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Provision of basic genetic counseling services by primary healthcare providers after an educational intervention: Lessons learned from the MilSeq Project

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CONFLICT OF INTEREST NOTIFICATION PAGE

The authors do not have any commercial association that might pose, create or create the appearance of a conflict of interest with the information presented in the submitted manuscript.

ABSTRACT

*PURPOSE***:** With few trained genetics professionals, the Military Health System is ill-equipped to manage the rapid expansion of genomic medicine. The MilSeq Project introduces an alternative service delivery model (ASDM) in which primary healthcare providers (HCPs) provide post-test counseling (PTC) to healthy Airmen who have undergone exome sequencing. We describe HCP performance after a pre-requisite educational intervention (EI). *METHODS:* After a brief EI and pre-/post-education surveys, HCPs were eligible to provide PTC with a genetic counselor available for consult. PTC was recorded, transcribed, and reviewed. Opportunities for improvement were organized into 4 error adjustment categories: (1) "Knowledge Limitation," (2) "Minor," (3) "Moderate," and (4) "Critical." Thematic analysis was also performed. *RESULTS:* Pre-/post-education survey responses revealed statistically significant improvements in all domains. "Minor" error adjustments were most represented (n=93), followed by "Knowledge Limitation" (n=39) and "Moderate" (n=19). No "Critical" errors were identified, and 17 transcripts required no adjustment. Thematic analysis revealed 4 themes that would benefit from more focused education: (1) Family-Centered Care, (2) Conveying Risk, (3) Disease Knowledge, and (4) Assay Knowledge. *CONCLUSION:* HCPs demonstrated competence in basic PTC after a brief EI**.** This ASDM may be a viable interim response to the shortage of genetics professionals in some systems.

KEY WORDS

Genetic counseling, genetic services, education, intervention, exome sequencing

INTRODUCTION

As genomic sequencing (GS) has broadened the scope and relevance of genetic medicine, the demand for expert clinical interpretation exceeds the supply of trained genetic professionals. Prominent medical genetics organizations have recognized this growing shortage and have initiated nationwide workforce analyses to address the identified gap.[1,2] Assuming approximately 70% projected career growth and a stable supply-to-demand ratio of 1 genetic counselor (GC) to 75,000 individuals, the Genetic Counselor Workforce Working Group estimates that the GC shortage in the United States (U.S.) may not equilibrate for another decade.[2]

The demand for genetic services in the U.S. military has increased in tandem with the civilian sector.[3] With few trained genetic professionals in its midst, the U.S. military is currently ill-equipped to manage the expanding role of genetic medicine in routine healthcare delivery. For this reason, military healthcare providers (HCPs) with training in basic pre- and post-test genetic counseling are crucial; particularly with respect to appreciating the nuances and specific concerns of military service.[4]

The MilSeq Project (Enabling Personalized Medicine through Exome Sequencing in the U.S. Air Force) was developed to explore an alternative service delivery model as an interim response to the shortage of genetics professionals in the near term. Because the Military Health System (MHS) is one of the largest and most complex healthcare institutions, with millions of beneficiaries and hundreds of military treatment facilities (MTFs) worldwide,[5] traditional and nontraditional (e.g., telegenetics, group counseling) models have not been sufficient to provide genetics services to the totality of its members.

The MilSeq Project introduces an iteration of the alternative service delivery model first piloted in the MedSeq Project,[6] in which the primary care workforce provides basic post-test genetic counseling. To minimize a "substitution effect,"[2] the MilSeq model includes a prerequisite GC-instructed educational intervention, point-of-care support and ongoing supervision by trained genetics professionals, and post-counseling evaluation. Here we describe HCP performance in their provision of basic genetic counseling services to 75 ostensibly healthy active-duty Airmen who have undergone clinical exome sequencing (ES).

MATERIALS AND METHODS

HEALTHCARE PROVIDER RECRUITMENT

A nonrandomized convenience sample of 3 staff internists, 5 resident internists, 1 staff Preventative Medicine physician, 1 staff Aerospace Medicine physician, and 2 Trainee Health nurse practitioners (n=12) were recruited by group announcement and personal advertisement at a single U.S. military installation. All HCP participants were active-duty Air Force. As a function of study design, the HCP cohort was small relative to the size of the patient cohort to maximize HCP-patient interaction.

PATIENT RECRUITMENT

A nonrandomized convenience sample of active-duty Airmen (n=93) were recruited by flyer, newsletter, social media posting, and personal advertisement in proximity to primary care clinics at a single U.S. military installation. In Phase I of recruitment, Airmen were asked to complete a baseline survey in electronic format, designed to assess knowledge, attitudes, and perceptions of GS. The baseline survey concluded with an invitation to participate in a second phase that involved clinical ES. Airmen electing to advance to Phase II (n=75) were scheduled

for an informed consent session with the GC project manager. Following voluntary informed consent, patient participants provided blood samples for ES and later received customized exome reports with interpretation and result disclosures performed by HCP participants. The patient cohort was intentionally unselected for Air Force occupation.

EDUCATIONAL INTERVENTION DEVELOPMENT AND INSTRUCTION

An educational intervention tailored to the needs of the U.S military was developed by an MHS-experienced GC and active-duty clinical geneticist. The educational module was further reviewed and curated by a larger, multidisciplinary team of research GCs, clinical geneticists, molecular geneticists, primary HCPs (civilian and military), bioinformaticians, bioethicists, and legal experts.

For consistency with standard medical genetics curricula, educational content was principally derived from *Medical Genetics*.[7] Content was balanced between foundational genetics topics (e.g., Mendelian inheritance, Punnett square crosses, pedigree nomenclature) and nuanced, anticipatory guidance for study-related post-test counseling (e.g., expressivity/penetrance, compound heterozygosity, pharmacogenomics). Structured common and complex clinical vignettes representative of each inheritance pattern were presented to exercise clinical reasoning. Characteristics unique to genetic test utilization within MTFs were also presented, including but not limited to: (1) electronic health record (EHR) system navigation, (2) laboratory capitation, and (3) internal versus external (i.e., MTF/telegenetics versus civilian) genetic referral logistics. As primary HCPs' availability for continuing education can be limited by administrative and clinical obligations,[8] the module was developed to be instructed in a 3-hour period and approved for 3 American Medical Association Physician Recognition Award Category

1 Credits™. HCP participants also received clinic aids which included counseling prompts and common motifs associated with autosomal dominant, autosomal recessive, and X-linked inheritance.

SURVEY ASSESSMENT

After obtaining informed consent, HCP participants were asked to complete pre-education surveys designed to assess their perceived self-confidence, preparedness, self-efficacy, and knowledge with regard to the provision of genetic services. Immediately following instruction, post-education surveys were administered to assess any change in these metrics.

Five items measured HCP participants' confidence, with response options on a 4-point Likert-type scale anchored on one end with 1 = "Not at all confident" and the other end with 4 = "Very confident."[9] Preparedness was assessed by asking, "How prepared do you feel to disclose results directly to patients?" using a 4-point Likert-type scale with response options from 1 = "Very prepared" to 4 = "Not at all prepared."[6] HCPs' self-efficacy was measured by 7 items using a 5-point Likert scale with response options anchored on one end by 1 = "Strongly disagree" and the other end with 5 = "Strongly agree."[10, 11] Genetic knowledge was assessed using 14 multiple-choice items (Tables 1-2).[11, 12]

Descriptive statistics, including means, standard deviations, medians, and interquartile ranges, were calculated to characterize HCP participant data. Average scores were computed for confidence and self-efficacy from each HCP's responses to all 4 confidence questions and all 7 self-efficacy questions, respectively. The total number of correct responses to genetic knowledge questions were summed for each HCP to calculate an individual genetic knowledge score. Since the confidence, preparedness, and genetic knowledge scores were not normally

distributed nor symmetric about the median, non-parametric sign tests were used to compare pre- and post-education differences in these measures. The self-efficacy score was normally distributed; so a paired t-test was used to compare pre- and post-education differences in this measure. All statistical calculations were performed using R software.[13]

PERFORMANCE ANALYSIS

Upon satisfactory completion of the prerequisite educational intervention, HCP participants were eligible to perform post-test counseling for patient participants with ongoing support and supervision from a Genome Resource Center (GRC), locally and remotely staffed by GCs, clinical geneticists, and molecular geneticists. Post-test counseling appointments were scheduled between HCPs and patients based on mutual availability. Exome reports were provided to HCP participants at least 1 week in advance of their scheduled appointments to allow sufficient time for review and GRC engagement as needed.

At the time of post-test counseling, the GC project manager was embedded in clinic for ad hoc point-of-care consult, and the 75 disclosures were audio recorded, transcribed, and reviewed by the GRC for accuracy and appropriateness. Reviews were conducted by teleconference to facilitate inclusion of local and remote GRC members.

To standardize evaluation and minimize intra-reviewer variability, a novel, adapted rubric was developed from Institutional Review Board regulations and guidelines pertaining to protocol deviation, violation, and adverse outcome reporting.[14] Opportunities for improvement identified during post-test counseling sessions were organized into 4 categories: (1) "Knowledge Limitation," lacking sufficient baseline knowledge and/or experience to comprehensively counsel the patient beyond the information provided in the report, (2)

"Minor" adjustments for errors posing minimal risk to optimal care, (3) "Moderate" adjustments for errors posing some degree of suboptimal care, and (4) "Critical" adjustments for errors endangering patient safety.

Adjustments were addressed as appropriate with individual HCP participants at the GRC's discretion and optional feedback was provided at the HCP participants' request after transcript review.

THEMATIC ANALYSIS

Inductive thematic analysis was performed to identify patterns within the qualitative data. Transcribed disclosures were reviewed in aggregate and HCPs' post-test counseling was manually coded to capture gaps in functional knowledge and practice. Related codes were then collated for a general overview of recurrence, and the resulting framework was used to define common themes.

RESULTS

SURVEY ASSESSMENT

Analysis of the HCP cohort's pre- and post-education survey responses revealed statistically significant improvements from baseline ($p < 0.05$) in all domains assessed (Table 3).

PERFORMANCE ANALYSIS

GRC transcript review data demonstrate that the "Minor" adjustment category, posing minimal risk to optimal patient care, was by far the most represented (n=93), followed by "Knowledge Limitation" (n=39) and "Moderate" (n=19) error adjustments, respectively (Table 4). These data yield an average rate of 1 to 2 "Minor" error adjustments per transcript, and sporadic instance (< 1 per transcript) of other adjustment types. Of note is that no "Critical" errors were

identified, and that nearly one quarter (17/75; 23%) of all transcripts required no GRC adjustment (Figure 1).

THEMATIC ANALYSIS

Thematic analysis of systematic errors derived from transcript review revealed 4 major themes that would benefit from more focused education: (1) Family-Centered Care, (2) Conveying Risk, (3) Disease Knowledge, and (4) Assay Knowledge.

I. FAMILY-CENTERED CARE

HCPs are traditionally trained in patient-centered care, in which the *individual's* needs and improved outcome drive healthcare decisions.[15] Therefore, they may overlook important counseling recommendations informed by family history. This was suggested by some providers' performance in contextualizing results within the pedigree, and in discussing cascade testing and implications for family members.

For example, a patient participant was identified to be heterozygous for a likely pathogenic variant in *LDLR* (c.862G>A), which is associated with autosomal dominant familial hypercholesterolemia (FH). The HCP appropriately counseled the patient that he is affected with this highly-penetrant condition, citing his most recent total cholesterol level of 300 mg/dL and prescribing a statin for medical management. However, the HCP did not address that the same health risks apply to at least one of the patient's biological parents due to the condition's autosomal dominant segregation and penetrance. The HCP also did not address the expert consensus for pediatric FH screening, which is relevant because the patient has 2 young sons for whom early pharmacologic therapy can be considered:

> The phenotypic diagnosis of FH in children is established with two LDL-C levels […] If a parent has a documented FH gene mutation, then an LDL-C >130 mg/dl is sufficient. DNA testing confirms the diagnosis. […] The goal of therapy is a 50% reduction in LDL-C levels, preferably to <130 mg/dl. If dietary and lifestyle modifications fail to achieve this, pharmacologic treatment with statins is recommended beginning at ages 8-10 years.[16]

II. CONVEYING RISK

HCPs in routine medical practice treat common conditions and manage overall health. Therefore, they may experience challenges in distinguishing the rarity of monogenic conditions, and in conveying relative risk and polygenic risk.

For example, a proportion of patient participants were identified to be heterozygous (n=22) or homozygous (n=3) for the established Alzheimer disease risk variant in *APOE* (c.388T>C), also known as the *APOE*E4* allele. HCP participants who were assigned these exome reports for disclosure often discussed the associated odds ratios only superficially with their patients. While they appropriately counseled that the finding was not predictive of disease, but rather imparted increased risk, they often presented patients' relative risk arbitrarily rather than as a defined value calculated from the information provided in the report.

III. DISEASE KNOWLEDGE

HCPs are generally less accustomed to the nuances of genetic conditions and genetic testing, and may be disinclined to use unfamiliar, genetic-specific resources such as GeneReviews® or Online Mendelian Inheritance in Man®. This was evidenced by some providers' performance in describing disease phenotype and natural history.

For example, a patient participant was identified to be heterozygous for the reduced penetrance allele in *HFE* (c.187C>G), which is associated with hereditary hemochromatosis (HH). While the HCP explained the patient's carrier status, autosomal recessive inheritance, and reproductive risk correctly, he confused the pathophysiology of HH with polycythemia; counseling that the condition is characterized by increased erythropoiesis, elevated hematocrit, and thrombotic risk rather than iron overload, organ deposition, and iron-induced tissue damage. However, because therapeutic phlebotomy is common to both conditions, the patient was properly informed of primary treatment.

IV. ASSAY KNOWLEDGE

Most laboratory tests ordered in routine medical practice are chemical assays for which there are standard ranges and results are clearly defined as "normal" or "abnormal." Therefore, the complexity of advanced, high-throughput next generation sequencing assays with bioinformatic analysis may require more dedicated orientation.

For example, a patient participant was identified to be heterozygous for a pathogenic variant in *FANCC* (c.1642C>T), which is associated with autosomal recessive Fanconi anemia (FA). The patient reported his 24-month-old son to have multiple congenital café-au-lait spots and cystic hygroma, both of which have been linked to FA,[16] as well as a negative neurofibromatosis (*NF1*) evaluation. Given this history, the HCP appropriately discussed carrier testing for the patient's spouse. However, this discussion was abandoned when the patient reported that his spouse had undergone direct-to-consumer (DTC) genetic testing through a company that advertises limited *FANCC* variant analysis. The primary HCP was unaware of the distinction between DTC genotyping and clinical-grade GS, and was therefore unprepared to discuss the caveats of DTC

genetic testing, such as the high false-positive rate requiring clinical confirmation,[18] or false reassurance from a negative screen that does not exclude residual carrier risk.[11]

DISCUSSION

These preliminary data suggest that the investigated alternative service delivery model, in which genetics expertise is extended through GC- and geneticist-mediated primary care support, performed successfully in the MHS microcosm. As determined by a team of trained genetics professionals, HCP participants demonstrated competence in basic post-test genetic counseling after a brief, highly-specific educational intervention. The majority of errors scrutinized were negligible to patients' general understanding of their result and overall health, requiring minimal adjustments. It is also noteworthy that no critical errors endangering patient safety, such as irreversible treatment decisions, were observed. In fact, most patient participants received accurate and appropriate medical management information.

When surveyed, all HCP participants reported statistically significant increases in self-confidence, preparedness, self-efficacy, and knowledge after the GC-instructed educational module; findings which were reinforced by their satisfactory counseling performance. While the HCP cohort was intentionally small, compensatory non-parametric analyses and lack of outliers indicate that the dataset's statistical significance is valid despite small sample size.

That being said, the generalizability of these results should be interpreted judiciously, as the study was conducted in a closed healthcare system with universal EHR integration and broad access to healthcare resources. Study materials were also developed to fulfill specific Air Force requirements and were almost exclusively dedicated to ES.

As it was not our objective to train primary HCPs to be as knowledgeable or effective as genetics professionals, gaps in functional knowledge and practice were expected and are regarded as opportunities for improvement. The educational intervention for this population was developed without precedent and further refinement was anticipated based on study outcomes. Future versions of the educational module can be adapted to more thoroughly address considerations unique to the provision of genetics services in the primary care workforce.

It has been established that the shortage of trained genetics professionals has restricted access to genetic services due to either proximity or availability constraints. Consequently, there is a heightened demand for genetic services in routine medical practice and HCPs trained in other fields play an increasingly more active role its provision.[19,20] The alternative service delivery model introduced by the MilSeq Project may be a viable stopgap measure for the provision of genetics services within the context of this shortage. The collaboration between primary HCPs and the few trained genetics professionals in the U.S. military would triage genetic referrals, alleviating the demand and strain on these limited human resources. Based on our experience crafting and instructing a short educational intervention, providing real-time, point-of-care HCP consult, and retrospectively evaluating HCP performance, it is feasible to have non-genetics providers perform genetic counseling for some routine clinical indications with appropriate support.

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The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR 219 and AFI 40-402, Protection of Human Subjects in Biomedical and Behavioral Research.

Members of the MilSeq Project are as follows:

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Table 1. MilSeq Healthcare Provider Self-Confidence and Preparedness Items

Items	**Self-Confidence: # Respondents by Likert Option (n=12)**			
Genomic sequencing knowledge	**Not at all**	**Not very**	**Somewhat**	**Very**
Pre-education	5	5	2	0
Post-education	0	0	10	2
Explain a pathogenic result	**Not at all**	**Not very**	**Somewhat**	**Very**
Pre-education	2	7	3	0
Post-education	0	1	8	3
Recommendations for a pathogenic result	**Not at all**	**Not very**	**Somewhat**	**Very**
Pre-education	4	6	2	0
Post-education	0	0	9	3
Understand and disclose an exome report	**Not at all**	**Not very**	**Somewhat**	**Very**
Pre-education	5	7	0	0
Post-education	0	0	7	5
Item	**Preparedness: # Respondents by Likert Option (n=12)**			
How prepared do you feel to disclose results directly to patients?	**Very prepared**	**Prepared**	**Slightly prepared**	**Not at all prepared**
Pre-education	1	0	6	5
Post-education	2	10	0	0

Table 2. MilSeq Healthcare Provider Self-Efficacy Items

Items	Self-Efficacy: # Respondents by Likert Option (n=12)				
Understand a genomic sequencing result	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	2	7	2	1	0
Post-education	0	0	1	10	1
Obtain information to understand a result's significance	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	2	4	5	1	0
Post-education	0	0	1	9	2
Understand a result's effect on patient health	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	1	4	3	4	0
Post-education	0	0	1	11	0
Understand a result's influence on disease risk in general	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	0	3	3	6	0
Post-education	0	0	1	9	2
Understand how a patient's genetic constitution may affect disease risk	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	1	2	2	7	0
Post-education	0	0	0	11	1
Explain how a patient's genetic constitution may affect disease risk	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	0	5	3	4	0
Post-education	0	0	0	11	1
Identify resources to obtain additional information about a result	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
Pre-education	2	5	1	4	0
Post-education	0	0	0	9	3

Table 3. MilSeq Healthcare Provider Domain Assessment

Domains (n = # of Items Averaged)	**Statistics**	
Self-Confidence (n = 4)	**Mean (SD*)**	**Paired Sign Test**
Pre-education	1.8 (0.51)	$p < 0.001$
Post-education	3.3 (0.35)	
Self-Efficacy (n = 7)	**Mean (SD*)**	**Paired T-Test**
Pre-education	2.8 (0.69)	$p < 0.001$
Post-education	4.1 (0.25)	
Preparedness (n = 1)	**Mean (SD*)**	**Paired Sign Test**
Pre-education	3.3 (0.87)	$p = 0.006$
Post-education	1.8 (0.39)	
Genetic Knowledge (n = 14)	**Mean (SD*)**	**Paired Sign Test**
Pre-education	9.9 (1.38)	$p = 0.021$
Post-education	11.5 (1.45)	

* Standard Deviation

Table 4. MilSeq Adjustment Category Organization: Select Transcript Excerpts

Adjustment Category	Transcript Excerpt	Genome Resource Center Rationale
Knowledge Limitation • Lacking sufficient baseline knowledge and/or experience to comprehensively counsel the patient beyond the information provided in the report	"What this would be testing for specifically is, […] we know you have this gene: *GJB2*. […] This is your mutation, right? So, we need to know, is her *GJB2* gene affected?"	The healthcare provider understands autosomal recessive inheritance, counseling reproductive risk and offering carrier testing for the patient's spouse appropriately. However, the healthcare provider offers carrier testing only for *GJB2* and not *GJB6*, because he is unaware of the digenic relationship between the genes and it is omitted from the report.
Minor • Errors posing minimal risk to optimal care	"Yes, you have this one variant, but your husband, partner, would have to have the same variant. […] Let's say your husband just so happened to also have the same mutation. […] There's a 25% chance that your child will not be affected, will get 2 good genes. There is a 50% chance that your child will be a carrier, just like you are. […] Then there's a 25% chance that your child would have the disease and would have two affected alleles on that gene."	The healthcare provider understands autosomal recessive inheritance, counseling transmission appropriately. However, the healthcare provider implies that the couple must have identical variants for reproductive risk, rather than any pathogenic variant in the same gene.
Moderate • Errors posing some degree of suboptimal care	"I'd seen that you were going for fertility treatments, is that correct? […] And I noticed you were shorter in stature. So, Turner syndrome is a genetic condition in which one of your X chromosomes is not there. Typically, these patients can't get pregnant at all, though. They have very kind of small ovaries that don't really release eggs […] Some women can have a partial Turner syndrome so to speak, but since you're pregnant probably unlikely."	The healthcare provider excludes a mosaic Turner syndrome differential diagnosis based on the patient's self-reported pregnancy, despite provocative clinical features such as significant short stature when compared to first-degree relatives and documented fertility concerns. It was explained to the healthcare provider that many women with mosaic Turner syndrome can achieve pregnancy but are still at risk for other syndromic health complications (e.g., cardiac) and may have some reproductive risk.
Critical • Errors endangering patient safety	None identified.	Not applicable.

Figure 1. MilSeq Healthcare Provider Performance