The MilSeq Project: Enabling Precision Medicine through Exome Sequencing in the U.S. Air Force

Study Protocol and Statistical Analysis Plan
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1. RESEARCH PLAN

Purpose of Study:
The purpose of this study is to explore the implementation of whole exome sequencing (WES) into clinical medical care in the United States Air Force.
Hypotheses, Research Questions, or Objectives:
The objective of this effort is to investigate: (a) military healthcare providers' (HCP) genomic knowledge before and after receiving a genomic educational primer and after disclosing WES results; (b) the genomic educational needs of military HCPs; (c) active-duty Airmen's knowledge and perceptions of genomic sequencing (GS); (d) reasons why active-duty Airmen choose to participate, or not to participate, in research involving GS; (e) how WES study patient-participants, including HCPs and sequenced active-duty Airmen, respond to and use WES results; (f) means of collecting medical, behavioral and healthcare utilization outcomes of integrating WES information into clinical care in the military; (g) how return of WES results and integration into the EMR (Electronic Medical Record) impact perceptions of mission readiness and duty assignments. Given the lack of prior research in this area in the Air Force, and the broad number of topics of interest, the aims of the study are predominantly exploratory and results may be hypothesis generating.
Significance:

The promise of genomic sequencing (GS) to enable personalized and precision care over a lifetime is increasingly within reach as GS technologies, including whole exome sequencing (WES) and whole genome sequencing (WGS), evolve and prices drop.[1] The military and related programs such as the Veterans Administration are already utilizing genomic testing for research, for forensics and to guide medical care. Examples include collecting DNA samples from military recruits for forensic purposes, testing of military personnel for sickle cell and G6PD deficiency screening, the Million Veteran Program for research, and diagnosing and treating S=service members and their families affected by genetic diseases.[2] As GS is increasingly being used in the setting of active-duty military and their families, three major barriers to the widespread adoption and implementation of GS in the military must be overcome: (1) Military HCPs must be educated about GS and its utility, benefits and limitations; (2) Empirical data are needed to determine, if GS were widely available in the military, what would be the uptake, impact on downstream healthcare utilization, and concerns and perceptions of GS among military HCPs and active duty Service Members; and (3) Preliminary data and future projections are needed to understand the potential long-term impact of GS on the military healthcare system more broadly.

Because of these considerations and needs related to genomic medicine in the military, rigorous research that explores clinical implementation of GS into military healthcare is critically needed. Our project team has a long history of designing and leading systematic outcomes research studies assessing how to apply, interpret, communicate, and manage GS results. Given our relevant expertise in the civilian sector, with the addition of our military HCP colleagues, we are well qualified to fulfill these research needs in the military setting. In this protocol, we will conduct a proof-of-concept study to address the barriers to widespread implementation and adoption of GS in the military.

As sequencing costs continue to drop this study can serve as a guide for larger clinical trials exploring the long-term health outcomes of genomic sequencing. It will provide important information about the feasibility of implementing GS in the military, and the benefits and harms of GS to inform discussions regarding the adoption of precision medicine in the military population.

Military Relevance:

The results of this research may be useful in: (1) determining future needs for the provision of genomics services in the military health system workforce and the ideal allocation of resources; (2) developing educational materials to address genomics knowledge gaps of military HCPs; (3) providing evidence regarding integration of WES results into the EMR; (4) and enhancing health outcomes of active-duty Air Force Airmen.

Background and Review of Literature:

The long-anticipated integration of genomics into the practice of medicine[3,4] is beginning to occur[5,6]. Genomic sequencing can simultaneously provide information that can diagnose disease, identify risks, inform reproductive choices and improve pharmacotherapy over the entire spectrum of human health. Yet today, genomics largely remains the province of small groups of genetics specialists. Current workforce issues limit the availability of geneticists and genetic counselors to be the sole providers of genetic counseling and testing services, yet primary care HCPs vary in their preparedness and comfort with genetic technologies and ability to provide genetic services.[7,8] As we prepare for a future in which any provider can readily order broad-based genomic sequencing for his or her patients, we must understand the motivations, benefits, risks and costs to all involved. We must study how HCPs apply, interpret, communicate, and manage WES results to understand the potential use of WES in preventive care. Because of the complexity in the analysis, reporting, and communication of genomic data, rigorous research that explores clinical implementation of WES results, including actions and perceptions of military HCPs and sequenced active Airmen, is critically needed. This study will assess HCPs' comfort with incorporating genomic information into medical care, assess how this impacts their medical care and their perceived fitness for duty, as well as address the perceptions of patient-participants who will be sequenced.

The MedSeq Project formally entitled "Integration of Whole Genome Sequencing into Clinical Medicine" is a Harvard-Baylor clinical research study, that was supported through an NIH U award to Investigators Green (PI), Rehm (co-PI) and McGuire (co-PI)[9]. This grant supported a randomized control trial exploring genomic sequencing in both a healthy population and a population of patients with cardiomyopathy. Patient-participants were randomized to receive standard of care including a thorough family history collection or this plus genomic sequencing. In the MedSeq Project, 21% of patient-participants who received GS were found to have a pathogenic/likely pathogenic/uncertain significance-favor pathogenic variant related to a previously undiagnosed monogenic condition.[Vassy et al, in submission] These data suggest that WES of an ostensibly healthy military population may reveal clinically-actionable variants and prompt re-evaluation of medical and family histories, leading to discovery of phenotypic features consistent with a genetic condition.[10]

In MedSeq, we developed critical processes for enrollment, sequencing, reporting, safety monitoring and outcomes collection by recruiting two very different HCP and patient populations.[9] We were particularly interested in understanding the impact of disclosing a broad spectrum of secondary and "unanticipated" findings, so we used genomic sequencing and reported carefully curated disease-associated variants from analysis of over 4600 genes associated with both dominant and recessive monogenic conditions, a small panel of pharmacogenomic findings, and even a novel panel of blood cell antigens identified through GS. In MedSeq we successfully met all of our recruitment goals and achieved all of our aims. Of 514 patients contacted by MedSeq study staff, 202 (39%) consented and were enrolled: 102 patients enrolled through 7 cardiologists and 100 patients enrolled through 9 primary care HCPs. Also, to enhance our understanding regarding barriers to GS, we studied reasons for decline and found that 173 patients who engaged in the consent process declined citing time constraints and unwillingness to meet protocol requirements

(59%) and ethical, legal and social risks (40%) such as fear of insurance discrimination.[11,12] We plan to implement a similar study strategy in this project.

In MedSeq we designed a "Genome Report" (GR) template appropriate for non-geneticist HCPs including a single page summary of the findings with categories for monogenic disease risk (MDR), carrier status, pharmacogenomics (PGx) and red blood cell (RBC)/platelet antigen typing.[13] Variants were included in the MDR section or carrier status section if the variant was classified as a Pathogenic Variant (PV), Likely Pathogenic (LP) or Variant of Uncertain Significance-Favor Pathogenic (VUS-FP) and in a gene with strong evidence for an association with disease. The subsequent 4-5 pages of the report included greater detail about the results for physician reference. PGx results included in the GR were reported for 18 variants associated with the metabolism of five drugs (metformin, clopidogrel, warfarin, simvastatin, and digoxin) commonly used in the treatment of our patient-participant populations. They were selected based on PharmGKB Clinical Annotation Levels of Evidence Class I and Class II variants.[14,15] Results were supplemented with a summary of the dose requirement or risk of adverse effects along with population genotype frequencies to allow HCPs to contextualize the prevalence of the patients' PGx diplotype. MedSeq also developed an innovative Blood Group Antigen Prediction module.[15] Similar reporting measures will be implemented in this study.

The ability of non-geneticist providers to safely interpret and make medical decisions using WGS results was a considerable focus. MedSeq addressed this through training, support, and safety monitoring, which encouraged physicians with liability concerns who were reluctant to engage in genomic medicine to enroll in MedSeq.[7] We provided a continuing education curriculum for MedSeq provider-participants with in-person and online, case-based genomics training,[16] which we found to be effective in increasing providers' confidence in their abilities to manage WGS findings, particularly among primary care HCPs.[7] Our MedSeq Genome Resource Center (GRC), staffed by genetic counselors (including Blout) and clinical geneticists (including Dr. Green), was available 24/7 to support our providers' Genome Report interpretation and decision-making and to ensure subject safety. Of the 18 provider-participants, 13 indicated they planned to use the GRC at study start, but only 7 actually consulted the GRC, 6 of whom were primary care HCPs. Provider-patient disclosure sessions were audio-recorded and transcribed. Transcripts were reviewed by the GRC for accuracy of genetic information and understanding of genetic concepts underlying clinical decisions, and errors/miscommunications were categorized as "high-risk," "low/medium risk" and "very low risk." In our limited yet highly monitored experience, provider-participants disclosed the information safely: among 195 disclosure transcripts there were no high-risk errors. There were only 4 low/medium-risk errors/miscommunications resulting in real time intervention (3 related to carrier risk, 1 to inheritance pattern)[17] and 38 very low-risk errors/miscommunications marked for end of study notification. Most very low-risk errors/miscommunications in the WGS arm were related to the WGS report, specifically incomplete counseling for very rare autosomal recessive (AR) conditions (e.g. not offering the option for carrier testing for relatives) or misunderstanding and miscommunication of the testing limitations. Of note, some misunderstanding and miscommunications were related to family history misinterpretation, and there were also errors

related to family history counseling in the control arm. Similar safety measures will be implemented in this protocol.

Surveys were developed as part of MedSeq to assess a variety of medical, behavioral and economic outcomes as well as patient-participant and provider perceptions. Preliminary analyses suggest no differences between randomization arms on time-averaged scores of anxiety and depression on a validated measure (p=0.32 and p=0.26, respectively, including subset analysis of the patients receiving secondary and unanticipated monogenic disease risks). Similar measures will be implemented in this project.

Similar studies of GS are ongoing in the private sector. The MedSeq project was one of 18 National Institute of Health (NIH) funded research studies making up the Clinical Sequencing Exploratory Research Consortium.[18] Our work within this consortium has allowed us to be integrated with the most cutting-edge clinical research in the field of genomics. Our group is also a leading site in the NIH funded NSIGHT consortium which is exploring similar issues in the newborn population.[19] Our work within these consortia has established our team as leaders in the field of GS. In this project, we will bring this collective knowledge to the military setting to explore issues that are unique to this population, and we will implement study improvements as guided by our prior research experience.

There are a number of potential benefits and challenges to incorporating genomic medicine in the military, some that are relevant to the broader civilian community, but some that are unique to this population. Some of these challenges, including how GS could affect fitness for duty, genomic discrimination, how to best deal with incidental or secondary findings as well as practical challenges of genomic implementation.[18] In this pilot study, we will explore these potential opportunities and challenges which will provide a basis for future study, and to begin to inform decisions regarding clinical care of active-duty service members.

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1. RESEARCH DESIGN AND METHODS

Research Design and Methods:

[See Study Schema]

Design: This is a nonrandomized convenience sample of both patients and privileged military health care providers (HCPs), employing mixed methodologies to answer the following research questions:

Clinician Research Questions

1. What is the baseline knowledge of genomics among HCPs?
2. At what rate will HCPs voluntarily participate in an educational program regarding Genomic Medicine?
3. At what rate will trained HCPs volunteer to participate in a clinic designed to receive and disclose Genomic Reports on patient-participants with the support of study staff?

4. How accurately do these HCPs present appropriate information to patient-participants in results disclosure sessions?
5. How do clinical recommendations based on study results impact the military healthcare system and the individual Airmen?
6. How does the educational program, combined with participation in study results disclosure sessions, affect HCP intent to change practice?

Patient Research Questions

1. What is the baseline knowledge of genomics among active-duty Airmen?
2. What are active-duty Airmen's perceptions and preferences regarding GS?
3. At what rate will active-duty Airmen voluntarily participate in a whole exome sequencing (WES) study?
4. How does participation in a WES study affect Airmen's intent to change health behaviors?
5. How does participation in a WES study affect Airmen's health behaviors over time?

Phase 1

1. Recruit, consent and enroll:

    a. Approximately 750 ostensibly healthy active-duty Air Force Airmen 18 years or older that receive medical care in military Primary Care, Internal Medicine and/or Family Practice (PC/IM/FP) settings to take the baseline survey (Phase 1).

2. Administer a baseline online survey to explore active duty Airmen's perceptions of and preferences for genomic sequencing and assess patient-participants' interest in taking part in the WES study (Phase 2)

    a. Identify motivations and barriers to active duty Airmen participating in a WES study

Phase 2

3. Recruit, consent and enroll:

    a. 75 ostensibly healthy active-duty Air Force Airmen that receive medical care in military Primary Care, Internal Medicine and/or Family Practice settings who in their baseline survey expressed interest in receiving WES through a research study

    b. 10-20 military Primary Care, Internal Medicine and/or Family Practice HCPs who volunteer to receive an educational primer in genomics and who will discuss each Airman's WES results with them

4. Provide a WES primer to HCPs and conduct pre- and post-test education surveys and conduct a final survey

after HCP-participants have experience disclosing genomic sequencing results.

5. Provide study HCPs access to the Genome Resource Center throughout the study, including in clinic support

6. Obtain WES at 125x coverage (i.e., at least 125 sequencing reads covering each position within the exome region of interest) in the Laboratory of Molecular Medicine's CLIA certified laboratory on 75 enrolled individuals

7. Generate RBC and platelet antigen phenotype predictions for each patient-participant

8. Use best current practices for interpreting WES data covering the spectrum of human genetic variation, in terms of previously reported and novel variants likely to influence the health of patients

9. Confirm clinically relevant variant findings from WES using an orthogonal method for non-pharmacogenomic variants

10. Create Genomic Reports in a clear format for communicating clinically-relevant genomic information to practicing HCPs

11. Monitor concepts communicated by study HCPs during disclosure sessions, and provide personalized genomics education and support, as needed

12. Assess healthcare utilization in response to WES results

    a. Evaluate study HCPs' experiences with receiving and interpreting patient-participants' genetic test results and how they communicate these results to these patient-participants

    b. Administer post-disclosure checklist within 2 weeks of results disclosure to study HCPs to assess healthcare utilization and recommendations

    c. Administer 6-week post-disclosure survey to patient-participants to evaluate how they respond to and use genomic results using validated scales (where available) of psychological impact, personal utility, and behavioral responses, as well as economic and health outcomes.

    d. Electronic medical record (EMR) health data will be examined by the project manager/genetic counselor (PM/GC) after the patient-participant result disclosure to determine any actions made based on study results

Please note that both active-duty Airmen who are patients (patient-participants) and Health Care Providers at Wilford Hall (HCP-participants) are being enrolled in this study. The patient-participants will complete an online survey (Online Survey/Phase 1 below) and then will be invited to participate in the main study (Sequencing Study/Phase 2 below). The HCP-participants will be enrolled to obtain genomic education and attend a Genome Medicine Clinic where they will disclose

WES results to the patient-participants who are participating in the main study (all part of the Sequencing Study below).

Online Survey/ Phase 1

Patient-participants – Consent Session (Patient-Participant in person visit 1)

Active duty Airmen will be recruited to fill out a baseline survey that assesses their attitudes and perceptions about genomic sequencing. They will receive this survey link as described in the below recruitment section. This baseline survey will have an electronic consent on the 1st page of the survey. This survey will assess Airmen's interest in participating in the larger study of WES, and those who fill out this survey are not required to or promised the ability to participate in phase 2 of the project. This survey will take approximately 15-30 minutes to complete.

Sequencing Study/ Phase 2

HCP-participants – Consent Session (Study HCP in person visit 1 - Part A)

Healthcare providers will be consented as per the Consent Process section noted below.

HCP-participants (HCP in person visit 1 - Part B or Visit 2)

Once the HCP-participant (study HCP) has signed the consent form they will complete a baseline genomic knowledge survey and then a genomics educational module. The educational module will be 3 hours. It will be composed of a didactic lecture that will include a general introduction to WES in the clinical context, review of case examples, and major academic papers in the field of genetics and genomics. **[See HCP Education Outline]** The study HCP will also be introduced to the format of the Genome Report and the Genome Resource Center (GRC), which will be staffed by medical geneticists and genetic counselors as part of the MilSeq Project to offer point-of-care information for the HCPs enrolled in this study regarding patient genomic results. The study HCPs will complete a brief survey, approximately 15-20 min, to assess knowledge and attitudes regarding genomic information before and after this education. When possible this education session will be held as a group training with multiple HCPs, but if needed it will be provided by the onsite PM/GC in a one-on one environment. The study HCPs will also be provided links to additional existing online genetics and genomics educational resources that they can reference on their own if they are interested.

Patient-participants – Consent Session (Patient-Participant in person visit 1)

See Consent Processes section below

Patient-participants will be consented at this visit per the consent process noted below. The PM/GC will then obtain the patient-participant's family history information by collecting a genetic pedigree. After the family history information is collected the patient-participant will be escorted to phlebotomy where they will have approximately 30mL of blood collected for WES.

Results Disclosure (Patient in person visit 2, Study HCP in person visit 2-12)

- Study HCPs will be asked to attend monthly Genome Medicine Clinics as their schedule allows to see the Patient-Participants enrolled in the study and to disclose genomic sequencing results. The PM/GC will contact each Study HCP to establish their availability each month. The number of patients matched to the study HCP in the *ad hoc* Genomic Medicine Clinic will be dependent upon the total number of HCPs enrolled in this study and their availability.

Once a patient-participant's Genomic Report has been generated (see Laboratory Processing and Pipeline Below), study staff will distribute a copy of the Genome Report and previously collected family history report to one of the participating HCPs who has been designated to see the patient-participant in Genomic Medicine Clinic. Upon receiving the reports, the study HCP will have the opportunity to prepare for the results disclosure session, which includes consulting the Genome Resource Center (GRC) as needed. If a Study HCP consults the GRC, the GRC staff will document the encounter in the GRC logbook.

The results disclosure visit will take place in an *ad hoc* Genome Medicine Clinic where the study HCP will review the results of the patient's family history report and his/her Genome Report. The patient-participant will be allowed to ask questions and the HCP may make healthcare recommendations. If a study HCP makes medical recommendations based Genome Report this will be documented in their medical record per standard of care. The results disclosure visit will be audio-recorded. The study PM/GC will provide the recorder in advance of the session to the study HCP and instruct them how to record the disclosure session. Audio recordings will be electronically stored on the MilSeq PM/GC's computer and shared with the study investigators at Baylor College of Medicine and Brigham and Women's Hospital. The PM/GC will listen to each disclosure session and will take notes and complete a study error checklist**.** She will consult the other members of the GRC as needed. The PM/GC will also be physically present during the Genome Medicine Clinic as an in person GRC resource. Questions study HCPs ask during this clinic will also be recorded in the GRC logbook.

HCP Post-Disclosure Checklist (HCP)

After the results disclosure visit the study HCP will be provided a link to complete the HCP checklist online within two weeks after the results disclosure. This is a one-page post-disclosure visit checklist which will take approximately 10-15 minutes to complete and will be stored on a secure REDCap database. **REDCap is a free, secure, HIPAA compliant web-based application.** The study HCP will document anything relevant to the patient's care as a result of this study in the patient's EMR, as is standard of care after any clinical encounter. After this disclosure visit, the results will be scanned into the EMR by the study project manager using the HAIMS (Health Artifact and Image Management Solution) software.

Study HCP Feedback Session (Optional)

A study genetic counselor or study MD geneticist from the Genome Resource Center (GRC; see below) will contact each HCP after they have disclosed at least one WES report to offer feedback about genomic information and family history information communicated in the disclosure session. This feedback may be provided by GRC experts in person, by videoconference, by phone or by email. Feedback sessions will be an opportunity to provide each HCP with personalized genomics education, answer the HCP's questions, and correct any misconceptions. This will be offered again when the provider has completed their disclosure sessions along with information about any errors they made.

6-week Post-Disclosure Follow-up Survey (Patient-participants)

Six weeks after the results disclosure session the study staff will send an email to administer the 6-week post disclosure follow-up survey to patient-participants. Responses will be compared to the baseline survey to examine changes in perceptions of WES. This survey will take approximately 30-45 minutes to complete. The study staff will promptly review survey items assessing depression and/or anxiety. If these items suggest concern for the safety of the patient-participant, the PM/GC and or PI will call the patient and review the item(s) and ask questions to monitor the safety and well-being of the patient. The PM/GC and or PI will document this conversation, and review the case with a study team GRC physician. The study team will use their best clinical judgement to determine if the patient-participant is at risk and will make appropriate referrals to the patient's primary care HCP and/or a mental health professional if needed. All cases of safety monitoring will be reviewed by the IRB and the MilSeq GRC according to our Adverse Event Reporting/Safety Monitoring Schema **[See AE Reporting/Safety Monitoring Schema]**.

Study HCP: Follow-up Survey

Six months prior to the end of the study, the study HCPs will complete a brief knowledge and attitudes survey regarding genomic information. The survey will be administered online via a link emailed to participating HCPs.

Study HCP: End-of-study education session (Optional)

After all results disclosure and surveys are complete the HCPs will have the opportunity to come in for an end-of -study education session. This session will review high level study results including common errors study HCPs made during results disclosure sessions and be used as a Q&A session. (Specific HCPs will not be identified in association with their errors, unless the HCP chooses to self-disclose.) This will provide an opportunity for the study team and the HCP-participants to learn from each other.

Genome Resource Center

The Genome Resource Center (GRC) will be available for expert consultation and safety monitoring. If the study HCPs have questions related to the Genomic Reports or family histories or the study in general, they can consult the GRC at any time during the study. The GRC will also be responsible for providing pre-study education. The PM/GC will also be present during the Genomic Medicine Clinic if the study HCPs require a consultation in real time. The GRC will monitor safety as outlined below and in the AE Reporting/Monitoring schema.

In addition to safety, the GRC will also categorize study HCPs' counseling errors as very low risk errors/misconceptions, low risk errors/misconceptions, or high-risk errors. High-risk errors, defined as posing a major safety risk, will be addressed per the AE Reporting/Monitoring schema **[See attached AE Reporting-Monitoring Schema]**. Low risk errors/misconceptions will be defined as errors or misconceptions that are not deemed a safety risk related to the Genomic Report that present potential near-term implications for the patient and their family, such as improper counseling for a common recessive carrier variant (this would have potential reproductive implications in a likely childbearing-age population). Very low risk errors/misconceptions will be defined as errors or misconceptions from the Genomic Report with potential long-term or unlikely family implications such as improper counseling for a very rare autosomal recessive disease, or explaining testing coverage incorrectly, and errors in family history interpretation and counseling.

Laboratory Processing and Pipeline

The Partners HealthCare Laboratory for Molecular Medicine (LMM) is a CLIA and CAP certified laboratory with deep experience with sequencing and interpreting single genes, panels and whole exomes for clinical service and clinical research studies such as this one. The LMM will utilize previously-developed methods to tailor the exome sequencing, analysis, interpretation and reporting pipeline for the MilSeq Project Genomic Report. This pipeline will be based on standard of care for clinical genomic sequencing.

Study staff will send all primary study samples to the LMM. The tubes of blood will be labeled and analyzed by using three identifiers which are typically preferred when performing whole exome sequencing in a CLIA-certified setting: 1) patient's name, 2) patient's date of birth and 3) patient's sex.

Two tubes of blood (20mL) will be sent to the BWH Blood Bank by the LMM for research-related red blood cell antigen phenotyping. The blood typing survey **[See Blood Typing Survey]** that patients fill out during the baseline visit will be sent to the BWH Blood Bank in addition to the blood tube. We will utilize WES data to generate RBC and platelet antigen phenotype predictions for each patient-participant. These predictions will be based on the custom algorithm developed and validated on 100 whole genome sequences in the MedSeq Project.[15] Adaptation and validation of the prediction algorithm using WES data in this study may advance the use of this technology as a potential alternative to conventional serology. RBC and platelet antigen results could significantly improve the efficiency of matching donors and recipients for blood transfusions.

One tube of blood (10 ml) will be used by the LMM for clinical Exome Sequencing and for any Sanger sequencing confirmation of reportable variants. The LMM is a CLIA-certified laboratory accredited through the Joint Commission. The Exome Sequencing test follows all CLIA-certified procedures, has been validated for performance, and includes a targeted capture that has been enhanced for clinically relevant regions. Once a patient's sequence is complete, variant calling, data storage, and interpretation occur within the LMM's secure servers. The LMM will then generate reports for each patient: the Genome Report will include highly-penetrant disease mutations, carrier status for recessive disease, disease-associated risk alleles, pharmacogenomic associations, and information about RBC and platelet antigen phenotype predictors (research data). Through standard clinical reporting mechanisms currently in place at the LMM, a board-certified molecular geneticist will sign-off on all reports prior to release. Genomic Report generation will take approximately 3-4 months from receipt of sample. The MilSeq Project study staff will distribute all Genomic Reports and family history outputs to the study HCP via a secure email. All sequencing results returned to subjects will be limited to tests that are CLIA-certified. All reports will be labeled with the patient's name, date of birth and sex per standards analyzing genomic information.

Procedures for variant interpretation

The MilSeq Project will explore the clinical reporting of large amounts of genomic data with different levels of evidence and known clinical significance. The Genome Report will contain variants with two levels of evidence for clinical significance: variants that meet established standards to be classified as pathogenic, and likely pathogenic. The study HCPs will be educated on the different levels of evidence for variants in the Genome Report, and the Genome Report will include statements regarding levels of evidence for particular variants to guide the HCPs. Additionally, the Genome Resource Center will be available to answer study HCPs' questions about particular variants on the Genome Report.

Incidental (Secondary) Findings Plan

As recruited Service Members will be ostensibly healthy active duty Airmen, nearly all findings in this study will be essentially incidental or unexpected. We will be reporting results in approximately 5000 genes that are known to have clinically-relevant implications. Results will be reported to the Airmen by their study HCP in accordance with the results disclosure plan described above and will be monitored for safety.

Medical Record Review

After all the patient-participants in this study have learned the results of the WES, have been enrolled in the study for at least 6 weeks, and had the opportunity to complete the 6-week post-disclosure survey, the study staff will conduct a review of the medical records. This will be done through a computerized medical record system. We are doing this to learn about whether genomic information affects things like the average number of office visits per year for patients or the number of medical imaging tests ordered by healthcare providers. The study staff may also review other aspects of patient-participants' medical record, such as notes written by healthcare providers **[See MilSeq Medical Record Review document]**. Study staff may review a patient-participant's medical record for data analysis up to one year post result disclosure.

Study Withdrawal

For any subject who withdraws from the study at any time, the study staff will complete a form documenting the reason for withdrawing from the study.

If a patient withdraws from the study prior to having their results disclosed to them by their study HCP, study staff will destroy the Genome Report and it will not be placed in their medical record. If the Genome Report has already been disclosed, it will be in their medical record and cannot be removed.

In the case when an active study participant is unable to come to his/her result disclosure visit because he/she receives a permanent change of station (PCS) order or deployment order, study staff will attempt to contact the patient-participant to arrange for video or phone disclosure of study results by the patient-participant's study HCP, or a study MD geneticist or genetic counselor. Airmen who are unable to be re-contacted will be considered lost to follow-up and will be withdrawn from the study and Genome Reports and blood or DNA samples will be destroyed and will not be uploaded to the EMR.

Procedures in the event of a deceased participant in Phase 2

During the informed consent visit, PM/GC will ask each patient-participant their wishes for how their results would be handled if they pass away during the study and before their results disclosure. This will include the option to destroy the Genomic Report or to provide this information to an identified next of kin. If a patient-participant dies prior to results disclosure the study team will follow their wishes as indicated on the informed consent form.

a. Interventions and Observations:

HCP-participants

The study HCPs will complete a knowledge and attitudes survey pre-education session, and 6 months prior to the end of the study. HCPs will also complete a very brief assessment following the educational module in order to capture the effectiveness of the module. Following each disclosure session, they will be asked to complete the HCP Checklist within two weeks of results disclosure, which will ask HCPs to document all follow-up healthcare recommended and/or ordered and the reason(s) why they chose that plan of action.

Patients-participants

Surveys will be administered at baseline to all consented patient-participants in phase 1 **[See Patient Baseline Survey]**. The baseline survey will assess: perceptions of genomic sequencing, perceived risks and benefits, and knowledge of genomic sequencing. For baseline patient-participants who express interest in participating in the genomic study, the survey will also assess motivations, preferences, and expectations. For those who indicate that they would not be interested in participating in the genomic study, the survey will explore barriers to participation. Patient-participants who enroll in Phase 2 will receive whole exome sequencing

and will have their family history collected by the PM/ GC. WES results will be disclosed by a study HCP and they will receive a 6-week post disclosure follow-up survey. The post-disclosure surveys will assess: perceptions of genomic sequencing, perceived risks and benefits, knowledge of genomic sequencing, whether expectations were met, behavioral responses, satisfaction with WES, and decisional regret.

b. Setting:

Recruitment

Recruitment of Airmen for a baseline survey may occur in military Primary Care, Internal Medicine and/or Family Practice clinics, or via an electronic newsletter.

Recruitment of 75 active-duty Air Force Airmen for a WES study will occur via a question on the baseline survey assessing interest in participating in a WES study. Airmen who express interest will be contacted by the study staff by phone, email or mail to assess interest in coming in for an in-person consent session**.**

Recruitment of 10-20 military Primary Care, Internal Medicine and/or Family Practice HCPs will occur via clinician conferences, or mail/email to these clinicians requesting interested volunteers to receive a genomics education module and serve as Genome Medicine providers for interested patient-participants.

Consent

Consent will take place in a private room in or near the clinic space.

Surveys:

Surveys will be administered online, hosted by REDCap. If necessary, surveys may also be administered via phone or mail. The associate investigators at Baylor College of Medicine (BCM) will develop and program the surveys.

Analysis

Exome analysis will take place at the LMM. Analysis of survey data will take place Brigham and Women's Hospital (BWH), with survey data hosted on a secure BWH REDCap server. Analysis of survey data will be performed by associate investigators at BCM and BWH. Audio-recordings will be transcribed and analyzed by the onsite PM/GC and transmitted through a secure server with other GRC staff and project investigators as needed.

c. Date(s):

Recruitment of patient-participants and HCPs for this study will begin after IRB approval is obtained (estimate summer 2017) and is expected to continue through June 2018. Analysis of WES information, generation of Genome Reports, and incorporation of Genome Reports into patient medical records is expected to occur through September 2018. These dates may vary slightly based on the IRB approval date.

d. Subjects:

Subjects are individuals who meet the inclusion/exclusion criteria below. Subjects will not have a relationship with the PI's or AI's.

e. Inclusion/Exclusion Criteria:

Inclusion Criteria	Health Care Provider-Participants I. An active or DoD civilian primary care, internal medicine, or family practice Health Care Provider (Physician, Physician Assistant or Nurse Practitioner) or resident practicing at Wilford Hall Medical Center. Patient-Participants I. 18 years or older II. An active Air Force Airman III. Fluent in English IV. Seen or eligible to be seen by a provider at Wilford Hall

Exclusion Criteria	Health Care Provider-Participants I. Providers who do not meet the above inclusion criteria II. Providers with an active PCS order or deployment order and expected to leave San Antonio in 6 months or less. III. Providers expected to be discharged from the Air Force in 6 months or less Patient-Participants I. Those who do not meet the above inclusion criteria II. Those with clinically concerning scores on anxiety and distress scales in baseline survey III. Trainees (basic military training or tech school) IV. Airmen with an active PCS order or deployment order and expected to leave San Antonio in 6 months or less. V. Airmen expected to be discharged from the Air Force in 6 months or less

Source of Research Material per Participant (Procedures)	**# Routine Care**	**# Research Driven**	**# Total Procedures**
Blood Sample	0	1	1
Survey – HCP-Participants	0	3	3
Survey- HCP Checklist		1-15 (dependent on # of patient participants seen)	1-15 (dependent on # of patient participants seen)
Survey – Patient-Participants	0	3	3
Medical Record Review	0	1-12 (dependent on safety monitoring and study funding)	1-12 (dependent upon safety monitoring and study funding)

Medical records will be reviewed to look for referrals, tests and interventions recommended that are directly related to WES or family history collection as part of the study. The AHLTA Military electronic medical records system will be reviewed (this may be upgraded to Genesis by the end of the study) **[See attached MilSeq Medical Record Review]**.

"All specimens kept at Partners LMM will be handled and disposed of in accordance with federal regulations."

g. Instruments

[See attached surveys]

Baseline surveys

Baseline surveys will assess patient-participants' attitudes and perceptions toward, as well as interest in and barriers to, genomic sequencing. We will also assess baseline genetic knowledge and health behaviors including, diet, exercise and smoking habits, and medication and supplement use. Data on patient-participants' current insurance status, general socio-demographics, and health history will also be collected. Measures will be published validated scales, adapted measures used in similar studies, or novel and developed for this study population. Any novel scales developed will be reviewed for reliability prior to conducting analysis. Items measuring anxiety and depression will be administered and responses reviewed for study inclusion.

6-week post-disclosure survey

Six weeks after receiving WES results we will administer a survey to assess changes in attitudes and perceptions toward genomic sequencing and genetic knowledge. We will also assess satisfaction with receiving WES results and the impact on health behaviors and anxiety and depression. Similar measures from the baseline survey will be used in the follow-up survey to allow for pre- and post-intervention analyses.

Laboratory for Molecular Medicine Quality Data for Sanger Confirmation and Exome Sequencing

LMM Sanger-Confirmed Variants (v1.6)	WES-FAST1.1
True Negatives (TN)	665,492
True Positives (TP)	427
False Negatives (FN)	0
False Positives (FP)	15
Sensitivity (All Variants) *TP/(TP+FN)*	**100.00%** ($CI_{95\%}$: 99.11-100.00%) *427/427*
Sensitivity (SNVs) *TP/(TP+FN)*	**100.00%** ($CI_{95\%}$: 99.07-100.00%) *410/410*
Sensitivity (In/Dels) *TP/(TP+FN)*	**100.00%** ($CI_{95\%}$: 81.57-100.00%) *17/17*
Specificity *TN/(TN+FP)*	**99.99%** ($CI_{95\%}$: 99.99-100.00%) *665,492/665,919*
Positive Predictive Value *TP/(TP+FP)*	**96.61%** ($CI_{95\%}$: 94.48-97.93%) *427/442*
NIST Genome in a Bottle Dataset (v3.3.1)	**WES-FAST1.1**
True Negatives (TN)	36,382,862
True Positives (TP)	23,848
False Negatives (FN)	332
False Positives (FP)	213
Sensitivity (All Variants) *TP/(TP+FN)*	**98.63%** ($CI_{95\%}$: 98.47-98.77%) *23,848/24,180*
Sensitivity (SNVs) *TP/(TP+FN)*	**99.21%** ($CI_{95\%}$: 99.09-99.32%) *22,717/22,898*
Sensitivity (In/Dels) *TP/(TP+FN)*	**88.22%** ($CI_{95\%}$: 86.34-89.87%) *1,131/1,282*
Specificity *TN/(TN+FP)*	**99.99%** ($CI_{95\%}$: 99.99-100.00%) 36,382,862/36,383,075
Positive Predictive Value *TP/(TP+FP)*	**99.11%** ($CI_{95\%}$: 98.99-99.23%) *23,848/24,061*

[1] *The validation used the NIST v3.31 dataset for evaluating performance*

[2] *The validation used the LMM Sanger-confirmed variants v1.6 for evaluating performance*

2. HUMAN SUBJECT PROTECTION

Recruitment and Consent Processes:

Recruitment Processes

HCP-participants

Any active-duty study investigator will be attired in civilian clothing and will not reference his/her military rank when interacting with participants or potential participants to avoid undue influence of rank.

Air Force HCPs who practice in primary care, internal medicine, or family practice may be approached during clinician conferences and through mail/email from the study PM/GC and/or study team. The consent will be distributed to all interested HCPs via email or in person. The study team will answer any questions from the HCPs. If the HCP requests to speak with Dr. Gardner, Dr. Green or other project leaders, study staff will connect them.

The PM/GC and the study staff will keep track of the HCPs who decline study participation and document the reasons why **[See Study Decline Log – HCP].** Interested HCPs will be consented by the study team at a mutually agreed upon time.

Patient-participants

Active-duty Airmen may be recruited in the following ways: (1) in-person recruitment by the study Project Manager/Genetic Counselor. (2) HCPs may mention the study to their eligible patients and provide them with a study brochure or flier that includes information about the baseline survey. (3) Fliers and brochures, including inclusion and exclusion information, will be placed in Wilford Hall medical clinics. (4) Fliers and brochures will be distributed via base newsletters. These fliers /brochures will include information about the study and how to access the baseline survey. The link to the baseline survey will first pull up the electronic consent for the survey. Patients who electronically consent to the baseline survey will be enrolled in Phase 1 of the study, which includes the baseline survey only, and enrollment will be tracked. Survey questions will include a question assessing interest in participating in a whole exome sequencing study (Phase 2 of the study - the WES study). Text introducing this question will make it clear that answering “Yes” to this question does NOT guarantee participation in the WES phase of the study nor require participation. Airmen who answer “Yes” that they are interested in participating in the baseline survey will be prompted to enter their name and contact information so that they can be contacted at a later time. This

information will be contained in a secure REDCap database and will be shared with the Project Manager/Genetic Counselor who will call the participants.

Once the baseline survey is completed, the study staff will review items assessing anxiety and/or depression. If a patient's answers suggest they are experiencing elevated depression and/or anxiety, a study PI and/or a study genetic counselor will speak to the patient by phone regarding their score to determine if appropriate referrals are needed. If the patient has clinically-significant anxiety or depression they will be excluded from study participation.

If a patient-participant has indicated they may be interested in participating in the WES study on their baseline survey, and if they qualify based on the inclusion/exclusion criteria for the WES study, they will be prompted with a question asking for their name and email address. This information will be kept on a secure REDCap database. The study Project Manager/Genetic counselor will access this information and will contact interested individuals to provide information about the study **[See MilSeq Recruitment Phone Script]**. Those who are interested will be offered an appointment for informed consent.

The study Project Manager/Genetic Counselor will seek permission from Wilford Hall Primary Care, Internal Medicine and Family Practice clinics to set up space in the clinic for recruitment on a schedule that is mutually agreed upon by the clinic and the PM/GC. This will facilitate in-person conversations about the study between interested individuals and the PM/GC. If a patient is interested in participating, the baseline survey may be completed in the clinic space: the Project Manager will log in and allow the patient to read through the online Phase 1 consent and ask any questions. The patient-participant can then respond to the baseline survey on the study laptop. If the patient-participant meets inclusion/exclusion criteria as described above, and they are interested in enrolling in Phase 2, the patient-participant will be allowed to schedule their consent visit for phase 2 at this time.

We will aim to have 750 patients complete the baseline survey. Anticipating a 10% enrollment rate into the WES phase, In the event of loss to follow-up or patient withdrawal, we will reinstitute recruitment procedures to meet our goals of having 75 patients who receive WES result disclosure by a military HCP.

Consent Processes:

HCP-participants

Interested HCPs will be provided a copy of the consent form in advance of the consent session by email. HCP-participants will be

able to consent anytime they are ready during the enrollment period; there will not be a designated waiting period. A consent session will be scheduled for a time that is convenient for the HCP and PM/GC. This consent may take place in conjunction with

the physician education session but will happen before any study activities take place. This consent session will occur at a location convenient to the HCP and Project Manager. This consent session will take approximately 15-30 min. The PM/GC will consent the HCP-participant and answer questions. The PM/GC will keep track of the HCPs who decline study participation and document the reasons why and will keep track of the HCPs who consent. The PM/GC will then assign each consented HCP a study ID number. The PM/GC will store the signed consent forms in a locked file cabinet in her office.

Patient Participants

Consent for Phase 1 **[See Baseline Survey]** will be obtained electronically with a user-checked box statement of consent, on a secure web page before the first page of the survey.

Consent for Phase 2 (WES study) will occur in person between the patient-participant and the PM/GC. Patient-participants will be able to consent anytime they are ready during the enrollment period; there will not be a designated waiting period. This visit will take approximately 1-1.5 hours. The PM/GC will keep track of the reasons patient-participants decline participation after initially expressing interest on their baseline survey and will keep track of the patients who consent. Patient participants will be consented in a private room near or in the clinic space. Consent will take approximately 20-45 minutes. Once consented the Project Manager will assign each patient a study ID number then will collect a family history and the patient will have their blood drawn. Three 10ml tubes of blood will be collected from all patient-participants. The patient-participant will all complete a blood questionnaire. After the blood is drawn, the first visit will be complete. The Project Manager will store the signed consent forms in a locked file cabinet in her office. Each active duty member will receive a payment of $50 when they have completed their blood draw, based on 24 USC 30.

Benefits:

Potential benefits to Patient-Participants

There may be no direct benefits to participating individuals. Patient-participants may learn genetic information about themselves or family members that is beneficial to them in terms of managing current disease, identifying risk of future disease which would allow the opportunity for surveillance and/or prevention, or identifying genetic information that provides personal utility, such as family planning or satisfying one's curiosity about their own genetic makeup.

Potential benefits to Health Care Provider-Participants

There may be no direct benefits to participating HCPs. HCPs may learn more about genetics and exome sequencing as a result of participating in this study. HCPs may also benefit from a strengthened HCP-patient relationship with patients enrolled in this study.

Risks:

Potential risks to Patient-participants:

- Emotional or psychological distress from learning genetic information about oneself or family members, including learning information about current or future children's risk to develop a genetic condition or from learning uncertain genetic information or information that could change over time.
- Loss of position due to the identification of a secondary finding that is found to put the patient-participant at risk during an active-duty situation. There are protections in place by the Air Force to limit discrimination—this includes the Directive-Type Memorandum: Implementing Disability-Related Provisions of the National Defense Authorization Act of 2008- **E3.P4.5.2.2** Hereditary and/or Genetic Diseases clause. However, if a patient-participant is identified to have an unexpected (incidental or secondary) genetic variant that could put them at risk during an active-duty situation, they may risk loss of position or adverse career consequences (affecting promotion and/or career progression) **[See Information on Genetics for Airmen]**.
- Inability to obtain future insurance coverage not protected by DTM on Implementing Disability-Related Provisions of the National Defense Authorization Act of 2008 Hereditary and/or Genetic Diseases clause, or if discharged and in the civilian sector not covered by the Genetic Information Nondiscrimination Act (GINA).
- Loss of privacy.
- Risks from a normal blood draw including bruising and infection.

Potential risks to HCP-participants:

- There are no anticipated common or uncommon risks associated with participation in this study. Study HCPs will operate within the routine practice of medicine and adhere to professional standards. The genomic information about Airmen patients derived as part of this study is an additional informational resource that may or may not be useful in the care of these patients just as other sources of information are used in medicine.

- Study HCPs may feel uncomfortable with genomic information about patients derived from this study, but the training offered in the Education Module and the availability of the Genome Resource Center Staff will support them. HCPs may also contact the MilSeq DSMB Committee directly with any concerns during their study participation.

Study personnel will take the following measures to ameliorate these risks:

- Patient-participants enrolled in the WES phase of this study will undergo a detailed in-person informed consent process with a Project Manager/Genetic Counselor, which includes discussion of each of these uncommon risks and prepares the patient-participant for the many categories of results that could be discovered.
- The Genome Resource Center (GRC) staff will review all cases for situations that may impact patient safety **[See attached MilSeq AE Reporting- Monitoring Schema- page 2]**. The GRC will create a mechanism to provide feedback regarding miscommunication or misunderstanding of information between HCPs and patients. The GRC will write a cumulative report for the DSMB twice annually, or ASAP if the safety issue is deemed to be urgent. The IRB will be alerted of all issues identified through the GRC review in a cumulative adverse event report.
- The study PI will monitor all cases and seek action in real-time as appropriate. The IRB will be alerted of all Serious and Non-Serious Adverse Events according to our protocol **[See attached AE Reporting- Monitoring schema].**
- Study personnel will take every precaution to keep patient-participants' personal identifiers confidential and protect each patient-participant's privacy in all parts of MilSeq in which these data are used.
- The GRC will be available for phone or email consultations to study HCPs throughout the course of the study.

Costs:
N/A

Safeguards for Protecting Information:
• The PIs will be responsible for monitoring the quality of the data collected as part of this study. • All survey, audio-recorded and transcribed data will be analyzed using the patient's study number and not his/her name or other identifiers. • Audio-recorded visits will be digitally converted to audio ".wav" files.

- Audio recordings will be transcribed and both will be kept for at least 3 years after the completion of the study. They will be electronically stored, double password-protected, on the MilSeq Project Manager's computer. De-identified transcripts will be shared with MilSeq investigators at Baylor College of Medicine and Brigham and Women's Hospital.
- The link containing patients' study ID to personal identifiers will be double password-protected and maintained in a password-protected folder on an Excel spreadsheet in a secured share drive with limited access. This will be stored for at least 3 years per regulations.
- The Project Manager will store the signed consent forms in a locked file cabinet in her office. This will be kept by the Study PM or the study PI for at least 3 years per regulations.
- Survey data will be stored in a secure REDCap database for at least 3 years.
- All blood samples and exome data will be analyzed in a CLIA-certified setting.
- WES and the generation of reports using WES data will be conducted in a CLIA-certified setting utilizing clinical genetics reporting standards already in place.
- The patients' WES data and any reports generated from that data will be stored by the LMM within the HIPAA-compliant datacenter at Partners HealthCare* (raw data files for at least the duration of the grant but no less than 2 years and .vcf files and the patients' Genome Reports indefinitely).

If a patient withdraws from the study prior to having their results disclosed by a study HCP, we will destroy the Genome Reports.

*All systems are secured behind an Information Security firewall. They comply with Information Security policies for authenticated, secure and minimum access. All systems are patched, monitored and scanned routinely for vulnerabilities and intrusions. Data is encrypted, where applicable, in compliance with State and federal government standards and regulations. All configuration changes that could affect accessibility or security are approved.

The Laboratory for Molecular Medicine (LMM) shares detailed information on variants interpretations with the broader community through efforts such as ClinVar. ClinVar is a publicly available database of genomic variation and its relationship to human health, maintained by the National Center for Biotechnology Information (NCBI) and funded by the Intramural Research Program of the National Institutes of Health (NIH), National Library of Medicine. ClinVar catalogs and aggregates variant submission with their reported clinical significance and supporting information, when available. ClinVar adds value to submitted interpretations by standardizing descriptions of variants, conditions, and terms for clinical significance. This information is made publicly available through ClinVar for use in the healthcare community. Data shared by the LMM to this resource is limited to individual interpretations and is independent of any case-level or identifiable data.

Safeguards for Protecting Subjects Relative to Reasonably Expected Risks:

Safety Monitoring and Reporting
The PI will ensure that mishaps or injuries sustained during research will be reported.

Patients will be monitored for levels of significant anxiety and/or depression via survey items administered after learning the results of their Genomic Report and family history review. The Genome Resource Center (GRC) staff will review all cases for situations that may impact patient safety. The GRC will create a mechanism to provide feedback regarding miscommunication or misunderstanding of information between the HCP and patient. The IRB will be alerted of all issues identified through the GRC review in a cumulative adverse event report. Serious Adverse Events (SAEs) will be reported immediately (within 24 hours) to the PI and within one week to the IRB. Non-serious Adverse Events (AEs) will be reported annually to the IRB.

3. DATA ANALYSIS

Data Analysis:

Quantitative Analyses

Descriptive statistics will be used to characterize HCPs and patients in terms of demographic variables, motivations for and barriers to participating in this study, and disclosure preferences. Descriptive statistics will also be used to characterize patients in terms of genetic knowledge, psychological impact and personal utility of testing, and perceptions of risks and benefits, expectations and satisfaction of study participation, and behavioral responses.

Outcome Measures:

See attached surveys

Measures will be published validated scales when available, adapted measures used in similar studies, or novel and developed for this study population. Any novel scales developed will be reviewed for reliability prior to conducting analysis.

Health Care Providers

The outcome measures for HCPs include: genomic knowledge, attitudes toward genomic sequencing, and healthcare ordered and/or recommended in response to genomic information about a patient and the reason(s) for that plan of action. Variables assessed in the baseline and end-of-study surveys will be compared to assess changes.

Patients

The outcome measures for patient-participants include: perceptions of genomic sequencing, perceived risks and benefits, knowledge of genomic sequencing, motivations, preferences, expectations, barriers to participation, psychological impact, whether expectations were met, behavioral responses, satisfaction with WES, and decisional regret. Variables assessed in the baseline and 6-week post-disclosure surveys will be compared to assess changes.

Sample Size Estimation/Power Analysis:

Anticipated sample size:

Phase 1 – baseline survey: 750 active duty Airmen patient-participants

Phase 2 – WES study: 75 active duty Airmen patient-participants and 15-20 healthcare providers

Given the lack of prior research in this area in the Air Force, and the broad number of topics of interest, the aims of the study are predominantly exploratory and results may be hypothesis generating.

Statistical Analysis:

For measures where we have both baseline and post-disclosure survey data we will use standard pre-post analyses (e.g., paired t-tests, repeated measures analyses) to assess whether significant changes occurred in these domains following receipt of test results.

Number of Subjects:				
	# Planned to Enroll	# Enrolled	# Planned to Complete Study	TOTAL
Number of Airmen Subjects at 59 MDW – Phase I	750			750
Number of Airmen Subjects at 59 MDW – Phase II	75*			75
Number of HCP Subjects at 59 MDW	10-20			20

***The 75 subjects for Phase II are part of the Phase I group who completed the online survey and expressed a willingness to participate in Phase II of the study**