The ClinSeq® Newsletter

Volume 15, Winter 2018

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To our valued participants,

It is quite shocking to me that 2018 has come upon us. It has been more than 10 years since we first began ClinSeq® and we have learned a lot from you and from your sequencing data. At least 70 scientific publications have been based on your data. But more importantly, your participation in this study has helped to change the practice of medicine.

As we are now in our second decade, the passage of time has encouraged and enabled many other groups to pursue clinical genomics research. One of the other major accomplishments of ClinSeq® is that we learned how to do a new kind of research – what we are calling "genotype first" testing. What this means is that we look in your sequencing data for gene variants that are predicted to be interesting, unusual, and rare, and then make a scientific prediction as to how that variant might affect you – your disease risk, the shape of your toes, how you metabolize a drug, whatever. We then invite you to the NIH Clinical Center to confirm if that finding is present or absent. This is a scientific method for measuring our ability to predict health and disease from your DNA and is what predictive genomic medicine is all about. Our challenge is that ClinSeq® is only 1,500 people and we need many more people to find many more variants to support this kind of research.

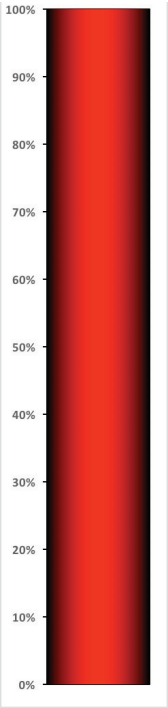
We are, therefore, excited to announce a new phase of ClinSeq®. We plan to combine your sequence data with data from other research participants. Our goal is to have 10,000-50,000 individuals in the new, merged cohort. We have a commitment for a cohort of nearly 8,000 sequenced people to join us and are looking for more. The new phase will also make the variants in your genes visible to a wider array of researchers by a web site to encourage more research. This will be done in a way that provides extremely strong privacy protections – only one variant at a time can be viewed and no two variants in a single person are ever connected to each other.

We hope that researchers will dive in to your data and propose new projects and studies that you can participate in. We won't share your name, or other identifying information unless we contact you and you give us a thumbs up. It is always up to you. If you have questions or concerns about this new effort, we encourage you to contact us. We can explain it further and anyone who wishes to opt out may do so, as is always your right. We are eager to open this new aspect of the study and work further with you in the years ahead to make even more discoveries.

Leslie G. Biesecker, M.D.
Principal Investigator
Chief, Medical Genomics and Metabolic Genetics Branch
NHGRI

Thank you: We have reached our recruitment goal of 500 participants for the African American, African, and Afro-Caribbean cohort!

Enrollment Update



We are excited to tell you that we have reached our goal of enrolling 500 participants in the African American, African, and Afro-Caribbean (A2) ClinSeq® cohort! This is a huge milestone for our project and it would not have been possible without your participation and help in spreading the word about our study. We are starting to send samples for all A2 cohort participants to the lab for sequencing. We will be in touch if we find any genetic variants that could be important to your health or the health of your relatives.

90% of the A2 participants completed a survey when they joined the study. This survey asked about many topics, including participants' knowledge about genetics, personality traits, and intentions to receive genetic results. We plan to write several research papers using the survey data, but are showing a few early results in the box below.

CLINSEQ® A2 COHORT PARTICIPANTS :

- 11% have previously received a genetic test result
- 80% looked for ways to stay healthy or feel better in the 30 days before taking this survey
- 89% identify their racial/ethnic group as Black or African American
- 11% identify as Afro-Caribbean, American Indian, Mixed, or Other

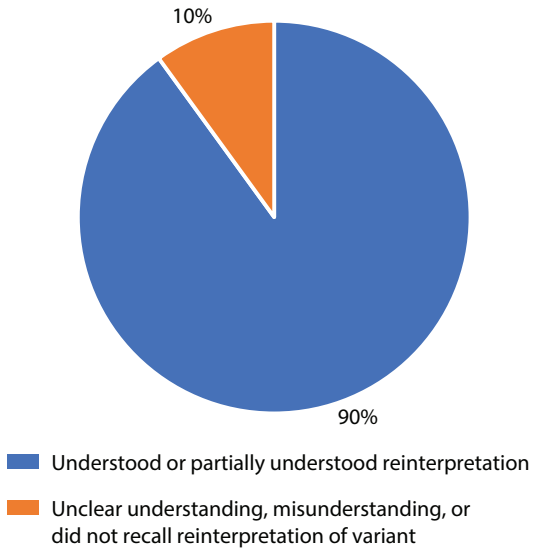
Recent Research: Reactions to Reinterpretation of a Genetic Variant

The field of genomics is constantly changing, and new information about genes is available daily. Because of this, we sometimes need to update our interpretation of a genetic testing result over time. A researcher on the ClinSeq® study, Dr. Jennifer Taber, recently published a study on how people react to receiving updates to their genetic testing results over time.

Twenty-nine ClinSeq® participants were told that they were carriers for a genetic condition called Duarte variant galactosemia. This was based on a variant they had in a gene called *GALT*. Over time, we learned more information about this gene and found out that a different variant in the gene actually makes people carriers for Duarte variant galactosemia. 29 people were retested to see if they had the "real" variant: 19 did, and 10 did not. We contacted all 29 people about their updated results. For Dr. Taber's study, we asked all 29 people to take two surveys about their reactions to results. We also surveyed 29 participants who received similar results, but did not have this variant or any updates to their results over time, for comparison.

The survey results showed that most participants accurately remembered what we told them about the update to their results (see Figure below) and intended to share the information with their families. Most

Accuracy of Immediate Recall of Variant Reinterpretation



participants also had positive or neutral emotional reactions to the update to their result. For example, one participant said this was "no big deal." The findings of this study provide some evidence that ClinSeq® patients and those who are similar to them are likely to react well to minor updates to their genetic testing results over time. More research is needed about how other patients react to these updates, and whether this holds true for more significant updates to genetic testing result

The findings of this study were published in the journal Genetics in Medicine in 2017.

Featured Staff: Celina Montemayor Garcia

What is your position at the NIH?

I am a Staff Clinician in the Department of Transfusion Medicine at the NIH Clinical Center. Our department collects and issues blood products for all Clinical Center patients, and we also process and manufacture cellular therapy products for clinical protocols in this hospital.

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

Blood transfusion is in a way the oldest form of "personalized medicine", since we have to provide blood products for a patient from a compatible donor. This compatibility for blood product transfusion can now be determined at the genetic level, and in some patients, it extends beyond the commonly-known ABO blood group: it can encompass multiple combinations from over 350 blood group antigens! The ClinSeq® study is a valuable and unique platform that allows us, for the first time, to design and validate a complex informatics system that can translate a patient or donor's genomic sequence data into multiple predicted clinically-important blood group antigens. This is an important research step towards the development of new systems to provide safe and precise transfusion support for patients.

What are your other research interests?

I am also working on identifying the genetic basis of novel blood group antigens, and elucidate the role that each of these antigens play, at the molecular level, to maintain the integrity and the oxygen-delivery function of circulating red blood cells.

Featured Staff: Jeff Dudley

What was your training and education prior to working on the ClinSeq® project?

I graduated from the University of Maryland with a B.S. in General Biology.

What is your position on the ClinSeq® Study?

My responsibilities within the ClinSeq® study include processing of patient blood in order to collect DNA, RNA, serum, and plasma.

What motivated you to become involved with the ClinSeq study?

I was motivated to join the ClinSeq® study because it exists at the intersection of my two great passions; genomics and patient care.

What are your plans upon completion of your post-bac with ClinSeq®?

In the coming years, I hope to attend Medical School or continue genomic research in Graduate school.

Return of Results Update

We are continuing to review our participants' genetic data and to share results with them as they become available. On the next page is a list of the results we have returned to participants so far.

Please note that all of these results **have already been returned.** If you have not heard from us, it means that we do not have a result to return to you yet. **However, that does not mean that we have ruled out your risk for the conditions on the next page.**

Genetic 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, PKP2	*12*	*Problems with heart rhythm and structure*
BRCA1, BRCA2, SDHC, SDHB, MSH6, PMS2, MUTYH	*28*	*Increased risk for certain types of cancer*
RYR1	4	Malignant hyperthermia, which causes a fast rise in body temperature and severe muscle contractions after anesthesia
PMP22	2	Numbness or weakness in the limbs
LRRK2	2	Risk for 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 risk of HIV infection, possibly increased risk of West Nile Virus
PPARG	1	Predisposition to abnormal patterns of muscle and fat in the body and abnormal lab values
FLCN	2	Susceptibility to Birt-Hogg-Dube syndrome, which has symptoms like benign skin tumors, cancerous or non-cancerous kidney tumors and lung cysts
SGCE	1	Predisposition to myoclonus-dystonia, which causes muscle jerking, twitching and cramping
PROS1	1	Susceptibility to developing abnormal blood clots
MTND4	1	Susceptibility to an inherited form of vision loss
SLC4A1	1	A problem with red blood cells that can lead to anemia
SLCO1B1 and SLCO1B3	10	Increased risk to have side effects from medications prescribed to lower cholesterol
Carrier Results	550	Conditions that are inherited in a specific pattern such that they do not affect your health, but could affect future generations.
Various	*103*	*Potential susceptibility to specific types of heart disease and other conditions.*

Results that are italicized have been returned in the last 6 months.

Contact Information Updates

Are you relocating or changing your phone number? If so, 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 let you know when genetic results become available for you.