superlative recruitment coordinator Sandra Epps. Sandra has been recruiting participants using her connections with local community leaders, through church groups, and also by a massive grass roots-style, word-of-mouth campaign.




Additional boons to enrollment have aided Sandra on her campaign to fill ClinSeq®'s ranks with willing and able participants. Dr. Biesecker earned the project some positive publicity earlier this year, appearing in the New York Times to discuss the genetics of early onset heart disease – this in turn brought in wave on wave of enthusiastic participants from across the nation.

Finally, and perhaps most importantly, the body of ClinSeq® participants themselves contributed greatly to our cause through your positive reviews and motivated recruitment of friends and family. We are grateful for your efforts!

Though the combined strategies listed above, we have made great strides in ClinSeq® enrollment, and as it stands, we have filled almost all of the slots in our non-African American cohort. We have also experienced some success in enhancing the racial diversity of study participants by starting to recruit a group of 500 African American participants. The graphs below show the racial make-up of ClinSeq® participants in 2009 versus present day.

We have enrolled almost 200 participants in our African American cohort, and hope to enroll another 300 in the coming years. We plan to continue to recruit African American participants into the foreseeable future, and we appreciate your help in spreading the word. If you would like to refer a potential participant, or know of an upcoming community gathering that we could attend for recruitment, please contact Sandra Epps directly at (301) 402-0020.

## Featured Associate Investigator: Barbara Biesecker

***1. What is your position at NIH?***

I am an Associate Investigator in the Social & Behavioral Research Branch at the National Institutes of Health and Director of the Johns Hopkins University/NHGRI Genetic Counseling Training Program.

***2. What motivated you to become involved with the ClinSeq® study?***

In the early days of ClinSeq®, I co-designed the studies looking at preferences for information with Flavia Facio and had the opportunity to ask important questions about the use of sequence information. Currently I am interested in communicating sources of uncertainty that cloak sequence information. And the ClinSeq® team is great to work with.

***3. What are your other research interests?***

Other research interests of mine are decision-making, consenting to sequencing and adapting to life with a genetic condition or risk.