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Dear ClinSeq® Participant,

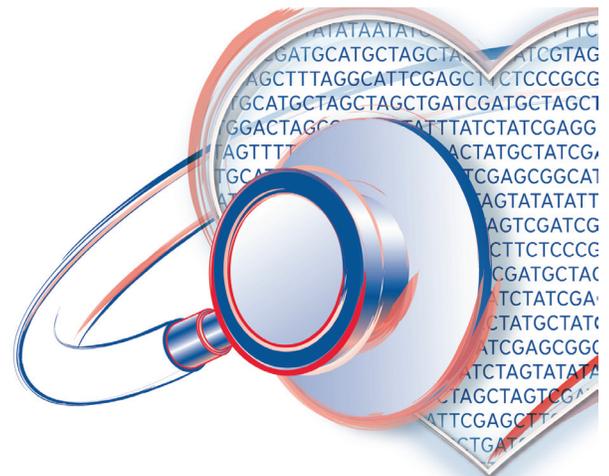
The main news for this edition of our newsletter is the ongoing progress of the carrier results intervention, the drug metabolism study, and the variants of unknown significance study. They are progressing well and are generating important and useful results. As always, we are incredibly grateful to our participants for the time and energy they are willing to invest to our study – it is your commitment that makes this work.

We should also alert you to a change we are hoping to make in data sharing going forward. It is clear that the sequence data from ClinSeq® are valuable. We can make them more valuable to researchers by sharing this data more widely. To that end, we are doing two things. First, we have deposited your sequence data and selected parts of your original intake evaluation (e.g., clinical laboratory tests, EKG, etc.) in a database at the National Library of Medicine. The database is called “dbGAP” – the database of genotypes and phenotypes and is a large data repository that can be accessed by scientists. In order for scientists to gain access to the data, they will go through a very thorough and strenuous review. Further, they must provide detailed assurances about the confidentiality of the data. The database does not include personal information such as name, date of birth, etc. The only information that an unapproved individual can see is a description of the ClinSeq® study and some summary statistics regarding the findings of the study group as a whole. You are welcome to browse this summary at: http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000971.v1.p1

Second we are proposing to combine our data with the data from another center that has sequenced thousands of research participants. We propose to upload the data to a web site that will summarize how many of you have a given genetic variant. There is minimal risk of confidentiality issues because we will only show summary statistics, one variant at a time. No individual’s genetic profile should be extractable from this. We are planning to use a web site structure that is much like that of the ExAC (EXome Aggregation Consortium) in Boston. This will encourage researchers to find ClinSeq® participants with unusual gene variants and propose follow up studies to evaluate them. This is similar to what we have done with McArdle disease, GCKR, and the heart rhythm study. I encourage you to look at that website if you are curious: <http://exac.broadinstitute.org>

Again, this is an example of what we propose to do. This will allow us to share your data, with very little risk to the confidentiality of your data, and identify important research questions. We can then answer these questions by pooling data and encouraging outside researchers to work with us. We look forward to hearing from our participants if they have thoughts on this expansion of our study. These exciting advances will keep ClinSeq® at the cutting edge of clinical genomics. As always, we are terribly grateful for your enthusiastic participation in the study.

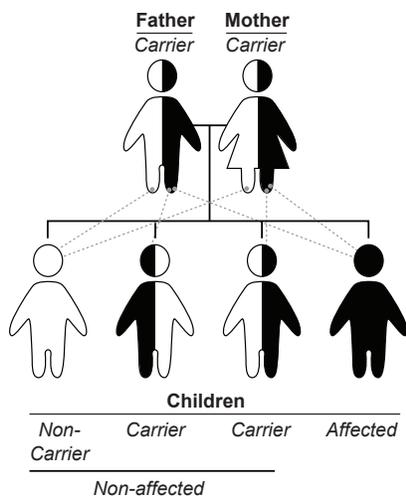
Leslie G. Biesecker, M.D.
Principal Investigator
Chief, Genetic Disease Research Branch
NHGRI





Determining Disease Prevalence from ClinSeq® Data

McArdle disease is a genetic disorder that causes sugars to be broken down incorrectly in muscle cells. People with McArdle disease may have muscle pain, cramps, and fatigue within a few minutes of exercising. With rest, these symptoms often go away. In severely affected individuals, repeated exercise can lead to muscle breakdown and kidney failure. The severity of the symptoms varies across individuals and may be mild. It is inherited in a recessive pattern, which means that both copies of the gene (the one inherited from your mother and the one inherited from your father) must have mutations in order for you to be affected, as shown below.



Experts had thought that 1 out of every 100,000 people were affected with McArdle disease. Since the symptoms can be very mild, ClinSeq® researchers wondered if those numbers were an underestimate. They looked at genetic data in the ClinSeq® project and another large study which includes people with mutations

in the *PYGM* gene, which is related to McArdle disease. Some ClinSeq® participants received a call with questions about symptoms related to the disease. It is important to note that we called individuals with and without genetic changes.

ClinSeq® researchers found that 120 participants have changes in the gene *PYGM*, which is associated with McArdle disease. When only the two changes in the *PYGM* gene that are most likely to cause McArdle disease are included in the calculations, the prevalence is 1 out of 42,355 people, higher than previously reported. Researchers note two possible reasons for this difference:

1. McArdle disease is more common than we think, but goes undiagnosed in many people.
2. Some changes that are reported to cause McArdle disease may not always cause McArdle disease.

This study points toward a benefit of predictive medicine. In the future, patients may be identified with an increased risk for McArdle disease based on their genetics. Currently, the medical system relies on descriptions of people who seek medical care.

ClinSeq® Participants are Early Adopters of New Technology

Many of you have taken a survey on your personality traits, thoughts and attitudes about receiving genetic testing results. Some of this data was in our last newsletter. A recent paper described the characteristics of ClinSeq® participants. This description is important because ClinSeq participants represent a bigger group of people who are excited to have genome sequencing while it is still a new technology. We call this group “early adopters”. From previous studies, we know that early adopters are different from later adopters. Early adopters are more likely to tolerate uncertainty well or to be open to new experiences.

We reviewed survey responses from 630 participants in the ClinSeq® study. We confirmed previous studies that 74% of you have an annual household income greater than \$100,000 and that 87% have graduated college. You have higher incomes and education than the average person in the United States. However, you are similar to other early adopters of genetic testing and perhaps to those who will seek genome sequencing in the near term. As a group, you are also highly optimistic. Optimism is an ability to see facts in a favorable light. We predict this may shape the way you view your future results.

You are also high in three personality traits known as agreeableness, openness and conscientiousness, as shown in the table below.” People who are high in conscientiousness and agreeableness are called “effective altruists”. This unique group of people is motivated to achieve their personal goals and work toward the good of a larger group. This echoes many of your motivations to join our study: to improve your health, but also to help others.

Personality traits help us describe groups who have been sequenced. The same personality traits that led you to our study may affect how you react to your results. These traits are important in guiding our understanding about your reactions to results. This research will also help us understand how similar early adopters are to later adopters.

Personality Traits of ClinSeq® Participants

Personality Traits (examples of the trait)	Average	Possible Range
Conscientiousness (does a thorough job, is a reliable worker, does things efficiently)	4.04	1-5
Agreeableness (has a forgiving nature, is considerate and kind, is generally trusting)	3.95	1-5
Openness (is inventive, values artistic experiences, likes to play with ideas)	3.9	1-5
Neuroticism (can be tense, worries a lot, gets nervous easily)	2.42	1-5



We have encouraged all of our participants to take this survey. Survey recruitment is ongoing. These data may be used in future papers, and may qualify you for research studies. If you have not completed this survey and would like to, please call Kristen at 301-443-6160.

Return of Results Update

We continue to review our participants' genetic sequences. We aim to share results with you as they become available. As in

previous issues of the newsletter, below is a list of the results we have returned so far.

Please note that 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 you do not have genetic variants or that we have ruled out your risk for these conditions.

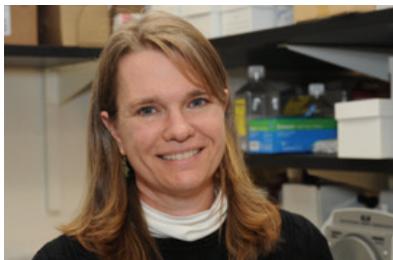
Genetic Results Returned to ClinSeq® Participants

Gene with Variation	Number of Participants with Results Returned	Health Implications
LDLR or APOB	13	High cholesterol at a young age that requires 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-Dubé syndrome, which is a condition with benign skin tumors, 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	350	Carrier results - conditions that are inherited in a specific pattern such that they do not affect your health, but could affect future generations.
LAMA4, LBD3, TMPO, EYA4, LMNA, MYOZ2, DES, DTNA	13	Potential susceptibility to heart disease and other conditions.

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.



Featured Associate Investigator: Dr. Jennifer Johnston, Ph.D.



1. What is your position at NIH?

I came to the NIH in 1999 to complete a fellowship in Clinical Molecular Genetics and have worked in the laboratory of Dr. Leslie Biesecker since 2001. After completing my fellowship and obtaining board certification, I began offering molecular diagnostics to families who were involved in rare disease research through the Biesecker Lab.

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

When the ClinSeq® project generated the initial exome sequence data I became intrigued with all of the useful information that was being generated and the process of distilling that information so that it would be useful to the ClinSeq® participants. My current involvement in the project entails both studying variants to understand their health impact and then confirming those variants so they can be returned to participants.

3. What are your other research interests?

Beyond ClinSeq®, I am involved in rare disease research trying to understand the genetic causes for rare developmental disorders.

Contact Information Updates

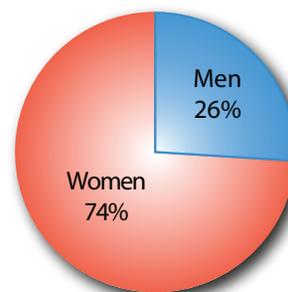
Are you relocating or changing your phone number? If your phone number(s) or address changes, please let us know. You can call (301) 443-6160 or e-mail clinseq@mail.nih.gov. We need to have your up-to-date contact information so that we can share the latest ClinSeq® information with you and let you know 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.

Enrollment Update

We have recruited ~375 participants for our African American, African and Afro-Caribbean cohort. We aim to recruit 500 individuals before the end of the study. At our current pace of recruitment, we will not reach our goal until 2017, as shown in the graph below. We will not send the samples for anyone in the cohort to the laboratory for genetic testing until all 500 participants are recruited. As you can see from the graph below, the majority of our participants are women. It is important that we recruit more men to our study in the coming months. We are looking for African American, African or Afro-Caribbean men and women aged 45-65, who have not smoked within the past 12 months, and are willing to participate in our study. Please encourage them to contact our recruitment coordinator, Sandra Epps, at 301-402-0020. Similarly, if you know of any community events where we can recruit for our study, please let us know!

Gender Split of ClinSeq®
African American Cohort



African American Cohort Enrollment Projections

