Genetic screening for hypertrophic cardiomyopathy in large, asymptomatic military cohorts

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Abstract
Sudden cardiac death (SCD) is one of the leading causes of mortality in the U.S. military and competitive athletes. In this study, we simulate how genetic screening may be implemented in the military to prevent an SCD endpoint resulting from hypertrophic cardiomyopathy (HCM). We created a logistic regression model to predict variant pathogenicity in the most common HCM associated genes MYH7 and MYBPC3. Model predictions were used in conjunction with the gnomAD database to identify frequencies of pathogenic variants. Extrapolating these variants to a military population, lives saved and cost benefit analyses were conducted for screening for HCM related to pathogenic variants in MYH7 and MYBPC3. Genetic screening for HCM followed by echocardiography in individuals with pathogenic variants is predicted to save an average of 2.9 lives per accession cohort, based on historical cohort sizes, and result in a break-even cost of ~$7 per test. The false positives, defined as disqualified individuals for military service who do not have HCM, are predicted to be 0 individuals per accession cohort. This study suggests that the main barriers for the implementation of genetic screening for the U.S. military are the low detection rate and variant interpretation.

KEYWORDS
Genetic screening, hypertrophic cardiomyopathy, population genetics, variant classification

1 | INTRODUCTION

Sudden cardiac death (SCD) is the most common cause of non-traumatic death in the military (Eckart et al., 2004), and hypertrophic cardiomyopathy (HCM) is the leading cause of SCD in competitive young athletes (Maron, Doerer, Haas, Tierney, & Mueller, 2009). HCM is a condition where the left ventricular wall of the heart is abnormally enlarged which compromises the heart’s ability to pump blood, especially during exercise. It is formally defined as left ventricular wall thickness ≥ 15 mm on transthoracic echocardiography when secondary causes such as hypertension, aortic stenosis, or infiltrative cardiomyopathies are absent (American College of Cardiology Foundation/ American Heart Association Task Force on et al., 2011). HCM has variable expressivity and incomplete penetrance, and the estimated prevalence ranges from 1 in 500 to 1 in 200 individuals (Ommen, 2011; Semsarian, Ingles, Maron, & Maron, 2015). Those with HCM have an estimated 0.39% annual incidence of SCD, which increases to 0.84% if the equivalent events such as appropriate implantable cardioverter defibrillator (ICD) shock or successful cardiopulmonary resuscitation are taken into account (Weissler-Snir et al., 2019; O’Mahony et al., 2018). Factors that increase the risk of sudden cardiac death include maximal wall thickness, family history of SCD, left atrial diameter, and non-sustained ventricular tachycardia (O’Mahony et al., 2014; Weissler-Snir et al., 2019). Individuals who are identified as having the
disease can be treated with lifestyle changes, which include limiting physical exertion, pharmacotherapy, or invasive procedures such as ICD placement, surgical septal myectomy, or alcohol septal ablation (Weissler-Snir et al., 2019).

An estimated 83% of HCM cases with a positive genetic test are attributed to pathogenic or likely pathogenic variants in the genes MYH7 and MYBPC3, while other genes explain only ≤2% per gene (Alfares et al., 2015; Cirino & Ho, 1993; Mademont-Soler et al., 2017; Walsh et al., 2017). Genetic testing in those studies employed Sanger sequencing or next-generation sequencing for a limited number of genes. Considering the decreasing prices and an increased availability of genomic sequencing, population-level testing for HCM and inclusion of new genes as a panel are becoming plausible. Currently, there is little data to evaluate effectiveness of genetic screening for HCM in military or athletic populations. Young athletes are similar to military recruits in age and physical demands, and several studies have looked at the effectiveness of screening young athletes with electrocardiogram (ECG) (Corrado et al., 2005). No hypertrophic cardiomyopathy screening test, including ECG, is currently included in the military’s entrance physical for individuals under 40 years of age.

Genomics is becoming an increasingly utilized tool in military medicine, particularly for screening as this population is generally young and healthy (De Castro et al., 2016). Screening for genetic conditions is not a new concept in the U.S. military, which has traditionally screened service members for glucose 6 phosphate dehydrogenase deficiency and hemoglobinopathies (De Castro & Turner, 2017). However, the inappropriate assumptions about sickle cell trait in the U.S. military have demonstrated the importance of strong medical evidence supporting a genetic screening. Thus, avoiding inadequate implementation and incorrect disqualification are essential during the military medical evaluation (De Castro et al., 2016). In this report, we explore the feasibility and cost-effectiveness of screening military recruits for HCM.

2 | METHODS

To analyze the benefits of screening military personnel for HCM, we used the following sequential stages: genome simulation, disease simulation, HCM screening, sudden death simulation, and cost analysis for the military. Figure S1 diagrams the workflow for these sequential stages. The population size was based on historical accession data, and we consider an “accession cohort” to be the officers and enlisted members who joined the military in a given year. Below is a brief description of simulation, more detail is found in the Supplemental Methods.

2.1 | Stage 1: Genome simulation

First, we simulated the presence/absence of pathogenic variants. To determine which variants would be considered pathogenic, we identified 90 variants in ClinVar database for MYH7 and MYBPC3 that were rated pathogenic or likely pathogenic with no conflicting interpretations and 346 that were rated benign or likely benign with no conflicting interpretations (www.ncbi.nlm.nih.gov/clinvar/). Variant pathogenicity for other variants was predicted using a logistic regression model that had been trained on the high-certainty ClinVar variants. The selected logistic regression model used allele frequency, combined annotation dependent depletion (CADD), dbscSNV, and indicated amino acid change as predictors (see Supplementary Methods for modeling details and predictor descriptions). We then constructed a ranked list of pathogenic variants for simulation, composed of the 90 ClinVar variants with high certainties of pathogenicity and no conflicting interpretations, followed by additional variants ranked by their model-based likelihoods of pathogenicity.

To simulate variant frequencies as they occur in the general population, we used the gnomAD database to estimate how frequently pathogenic variants should occur in our simulated population. The gnomAD database was used as a surrogate of the military population due to the asymptomatic nature of both populations. Of the six high-certainty pathogenic variants available in the 1,000 Genomes database (Siva, 2008), all had no co-segregation, and thus we worked under the assumption of independent and separate inheritance for each pathogenic allele.

2.2 | Stage 2: Disease simulation

Simulating HCM in the population requires assigning values to the probability of HCM if a pathogenic variant is present, annotated as \(P(HCM|VAR)\), and the probability of HCM given that a pathogenic variant is not present, annotated as \(P(HCM|VAR^c)\). These values are related to the prevalence of HCM in the general population \(P(HCM)\), the probability any given person has a pathogenic variant \(P(VAR)\), and the probability an individual with HCM has a pathogenic variant \(P(VAR|HCM)\) through Bayes’ Theorem as illustrated in Equations (1) and (2) below. Based on available literature, we set \(P(HCM) = 0.002\) (Ommen, 2011), \(P(VAR|HCM) = 0.3\) (Alfares et al., 2015; Walsh and others 2017), and \(P(HCM|VAR) = 0.3\) (Christiaans et al., 2011). This results in a \(P(VAR)\) of 0.002; thus we included the top 127 variants from the ranked list constructed in Stage 1. Equation (2) then yields \(P(HCM|VAR^c) = 0.0014\). Further discussion of these estimations is in the Supplementary Methods. We acknowledge that these probabilities are not experimentally derived; however, we utilize them as reasonable estimates based on current literature. We show them as reasonable estimates after a sensitivity analysis (see Supplemental Methods).

\[
P(HCM|VAR) = \frac{P(HCM) \times P(VAR|HCM)}{P(VAR)} \quad (1)
\]

\[
P(HCM|VAR^c) = \frac{P(HCM)}{1 - P(VAR)} \quad (2)
\]

2.3 | Stage 3: Screening the military for HCM

We simulated four different screening cases, described in Table 1. For practical purposes transthoracic echocardiogram was considered the
gold standard with 100% specificity and sensitivity for detection of left ventricular wall thickness \( \geq 15 \text{ mm} \). Genetic testing was simulated at 100% accuracy, which in our context means the test would correctly identify the presence or absence of each specified variant. Individuals screening positive for HCM were simulated as being discharged from the military and not experiencing an SCD endpoint. In the case of genetic screening followed by transthoracic echocardiogram for positive genetic test, “screening positive for HCM” is defined as a positive echocardiogram.

2.4 | Stage 4: Sudden cardiac death simulation

Likelihood of sudden cardiac death for those individuals with HCM \([P(\text{SCD}|\text{HCM})]\) remaining in the military (not discharged due to a positive screen) was 0.0039 per year (O’Mahony et al., 2018). Simulations were run for the complete careers of a combined cohort including officers, who spend an average of 11 years in the military, and enlisted members, who spend an average of 7 years in the military. The simulations were run for 1,000 cohorts.

2.5 | Stage 5: Cost analysis

Military accession statistics from the U.S. Department of Defense (DoD) were averaged over fiscal years 2012, 2013, and 2014 (Quester & Robert, 2015), and retention statistics were obtained from the Pew Research Center (Taylor, Parker, Cohn, Funk, & Mokrzycki, 2011). Costs associated with the military were obtained from the DoD (DOD Instruction 6130.03: Medical Standards for Appointment, Enlistment, or Induction in the Military Services, 2015), a Naval Postgraduate School study (Sharra, 2015), and a RAND corporation study (Dahlman, 2007). Costs associated with an echocardiogram reflect the average among Medicare billed U.S. hospitals in calendar year 2015 (“Health Data Initiative,” 2015). All monetary values were inflation-adjusted to represent the value of the U.S. dollar in March 2018 and can be found in Table S1. Further calculation details can be found in the Supplemental Methods.

3 | RESULTS

Results are summarized in Table 2. In this report, we display averages based on 1,000 cohort simulations, as well as percentile-based confidence intervals. The first results section describes the sensitivities and false discovery rates (FDRs) of the screening options. FDR is defined as the fraction of individuals who have a positive test who do not have disease (1—positive predictive value). Next, we discuss pertinent outcomes to the U.S. military and servicemembers including lives saved and costs saved. The size of each simulation cohort is based on historical annual accession data and consists of 168,775 individuals (16,721 officers and 152,054 enlisted members) (Quester & Robert, 2015).

| TABLE 1 | Screening cases being compared in cost/benefit analysis |
| Case 1 | No screening |
| Case 2 | Echocardiogram only |
| Case 3 | Genetic testing only |
| Case 4 | Genetic screening followed by transthoracic echocardiogram for positive genetic test |

| TABLE 2 | Simulation results |
|---|---|---|---|---|---|
| Case 1: No screening | Sensitivity | FDR | Lives saved | Break-even costs* | False positive (discharged without HCM) |
| | n/a | n/a | 0 | n/a | n/a |
| Case 2: Echocardiogram only | 1 (1–1) | 0 (0–0) | 9.52 (9.33–9.71) | n/a | 0 (0–0) |
| Case 3: Genetic testing only | 0.300 (0.298–0.302) | 0.700 (0.698–0.702) | 2.92 (2.75–3.08) | 12.2 (11.6–12.8) | 240 (239–241) |
| Case 4: Genetic screening; positive genetic test followed by echocardiogram | 0.300 (0.298–0.302) | 0 (0–0) | 2.92 (2.75–3.08) | 7.1 (6.5–7.8) | 0 (0–0) |

*Cases 1 and 2 do not have break-even genetic test (GT) costs as they involve echocardiograms only.
3.3 | False positives (discharged from U.S. military in the absence of HCM)

The only case resulting in false positives is Case 3 (genetic screening only). It is predicted to erroneously discharge 240 service members per cohort (95% CI, 239–241), which is unacceptably high.

3.4 | Break-even costs

Considering costs of training, death gratuities, and screening procedures, as designated in Supplementary Table 1, we compared the overall cost of no screening versus each screening strategy. The “break-even genetic test cost” shown in Table 2 is the maximum cost of a genetic test where the military would start to see a cost benefit to screening.

4 | DISCUSSION

The leading cause of nontraumatic death in the military is SCD (Eckart et al., 2004; Eckart and others, 2011). HCM is the most common cause of SCD in young athletes (Maron et al., 2009), and although screening athletes for cardiac risks is controversial, a mandatory screening program using ECG reduced the incidence of SCD in young athletes (Corrado and others, 2005). Moreover, ECG can detect other causes of SCD beyond the genetic causes discussed in this article, such as long QT syndrome and Wolf-Parkinson-White (Corrado and others, 2005). Military personnel are similar to athletes, especially early career where physical training and fitness are important. In this study, we explored the quantitative outcomes of genetic screening for HCM as a component of the military entrance exam. We found that screening all U.S. military recruits for HCM using echocardiogram would save an average of 9.5 lives per accession cohort; however, this approach is prohibitively expensive. Screening all recruits with a genetic test could be cost-effective and is predicted to save an average of 2.9 lives per cohort, but would erroneously discharge an average of 240 individuals per cohort. The combination screening approach—using genetic testing followed by echocardiogram to confirm—has the potential to save lives, be cost effective, and eliminate erroneous discharges. This scenario would allow for an average of 2.9 lives saved per 168,775 servicemembers that enter the military per year, a break-even cost of ~$7.10 per genetic test, and no individuals erroneously discharged.

The U.S. military has ethical considerations that differ from the civilian population. Although the Genetic Information Non-discrimination Act (GINA) prohibits nongovernment employers from making employment decisions based on the results of a genetic test, the military is distinctly excluded from this law. The military population which makes up a considerable fraction of the U.S. population and health care market deserves special consideration and is reviewed elsewhere by Castro and Turner (Mehlman & Li, 2014). Given the incomplete penetrance of most genetic conditions, special care must be taken before labeling an asymptomatic individual with a disease or syndrome. In this study, we confirmed the positive genetic screening findings with an echocardiogram.

Most cases of HCM, the most common cause of SCD, can be attributed to pathogenic variants in MYH7 or MYBPC3, but the detection rate using the two variants is only around 30%. The detection rate is expected to improve over the time with the addition of new genes and reclassification of variants of unknown significance. A limitation in our simulation study is the assumption that the pathogenic variant list constructed for MYH7 or MYBPC3 is accurate, that is, that the variants are truly pathogenic. We acknowledge that variant classification is a complex process that requires a trained geneticist and should follow the ACMG guidelines (Richards et al., 2015). However, by prioritizing ClinVar’s high certainty pathogenic variants and using predictions from a disease-specific classification model, we have constructed a variant list that best reflects current scientific knowledge. The averages reported in Table 2 would be consistent with any list of pathogenic variants whose total frequency is P(VAR), but, clearly, practical implementation would require validation of which particular variants comprise this list.

In conclusion, this report serves as an exploratory study to investigate the presence of barriers to use genetic screening in the military, or any large asymptomatic population, to identify individuals with increased risk for experiencing an SCD endpoint. Our simulation study suggests that, should a complete pathogenic variant list of high certainty be constructed for HCM, discharging individuals who screen positive for a variant and have a positive follow-up echocardiogram could provide monetary benefit to the military. Summarizing, the main barriers to overcome in order to implement genetic screening are the low detection rate of the current genetic testing and the challenge to interpret the variants. Likewise, psychological and ethical aspects remain to be fully explored; a responsible screening decision must include the conscientious consideration of nonmonetary costs as well. High-quality studies proving the validity of genetic screening are necessary before implementing any genetic screening in a large population.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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