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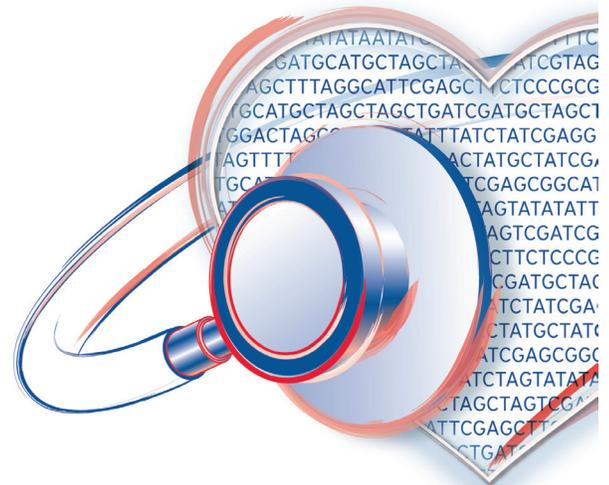
Dear ClinSeq® Participant,

ClinSeq® continues to blaze trails and make headway in the field of genomics. Members of our team have given a number of presentations and published scientific papers since our last newsletter. These include invited talks at leading universities and research institutes internationally. As is described later in the newsletter, Katie Lewis, Jennifer Johnston and their support teams have undertaken a huge effort to identify and return to participants their carrier results. We are doing this as part of an experiment to try cutting edge approaches to results return, not just perpetuating the same old medical models without evidence. This is a way that ClinSeq® and you as participants may actually change medical practice. We are also making big strides in the behavioral aspects of ClinSeq® by using the data that many of you contributed to in the baseline survey that we sent out a few months back – this provides a foundation for a number of current and future studies.

We are also launching a new pharmacogenetic research study within ClinSeq®. There is a great deal of excitement in the field regarding the use of genomic data to support individualized medication selection and dosage. Dr. David Ng is launching a study where we will identify ClinSeq® participants who have variants in genes that may affect how patients respond to statin drugs, which are used to lower cholesterol levels. Our experiment is to test the effect of rare variants in two genes and compare those effects to the commonly tested for variants. This is a way that ClinSeq® sequencing data can be used creatively to answer important scientific questions and provide more ways to use genomic data for health care.



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](mailto: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. Currently we are looking through your genetic sequence for variants 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.

Thus far, just over 200 participants have received results from us. We recently began a project to return a subset of results to at least 400 participants in our project. The project aims to learn whether one way of sharing results is more effective than another. All of the results returned through this project are not expected to affect the participant's health, but may be important for future generations of their family. We look forward to offering an opportunity to participate, and to sharing the results with you when they become available.

## The Importance of Privacy in Genome Research

During their initial visit to the NIH, every ClinSeq® participant gets a chance to hear about what is involved in the study and ask any questions they have about the project. This process is known as informed consent. During 2011 and 2012, we worked on a research project about your views on privacy and data sharing issues related to informed consent. This project was led by Leila Jamal, a graduate student in the Johns Hopkins University/ National Human Genome Research Institute's genetic counseling training program, as part of her Master's thesis. Ms. Jamal recently published a paper in the European Journal of Human Genetics that reports the findings of her study. Here, we describe her findings.

Participants were recruited from both ClinSeq® and the Whole Genome Medical Sequencing (WGMS) study. The WGMS study aims to find the genetic causes of rare diseases and has a similar consent process to ClinSeq®. Participants completed an interview with Ms. Jamal over the phone, which included questions

Gene with Variation	Number of Participants with Results Returned	Health Implications
<i>Various</i>	125	Conditions that are inherited in a specific pattern such that they do not affect your health, but could affect future generations.
<b>LDLR or APOB</b>	13	High cholesterol at a young age that may require medication
<b>KCNE1, KCNH2, SCN3B, MYH7, PLN, PKP2</b>	10	Variants associated with heart problems, including abnormalities in heart rhythm and structure
<b>BRCA1, BRCA2, SDHC, MSH6, PMS2</b>	11	Increased risk for various types of cancer
<b>RYR1</b>	4	Malignant hyperthermia, which causes a fast rise in body temperature and severe muscle contractions after a person is given anesthesia
<b>PMP22</b>	2	Numbness or weakness in the limbs
<b>LRRK2</b>	2	Susceptibility to Parkinson's disease
<b>PKD1</b>	1	Polycystic kidney disease, which causes cysts in the kidney that can lead to high blood pressure and kidney failure
<b>CCR5Delta32</b>	1	Decreased susceptibility to HIV infection, possibly increase susceptibility to West Nile Virus
<b>PPARG</b>	1	Predisposition to abnormal patterns of muscle and fat distribution in the body, abnormal lab values, such as high triglycerides
<b>FLCN</b>	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
<b>SGCE</b>	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
<b>PROS1</b>	1	Susceptibility to developing abnormal blood clots
<b>MTND4</b>	1	Susceptibility to an inherited form of vision loss
<b>SLC4A1</b>	1	<i>An problem with red blood cells that can lead to anemia.</i>

*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.*



about what they remembered from their informed consent, their preferences for data sharing, and thoughts on privacy. A total of 30 participants were interviewed for the project.

The researchers found two common themes from the interviews. First, they found that most people want control over how their data is used by others. Some participants said this control helps reduce their concerns that employers or insurance companies may use their genetic testing results against them. Other participants said that the desire for control came from the uncertain future of genomic research. One participant said:

*I just believe that people have a right to control their information. It doesn't matter whether anything bad would happen.*

Second, participants had differing views on how often they wanted to communicate with the study team about the use of their samples. Some participants preferred to talk about this one time at the beginning of the study, others said they would prefer to be re-contacted whenever their samples or information are being used for a study. Overall, there seemed to be a large desire for both a promise of privacy and ongoing communication.

Most participants made it clear that they were not too worried about losing privacy as a result of their study participation because of their trust for the National Institutes of Health (NIH). Participants seemed to have this trust based on faith in NIH researchers, the NIH as an institution, and the policy the NIH holds about the de-identification of genomic data. Overall, participants had a strong desire to see science move forward, and felt that the benefits of joining this type of study outweighed the potential risks of personal data sharing.

This project has provided us a chance to explore why people involved in genomic research care about privacy and data sharing. With this knowledge, we hope to shape the way that we do research on your genomic data so that we ensure that genetic information is both available and also meets privacy standards.

We would like to thank all of our participants whose continued support and activity in our ancillary studies has enabled us to continue our research. We value your participation and hope to be able to continue to work with you on future projects.

### **How do research participants think about 'uncertainty' in genome sequencing?**

The scope of uncertainty in genome sequencing has no rival in health-care. This uncertainty is fueled by the newness of the technology, the lack of established ways to interpret results and assign disease risk, the wide scope of results, and other factors. Researchers are interested in knowing more about how participants think about uncertainty.

A group of ClinSeq® researchers explored this topic using a series of focus groups in spring 2012. These focus groups were done with ClinSeq® participants in order to better understand their

thoughts about the results they might get from our project. In total, thirty-nine ClinSeq® patients, divided into six groups, took part in 90-minute discussions. The people in one of the groups had received at least one genetic result from the study; the other participants had not yet received any results.

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***"If it's that ambiguous I would still want to know, but I wouldn't necessarily change my lifestyle, or be upset or bothered by it."***

**- Focus Group 6, Participant 1**

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During the groups, participants were asked to consider the statement, "There will be a significant degree of uncertainty associated with the majority of sequence information that you may receive". They were then asked to write answers to two questions: (i) "What does this statement mean to you?" and (ii) "How do you feel about this statement?" The participants then discussed their responses. Researchers have analyzed these discussions to look for themes across group members. They recently published a paper in the journal *Genetics in Medicine*. Here, we review the findings of the paper.

Most participants said that uncertainty was just a part of genome information. Most said the uncertainty of sequencing information means it is "changing, fluid, developing, or ground breaking." One participant said:

*I think it's pretty clear with any scientific endeavor that our ability to comprehend what we're studying changes day-to-day. ... There is a learning curve that is uncertain. We don't know when we're going to know what we know. Of course it's going to be uncertain*

These responses also seemed to lead to optimism that better information might be available in the future. People also said they would want to receive their results even if they were uncertain.

Fewer participants described the uncertainty as "questionable, less accurate, limited, or poorly understood." These ideas seemed to weaken participants' faith in genome results. They were also related to a pessimistic view of future information. One participant noted "more questions may be raised by the research than answers" and another that she may therefore "not know what to do with the information."

Our findings suggest that ideas about uncertainty are related to basic beliefs about how much can be known about genetics. These beliefs may lead to expectations for an individual's genetic testing results. If healthcare providers can give people realistic ideas about what to expect from genome sequencing, it may help avoid negative responses to uncertainty. 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.

## Genetic Research on Malignant Hyperthermia Susceptibility

Several ClinSeq® participants have received a genetic testing result about risk for a condition called malignant hyperthermia (MH). MH is a reaction to some types of anesthesia. Commander Steve Gonsalves has been doing a thesis project on the topic of MH to learn more about the genetics and the diagnosis of this condition. Commander Gonsalves has presented his research at many meetings and published some of his findings in the November 2013 issue of the journal *Anesthesiology*.

MH is a reaction to anesthesia, which is commonly given before surgeries or dental work. Symptoms of MH can include muscle stiffness, rapid heart rate, and fever. In rare and serious cases, MH can lead to sudden death. People who survive MH may be left with symptoms, including kidney failure, muscle damage, or problems with other organs.

Genetic studies have shown that about 1/2,000 people have a genetic variant that makes them susceptible to MH. These variants most often occur in a gene called *RYR1*. Having a genetic variant in the *RYR1* gene means that someone has MH susceptibility (MHS), or that they are at risk to develop MH. Many people with *RYR1* gene variants never develop MH, even if they are given anesthesia. The diagnosis of MH is based upon personal and family history and genetic testing results. However, in some cases, a muscle biopsy may be needed to confirm the diagnosis. This has led to a growing interest in finding a test that confirms MHS that will not be invasive or painful.

Commander Gonsalves' study of MHS has two parts. The first phase involved reviewing the genetic data of ClinSeq® participants for variants that may be associated with MHS. In that phase, Commander Gonsalves found three variants that were known or highly likely to cause MHS based on the current literature and other factors. The first phase also revealed many variants that need to be researched further in order for conclusions to be made about them. This phase of the study proved that MHS variants can be found from exome sequencing and reported to healthy people, who may otherwise not know about their risk. This may help hurry the development of a genetic screening test for MHS in the future. Such a screening test could lower the number of MH events, particularly for those people with no known family history.

The second phase of the study is a lab test of the immune cells from participants with MHS variants. This testing will give more data on how likely it is that each variant causes MHS. The lab testing will

also help Commander Gonsalves determine whether a lab test using only those cells could be used to confirm MHS, rather than a muscle biopsy. Commander Gonsalves' work on this topic is ongoing and we look forward to sharing more results with you in the future.

*Commander Gonsalves is completing this research as he works toward earning his PhD in Nursing from the Uniformed Services University of the Health Sciences in Bethesda, Maryland. For more information on MH/MHS, please visit the Malignant Hyperthermia Association of the United States at [www.mhaus.org](http://www.mhaus.org)*

## Recruitment Update

ClinSeq® enrollment has grown to over 1,250 participants since our last newsletter! To enhance the racial diversity of study participants, we are focused on enrolling another 250 African Americans into the study. As the below graphics show, we are continuing to make progress toward this goal.

So far, the majority of African Americans enrolled in our study are women, and so we are hoping to enroll as many men as possible in the coming months. Our recruitment coordinator, Sandra Epps, has been leading these recruitment efforts by attending many community events and health conferences throughout the DC metropolitan area. We hope to continue our recruitment of African American participants and would appreciate your help in spreading the word! We owe much of our success to those of you who have spoken highly about our project to others, and for that we are very grateful. 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. Thank you for bringing your enthusiasm to the ClinSeq® project!

## Racial Makeup of ClinSeq® Participants in 2010 and Today

