The ClinSeq® Newsletter

Volume 10, Summer 2015

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Dear ClinSeq® Participant,

The big news from ClinSeq® is that our publication on predictive medicine appeared in early June in the American Journal of Human Genetics. In this study, we scanned the sequencing data from 951 of you for all gene variants predicted to "knock out" the function of a gene. This was then limited to genes where the loss of one copy of the gene is expected to cause a disease or finding. About 10% of you had such a variant. This is not news – a number of studies have shown a similar frequency of such variants. However, because of our amazing participants and the design of the study, we went further by calling those of you who had these variants to see how many of you actually had signs or symptoms of the disorder that the variant has been associated with. Among those that we could follow up with, about half indeed had signs or symptoms of the disorder and half did not. While half may not sound so impressive, indeed it is. Many of the genome medicine skeptics have suggested that the ability to predict such things from sequencing would be terrible, and half is a long way from terrible. The disorders that we found were quite varied and a number of the participants who had these variants were surprised by our findings. We diagnosed previously unrecognized cancer susceptibility, a rare form of lipodystrophy, and many others. All in all, 3% of you (32 participants) had one of these disorders, which highlights another conclusion. While each of these disorders is individually rare, that 3% of ClinSeq® participants have a rare disorder is remarkable. This is direct proof that rare disease is in fact common. Our estimate of 3% is most likely an underestimate – we only evaluated a subset of gene variants in known human disease genes.

This remarkable finding, which was highlighted in the online edition of the Washington Post, is a great example of what is remarkable about ClinSeq®. As noted above, our ability to do this study is entirely based on the enthusiastic participation of our volunteers, who generously donated their time and made themselves available for these follow-up studies, some of which were extensive. We are very grateful to them and to Dr. Johnston, who did the molecular lab work, and Dr. Ng and Katie Lewis who worked with our volunteers for this study.

There is more to come! We are about 75% done with our study to return carrier results, which we hope will be completed this fall. We are also launching a study to return variants that have uncertain significance – which like all of our studies can only work with the avid participation of our volunteers.

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.

Information Avoidance and Intentions to Learn Genetic Test Results

Some people are more willing than others to learn news that might be hard to hear. For example, testing results may bring news of disease or elevated risk for disease—think of getting a mammography and learning you have breast cancer, or taking a cholesterol test and learning you're at risk for coronary artery disease. Getting a genetic test result can also bring unpleasant health news. If people are concerned about learning unpleasant health news, they may opt to avoid a particular type of information altogether. For example, they may decide not to learn genetic information if they think it might bring unpleasant news. We call this "information avoidance." Avoiding information before knowing whether it's positive or negative is one way to cope with the possibility of unpleasant news. We asked ClinSeq participants to complete a scale that assessed whether they were high or low information avoiders. You might not be surprised to learn that we found that people who were higher in information avoidance ("information avoiders") were less interested in learning their genetic information. In particular, information avoiders were even less interested in learning genetic information about results that were described as having no medical action that could be taken to reduce or control the disease risk.

We believe that learning information about whether you're at risk for disease can be a good thing, particularly if there is medical action that can be taken in response to that information. So we also tested whether there were characteristics of people that made it less likely that being an information avoider would lead to less interest in learning genetic information. We looked at two personality characteristics: spontaneous self-affirmation and optimism. You may have heard about affirmation: people self-affirm by focusing on things that they're good at (their strengths) or things they care about (their values), such as family or religion. A lot of social psychological research has shown that if you ask people to self-affirm, a variety of positive benefits can occur: people score better on tests, perform more health behaviors, and are more likely to help other people. We were interested in seeing whether people self-affirm in their day to day lives, without researchers asking them to. Maybe you do this: when you're feeling anxious or threatened, do you ever focus on your strengths and values? Data from other studies suggest that people do. In this study, we found that information avoiders had lower intentions to learn genetic information only if they did not tend to self-affirm. In other words, self-affirmation offset the negative effects of information avoidance! This is exciting, because self-affirmation may be a skill that could be taught, and it may encourage people who are unlikely to seek out potentially negative health information to be more likely to do so.

We also looked at optimism. Optimism is expecting positive things to happen in the future. We again found that information avoiders had lower intentions to learn genetic information only if they were not very optimistic. Thus, we identified two potential psychological resources—spontaneous self-affirmation and optimism—that may promote interest in genetic information, especially when people are likely to avoid potentially negative information. We are continuing to look at different personality characteristics and beliefs that may influence whether people actually want to learn genetic information about themselves. By doing this research, we will be able to determine how best genetic information can be disseminated and used to improve people's health.

This article was written by Dr. Jennifer Taber, who is a Cancer Research Training Award (CRTA) Fellow at the National Institutes of Health. She has collaborated with ClinSeq researchers on several projects, and plans to conduct more research on health communication, risk perceptions and genetic testing in the future. The results described in this article were recently published by Dr. Taber and her colleagues in the journal "Cognition and Emotion".

Featured Associate Investigator: Dr. Parag Kumar

Dr. Kumar is currently collaborating with ClinSeq scientists on a project to learn how certain gene variants affect the way the body uses certain medications called statins. Statins are widely prescribed to lower LDL cholesterol. However, statins sometimes cause side effects like tiredness or muscle pain. There are certain genes that are thought to affect the way the body uses statins and how likely a person is to develop side effects. Participants are being recruited based on their genetic sequencing through the summer, and we anticipate that results of the study will be available in 2016.

1. What is your position at NIH?

   I currently serve as a pharmacokineticist for the Clinical Pharmacokinetics Research Laboratory (CPRL) of the NIH Clinical Center Pharmacy Department. A pharmacokineticist studies the way that drugs and nutrients are absorbed and used in the body.

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

   I believe projects like ClinSeq have the potential to pave the way for a paradigm shift in the way we treat patients, by leading us to the path of individualizing drug regimen choices based on patients pre-determine pharmacogenomic results.

3. What are your other research interests?

   My continued primary research interests include areas of Pharmacokinetics, Clinical Pharmacology, Pharmacogenomics, Clinical Trial Design, Protocol Writing, Large Molecules (antibodies, liposomes, nanoparticles, etc.), and PK/PD Data Analysis and

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, PKP2	10	Variants associated with heart problems, including abnormalities in heart rhythm and structure
BRCA1, BRCA2, SDHC, MSH6, PMS2	11	Increased risk for various types of cancer
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 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 increased 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
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
SLC4A1	1	A problem with red blood cells that can lead to anemia
SLCO1B1 and SLCO1B3	*9*	*Increased risk to have side effects from medications prescribed to lower cholesterol*
Various	*275*	*Conditions that are inherited in a specific pattern such that they do not affect your health, but could affect future generations.*

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.

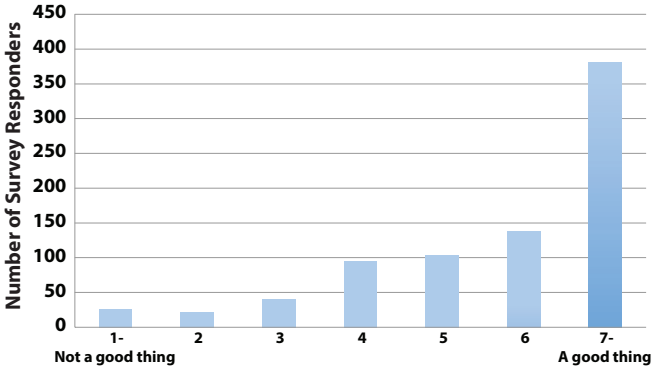
Interpretation. I am also currently an active member of the American Society of Clinical Pharmacology and Therapeutics, American Society of Pharmacometrics, and American College of Clinical Pharmacology.

Return of Results Update

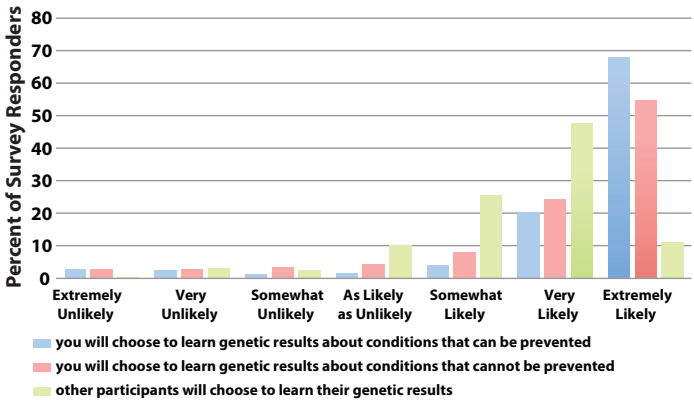
We are continuing to review our participants' genetic sequences and to share results with them as they become available. At the suggestion of a participant, we began publishing a list of the results we have returned thus far in each newsletter. We hope this list gives you a sense for the progress of our project, but it may also give you an opportunity to reflect on which results you would want to know if you are offered them.

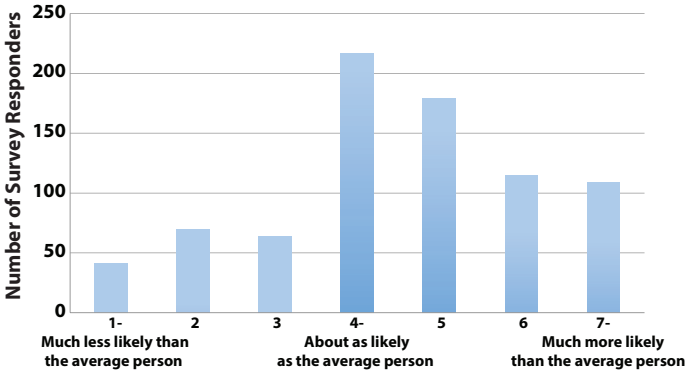
Thus far, only a small number of ClinSeq® participants have received results from us. We continue to work on our project to return a subset of results to at least 400 participants in our project, and have shared results with almost 300 participants thus far. All of those results fit into the last row of this table, and are not expected to affect the participant directly, but might be important for future generations.

For me, learning a result about a condition that cannot be prevented or treated would be:

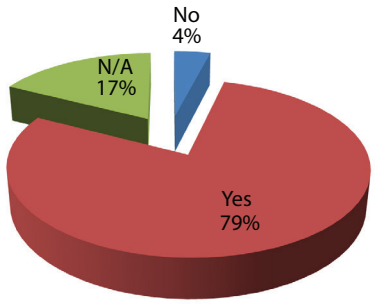


How likely is it that...

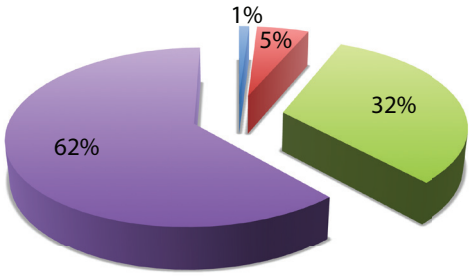




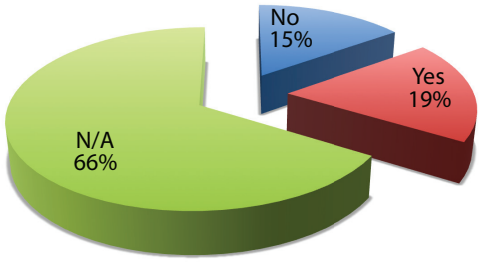
Have you told your spouse that you are in ClinSeq?



I see myself as someone who is curious about many things



Have you told your mother that you are in ClinSeq?



Baseline Survey

As we have reported in previous editions of this newsletter, we have been recruiting ClinSeq participants to complete a survey about their preferences, thoughts and personality traits prior to receive a genetic result. We started asking participants to complete this survey in June 2012 and still continue to collect new responses today. About 750 people in the study have completed surveys and we are beginning to learn more about our study participants by reviewing their responses to the surveys. We have published four papers from your survey responses so far, including one described in detail on page 2 of this newsletter, and plan to publish more soon. The graphs above show some examples of the data we have collected through the survey. If you have not yet completed the survey and would like to do so, please contact Kristen Fishler at 301-443-6160.

Enrollment Update

We are continuing to enroll African American, African and Afro-Caribbean participants in our study with hopes of reaching our goal of 500 individuals in this cohort before the end of the study. You can see our progress in the graph to the right. The majority of individuals we have enrolled to date, have been women, though, and so we plan to focus only on enrolling men in the coming months. If you know any African American, African or Afro-Caribbean men who are 45-65 years old and are willing to participate in our study, please encourage them to contact Sandra Epps at 301-402-0020.