

Chapter 31

UPDATE ON KEY STUDIES—THE MILLENNIUM COHORT STUDY, THE STAMPEDE STUDY, THE MILLION VETERAN PROGRAM, AND THE NATIONAL HEALTH STUDY FOR A NEW GENERATION OF US VETERANS

NANCY F. CRUM-CIANFLONE, MD, MPH^{*}; MICHAEL J. MORRIS, MD[†]; DARREL W. DODSON, MD[‡]; LISA L. ZACHER, MD[§]; AND RONALD M. PRZYGDZKI, MD[¶]

INTRODUCTION

THE MILLENNIUM COHORT STUDY

**Overview of the Millennium Cohort Study
Respiratory Outcomes Among Returning Service Members: Data
From the Millennium Cohort Study**

THE STAMPEDE STUDY

THE MILLION VETERAN PROGRAM: THE VETERANS AFFAIRS OFFICE OF RESEARCH AND DEVELOPMENT MEGACOHORT

**Background
Veterans' Attitudes Toward Genomic Research
The Million Veteran Program**

SUMMARY

^{*}Department Head, Deployment Health Research Department, Naval Health Research Center, 140 Sylvester Road, San Diego, California 92106-3521

[†]Colonel (Retired), Medical Corps, US Army; Department of Defense Chair, Staff Physician, Pulmonary/Critical Care Medicine and Assistant Program Director, Internal Medicine Residency, San Antonio Military Medical Center, 3551 Roger Brooke Drive, Fort Sam Houston, Texas 78234

[‡]Colonel, Medical Corps, US Army; Chief, Department of Medicine, Pulmonary/Critical Care Medicine, William Beaumont Army Medical Center, Fort Bliss, 5005 North Piedras Street, El Paso, Texas 79920

[§]Colonel (Retired), Medical Corps, US Army; Chief, Department of Medicine, Orlando Veterans Administration Medical Center, 5201 Raymond St, Orlando, Florida 32803

[¶]Acting Director, Biomedical Laboratory Research & Development, Office of Research and Development, US Department of Veterans Affairs, 810 Vermont Avenue, NW, Washington, DC 20420

INTRODUCTION

Several key studies have been initiated by the US Department of Defense (DoD) and the US Department of Veterans Affairs (VA) to provide critical information on the short- and long-term health and well-being of US military service members and veterans. As such, these research studies are vital in understanding emerging health conditions, including respiratory symptoms and conditions, among US military personnel returning from recent conflicts in Iraq, Afghanistan, and neighboring countries. In this chapter, several key epidemiological and clinical studies that can provide criti-

cal data in the area of respiratory outcomes among service members and veterans are reviewed. These studies include

- the Millennium Cohort Study (MCS),
- STAMPEDE (Study of Active Duty Military for Pulmonary Disease Related to Environmental Deployment Exposure),
- Million Veteran Program (MVP), and
- National Health Study for a New Generation of US Veterans.

THE MILLENNIUM COHORT STUDY

Overview of the Millennium Cohort Study

The MCS was initiated after the events that followed the 1991 Gulf War—a conflict in which nearly 700,000 US service members¹ were deployed. Thereafter, thousands of service members reported a variety of postdeployment symptoms and illnesses.² The DoD subsequently identified the need for a coordinated epidemiological research study to determine if military experiences, including deployments, affect long-term health outcomes. In response to recommendations³⁻⁵ for a large, longitudinal study of US service members, the MCS was launched in July 2001. The primary objective of this ongoing study is to evaluate the impact of military service, including deployments and other occupational exposures, on the long-term health of US service members. Fortunately, this study was begun prior to the beginning of military operations in Iraq and Afghanistan, thus providing robust baseline predeployment health data and behavioral data for a large cohort of US military service members.^{5,6} Given the >2 million service members who have deployed in support of the recent operations in Iraq and Afghanistan this past decade, the MCS offers unprecedented information on the effects of military deployments on both the short- and long-term health outcomes. The study, originally designed for a 21-year period (20 years of military service plus 1 year), is planned to be extended to 67 years to assess the total lifespan of the veteran.

The MCS currently consists of four panels enrolled separately in 2001, 2004, 2007, and 2011, totaling more than 200,000 participants from all five service branches and the Reserve/National Guard. Participants are surveyed at approximate 3-year intervals both during and following service. Participation in the study is by invitation to ensure that a random sample of the military population is enrolled. In 2001, the first panel was a cross-sectional population-based sample of the US military, whereas subsequent panels focused on younger service members with a range of 1 to

5 years of service, varying by panel (Table 31-1). Specific groups were oversampled in the various panels to have adequate sample sizes to access health outcomes in subgroups of interest (eg, Reserves/National Guard, Marines, and women). From 2001 to 2007, approximately 151,000 service members participated in the study, including 67,256 Army, 43,546 Air Force, 27,450 Navy/Coast Guard, and 13,316 Marines. An additional panel (Panel 4) is underway and will enroll an additional ~50,000 participants. Enrollment and follow-up of participants are ongoing and are projected to continue for several decades. As of 2012, 57.5% of participants (Panels 1–3) deployed at least once in support of the wars in Iraq and Afghanistan, 28% deployed multiple times, and 58% of these deployers reported experiencing combat. Currently, 39% of the MCS participants have separated from the military, thus allowing for the evaluation of the health of veterans.

The MCS uses standard methods for conducting its surveys, modeled after the work of Dillman.⁷ Mailings (postal and e-mail) are sent out over the course of a survey cycle (typically 18 months) to ensure that deployed service members are able to respond. The survey collects self-reported, individual-level data and consists of 100 items (many with multiple components, a total of >450 questions). The survey collects information on the service member's mental, physical, behavioral, and functional health and uses a variety of standardized instruments. These include the standardized Posttraumatic Stress Disorder (PTSD) Checklist-Civilian Version for assessing PTSD⁸⁻¹⁰ and the Patient Health Questionnaire-8 for depression and anxiety symptoms.^{11,12} Additionally, the survey captures data on self-reported health symptoms and health professional-diagnosed medical conditions. The survey also collects data on military experiences (including deployments, combat, occupational exposures, and other metrics [eg, sleep, diet, alcohol and tobacco use, and physical activity]). Functional status can be assessed using the Medical Outcomes Study

TABLE 31-1
COMPOSITION OF EACH PANEL IN THE MILLENNIUM COHORT STUDY

Panel	Dates Enrolled	Years of Service at Enrollment	Oversampled Groups	Roster Size (Date)	No. Contacted*	Total Enrolled (% of Those Contacted)
1	July 2001– June 2003	All durations (cross-section of military population)	Females, National Guard/ Reserves, and prior deployers [†]	256,400 (October 2000)	214,388	77,047 (35.9%)
2	June 2004– February 2006	1–2 years	Females and Marine Corps	150,000 (October 2003)	123,001	31,110 (25.3%)
3	June 2007– December 2008	1–3 years	Females and Marine Corps	200,000 (October 2006)	154,270	43,440 (28.2%)
4	April 2011– ongoing	2–5 years	Females and married	250,000 (October 2010)	‡	‡

*Invalid names/postal addresses and duplicates were excluded.

[†]Deployment to southwest Asia, Bosnia, and/or Kosovo after August 1997.

[‡]Panel currently being enrolled; ~50,000 service members will be enrolled in Panel 4.

Short Form 36-Item Health Survey, Veterans Version^{13,14} with calculation of the mental and physical component scores to determine functional impairment; in addition, general health and employment status are available. Follow-up surveys (administered approximately every 3 years) allow for longitudinal capture of the changing nature of the members' experiences and health symptoms, and their temporal associations.

To complement the measures ascertained on the survey, the MCS data may be linked to a variety of other data sources to provide objective measures of the service members' health and military experiences (Table 31-2). Data linkages include both military and civilian (via TRICARE) inpatient and outpatient care with ICD-9 (*International Classification of Diseases, Ninth Edition*), codes as well as pharmaceutical data from the Pharmacy Data Transaction System. In-theater injury data can be ascertained from the Joint Theater Trauma Registry and the Triservice Combat Trauma Registry-Expeditionary Medical Encounter Database. Environmental exposure data are available through the US Army Public Health Command (Aberdeen Proving Ground, MD). Information can also be obtained from the Career History Archival Medical and Personnel System, a comprehensive database that provides an individually based, longitudinal record of career events from the date of enlistment until the date of separation or retirement. Linkage with the DoD Serum Repository (Silver Spring, MD) provides a potential source of specimens because >99% of MCS members have at least one specimen in the repository.

Numerous published foundational studies have established the MCS as a well-representative sample of

the US military and confirmed the excellent reliability of the survey data.^{15–21} Additional analyses have also been conducted to investigate the potential for response biases;^{22,23} analyses have shown that health, as measured by healthcare use preceding invitation, did not influence responses to participate.²⁴ Methods to encourage nonbiased responses and retention in the MCS are in place and periodically updated.

Overall, the MCS is an essential component of the DoD's Force Health Protection & Readiness strategy. This large study is setting a new standard for prospective evaluation of the potential short- and long-term health consequences of military occupational exposures, among both active military personnel and the growing number of veterans. Unlike data assembled from Gulf War Veterans, the MCS collects predeployment information and follows service members over time to allow for the longitudinal assessment of military service experiences (eg, deployment), and a variety of mental and physical health outcomes.

Respiratory Outcomes Among Returning Service Members: Data From the Millennium Cohort Study

The MCS has been used to provide critical information on the potential association between deployment experiences and newly reported respiratory outcomes among service members. Data on 46,077 MCS participants from Panel 1 who completed baseline (July 2001–June 2003) and follow-up (June 2004–February 2006) surveys were

TABLE 31-2

LINKAGES OF THE MILLENNIUM COHORT STUDY WITH OTHER DATA SOURCES

Type of Data	Source
Medical record data from military medical facilities world-wide and civilian facilities covered by the DoD insurance system (TRICARE)	Standard Ambulatory Data Record (SADR) and the Standard Inpatient Data Record (SIDR) TRICARE Encounter Data (TED)
Deployment (location and dates) and contact data	Defense Manpower Data Center (DMDC)
Pharmaceutical data	Pharmacy Data Transaction System (PDTS)
Service and medical data from time of enlistment to separation	Career History Archival Medical and Personnel System (CHAMPS)
Injury data from in theater	Joint Theater Trauma Registry (JTTR) and the Triservice Combat Trauma Registry Expeditionary Medical Encounter Database (CTR-EMED); Total Army Injury and Health Outcomes Database (TAIHOD)
Spouse health, behavioral, and relationship data; some child outcomes	The Millennium Cohort Family Study
Environmental exposures	US Army Public Health Command
Links occupational codes between the military services and civilian counterparts	Master Crosswalk File from the DoD <i>Occupational Conversion Index</i> manual
Health symptoms and perception, as well as exposure data	Pre- and Post-Deployment Health Assessments (DD 2795 and DD 2796)
Medical status and resource utilization	Health Enrollment Assessment Review (HEAR)
Mortality data	Social Security Administration Death Master File, Department of Veterans Affairs (VA) files, Department of Defense Medical Mortality Registry, and National Death Index
Dates of service, military occupation, and locations	Defense Enrollment Eligibility Reporting System (DEERS)
Medical encounters at the Veterans Administration	Veterans Administration*
Blood samples	DoD Serum Repository

DD: Department of Defense; DoD: US Department of Defense; VA: US Department of Veterans Affairs

*Linkage pending.

used to investigate new-onset respiratory symptoms and conditions.²⁵ Participants were excluded who either deployed prior to baseline; completed the survey while on deployment; or whose surveys were missing outcome, exposure, or covariate data. Respiratory symptoms evaluated included persistent or recurring cough or shortness of breath, which were self-reported on the MCS survey. Respiratory conditions included asthma, chronic bronchitis, and emphysema that were based on self-reported, health professional-diagnosed conditions. All “newly reported” outcomes were those that were absent at baseline and newly reported at follow-up. Deployments, including the locations and cumulative length, were obtained from the Defense Manpower Data Center (DMDC; Washington, DC). A multivariate logistic regression analysis stratified by service and adjusted by rank, service component, occupation, and smoking status was performed.

In the models examining respiratory symptoms, approximately 24% had deployed. Deployers had a higher frequency of newly reported respiratory symptoms than nondeployers (14% vs 10%), whereas similar frequencies of chronic bronchitis or emphysema (1% vs 1%) and asthma (1% vs 1%) were observed. The incidence rate of chronic bronchitis or emphysema and asthma was 3.3 cases each per 1,000 person-years. An interaction between service branch (but not tobacco use) and respiratory symptoms was noted; hence, models were stratified by branch. Independent of smoking, demographic, and military characteristics, deployment was associated with respiratory symptoms in both Army (adjusted odds ratio [AOR]: 1.73, 95% confidence interval [CI]: 1.57, 1.91) and Marine Corps (AOR: 1.49, 95% CI: 1.06, 2.08) personnel (Table 31-3). Increased deployment length was linearly associated with increased symptom reporting in Army personnel (for deployment

lengths from 1 day to >270 days, AORs were 1.59–1.88, $p < 0.0001$), but not among other service branches. Among deployers, elevated odds of respiratory symptoms were associated with land-based deployment—compared with sea-based deployment—with those exclusively deploying to Iraq displaying the largest odds of respiratory symptoms (AOR: 2.16, 95% CI: 1.52, 3.07). There were no statistically significant associations between deployment and the development of any of the newly reported respiratory conditions (asthma, chronic bronchitis, or emphysema) (see Table 30-3). Findings from this study suggested that specific exposures during deployment may be determinants for postdeployment respiratory symptoms (persistent and recurring cough and shortness of breath). Significant associations seen with land-based deployment imply that exposures related to ground combat may be particularly important, but further studies are needed.

A second study was conducted within the MCS to specifically evaluate the effects of potential exposure to an open-air burn pit on respiratory outcomes among deployers to Iraq or Afghanistan.²⁶ Participants from MCS Panels 1 and 2—who completed surveys from 2004 to 2006 and from 2007 to 2008 and deployed to Iraq or Afghanistan from 2003 to 2008—were included ($n = 22,844$). Because of the small numbers of deployers in some service branches (Navy, Marines, and Coast Guard), the analyses were restricted to Army and Air Force members. The MCS survey was used to assess respiratory symptoms (ie, persistent or recurring cough or shortness of breath) and conditions (new-onset chronic bronchitis or emphysema, and new-onset asthma). New-onset conditions were defined as reported in the 2007 to 2008 survey with no previous endorsements. Information regarding deployment locations and dates were provided by

the DMDC. Potential exposure to an open-air burn pit was defined using the proxy of being deployed within a 3-mile radius of a burn pit at three different camps in Iraq (Joint Base Balad, Camp Taji, and Camp Speicher). Cumulative time near the burn pit (1–56, 57–131, 132–209, ≥ 210 days) and the specific camp location were also evaluated. The comparison group (“nonexposed”) consisted of deployers who were assigned to other areas in Iraq or Afghanistan with no days deployed near a documented burn pit. An alternate comparison group was also established consisting of deployers to Camp Arifjan in Kuwait that does not have documented burn pits. Using separate multivariable logistic regression models, the associations between potential burn-pit exposure (within a 3-mile radius) with newly reported chronic bronchitis or emphysema, newly reported asthma, and self-reported respiratory symptoms were examined. Models were adjusted for the following:

- sex,
- birth year,
- marital status,
- race/ethnicity,
- education,
- smoking,
- aerobic activity,
- service branch,
- service component,
- military rank, and
- occupation.

Of the 22,844 service members evaluated, 3,585 personnel had deployed within a 3-mile radius of a potential burn pit. Similar proportions of exposed and nonexposed groups

TABLE 31-3

ADJUSTED ODDS OF SELF-REPORTED NEW-ONSET* RESPIRATORY SYMPTOMS AND CONDITIONS IN DEPLOYERS COMPARED WITH NONDEPLOYERS: THE MILLENNIUM COHORT STUDY†

Service Branch	Respiratory Symptoms‡		Chronic Bronchitis or Emphysema		Asthma	
	AOR§	95% CI	AOR§	95% CI	AOR§	95% CI
Army	1.73	1.57, 1.91	1.25	0.94, 1.67	1.06	0.77, 1.44
Air Force	1.09	0.95, 1.26	0.93	0.59, 1.47	1.04	0.68, 1.60
Navy/Coast Guard	1.06	0.86, 1.32	0.79	0.42, 1.46	0.90	0.49, 1.65
Marine Corps	1.49	1.06, 2.08	0.94	0.24, 3.75	0.56	0.15, 1.98

AOR: adjusted odds ratio; CI: confidence interval

*New onset was defined as present at follow-up with no previous endorsement of the condition at baseline.

†The number of participants included in each model varied due to exclusion criteria dependent on each specific respiratory outcome.

‡Defined as persistent or recurring cough or shortness of breath reported at follow-up with no previous report at baseline.

§Adjusted for deployment status, sex, birth year, marital status, race/ethnicity, education, smoking status, service branch, service component, military rank, and occupation.

Data source: Smith B, Wong CA, Smith TC, et al. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: a prospective population-based study. *Am J Epidemiol.* 2009;170:1433–1442.

had respiratory outcomes: 1.5% vs 1.6% chronic bronchitis or emphysema; 1.7% vs 1.6% asthma; and 21.3% vs 20.6% respiratory symptoms (16.3% vs 14.6% new-onset respiratory symptoms). In the adjusted model, there was no statistically significant increase in any outcome comparing those potentially exposed to a burn pit with those without a documented exposure, such as:

- chronic bronchitis or emphysema—AOR: 0.91, 95% CI: 0.67–1.24;
- asthma—AOR: 0.94, 95% CI: 0.70–1.27; and
- respiratory symptoms—AOR: 1.03, 95% CI: 0.94–1.13.

Also, there were no statistically significant findings regarding the cumulative days potentially exposed, specific camp sites within a 3-mile radius, or an alternate 5-mile radius on self-reported respiratory symptoms or diagnoses. Only one finding was statistically significant; Air Force personnel deployed within a 2-mile radius of Joint Base Balad had increased odds for respiratory symptoms (AOR: 1.24, 95% CI: 1.01–1.52). However, this finding was marginally significant, with no evidence of trend (ie, no findings with cumulative deployment length), and this group did not have increased odds for any of the other respiratory outcomes. Finally, using the referent group of Camp Arifjan did not significantly change any of the results. In general, these study findings do not support an elevated risk for respiratory outcomes among personnel deployed within proximity of documented burn pits in Iraq.

There are some important limitations of the two studies to consider. All outcomes were self-reported and were not validated by medical record review. Further, the follow-up period was short; hence, long-term outcomes may have been missed. Lastly, the study examining potential burn pit exposures did not use direct quantitative or individual-level exposure data because these data were unavailable; rather, it used a proxy for possible burn pit exposure that has significant potential for misclassification.

Additional studies leveraging the MCS to examine respiratory outcomes are underway. An exploratory study was performed to evaluate the potential association of increasing levels of environmental particulate matter (PM) exposure with the risk of newly reported respiratory symptoms among deployers to southwest Asia. Time-weighted average values of PM₁₀ and PM_{2.5} from 15 PM sampling sites in southwest Asia were obtained from the US Army Public Health Command, which resulted from samples that were collected by the DoD Enhanced Particulate Matter Surveillance Program from December 2005 to January 2007. Army participants who completed MCS surveys from 2004 to 2006, from 2007 to 2008, and who deployed to one or more of the sampling sites surveyed by the Enhanced Particulate Matter Surveillance Program were identified. Unfortunately, there were

data on only 145 personnel meeting the inclusion criteria and no data on individual-level exposures limiting the ability to study PM levels and respiratory outcomes of interest. If additional environmental exposure data become available, the MCS will explore the potential for additional analyses.

Future studies within the MCS will examine the long-term consequences and the natural history of respiratory symptoms among deployers. Outcomes over time will be determined among those with

- postdeployment respiratory symptoms in terms of resolution or persistence of symptoms,
- development of respiratory diseases (eg, asthma, chronic bronchitis, emphysema, and bronchiolitis),
- medical care visits, and
- quality of life.

Because respiratory diseases may cause substantial health-care expenditures for the VA and may be of high interest to VA medical planners regarding the potential future health effects of military deployments, respiratory illnesses by deployment and military separation status will be examined. Panel 1 to 3 deployers to Iraq or Afghanistan who completed the baseline and follow-up surveys with up to a decade of data (2001–2013) will be used for these analyses. In addition, because combat deployments are associated with increased mental health outcomes (eg, PTSD and anxiety) and land-based deployers have the highest risk for new-onset respiratory symptoms, future analyses will attempt to explore the relationship of anxiety-related symptoms and combat new-onset respiratory symptoms among land-based deployers to Iraq and Afghanistan.

In summary, the MCS has been used to conduct analyses to examine the potential association between deployment experiences and newly reported respiratory symptoms and conditions. To date, the study results show an increased risk for respiratory symptoms among land-based deployers (Army and Marine Corps), but not among other deployed groups. Of note, no statistically significant associations between deployment and respiratory diseases (chronic bronchitis or emphysema, or asthma) have been found to date. Further, potential exposure (within a 3-mile radius) to an open-air burn pit was not found to be associated with respiratory outcomes, but this study did not include individual-level exposure data. Additional studies are underway to help clarify the role of deployment experiences and respiratory outcomes. In summary, the MCS has prospectively evaluated the impact of military experiences, including deployment, on a variety of health outcomes (including respiratory conditions) among US service members. As the largest study in US military history, the MCS will continue to provide ongoing militarily relevant data on health outcomes of interest to help inform DoD/VA leaders and policies.

THE STAMPEDE STUDY

The objective of the initial STAMPEDE study was to evaluate military personnel who have recently returned from the Operation Iraqi Freedom/Operation Enduring Freedom for evidence of lung disease related to prolonged environmental dust exposure in the current theaters of operation. The study was conducted as a prospective, observational study of active duty military personnel with recent redeployment and consisted of a completed enrollment of 50 patients. Patients were primarily recruited from Fort Hood, TX. Active duty military with redeployment within 6 months and new-onset pulmonary symptoms underwent a standardized evaluation at San Antonio Military Medical Center in San Antonio, TX. All participants completed a respiratory questionnaire with detailed exposure history. Clinical evaluation included the following:

- high-resolution computed tomography (HRCT) of the chest,
- full pulmonary function testing,
- impulse oscillometry,
- methacholine challenge testing, and
- fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) of the right middle lobe.

Transbronchial biopsy was only performed if there was evidence of interstitial changes on chest scanning.

Data analysis is currently ongoing. Current data indicate that 50 patients have been enrolled (80% male, mean age of 31.6 ± 8.2 years) and completed an initial evaluation to include fiberoptic bronchoscopy with BAL. Deployment locations were Iraq (66%), Afghanistan (24%), or both countries (10%) with a mean deployment length of 11.7 ± 3.6 months. This was the first deployment for 50% of the cohort. Chest radiographs were normal in all patients, and HRCT scans of the chest identified minor changes of mild focal airway trapping in three patients, bronchiectasis and

emphysematous changes in one patient, and several small subcentimeter nodules in four patients. None of the patients had diffuse infiltrates or parenchymal changes that warranted lung biopsy.

Pulmonary function studies demonstrated normal mean values as shown in Table 31-4. The final diagnosis was

- asthma (16%),
- airway hyperresponsiveness (20%),
- gastroesophageal reflux (4%),
- low diffusing capacity of the lung for carbon monoxide (8%),
- miscellaneous (12%), and
- no diagnosis (42%).

The incidence of lung disease in this patient population was primarily related to asthma-related disorders. There was minimal evidence of chronic inflammatory processes related to deployment based on HRCT or bronchoscopy findings. In this study, military deployment to Operation Iraqi Freedom/Operation Enduring Freedom was not associated with chronic inflammatory changes in the lung based on HRCT imaging and cellular findings in BAL. A significant percentage of patients had no specific pulmonary diagnosis based on normal test results and may have other underlying contributing factors for dyspnea, such as psychological or sleep disorders. Further follow-up is planned to determine continued symptoms in these patients. The suggestion that environmental exposures due to deployment cause interstitial or bronchiolar lung disease cannot be substantiated from this study. A more comprehensive research study is currently being conducted that is enrolling patients with deployment-related respiratory symptoms of any duration. This study will use a more comprehensive panel of testing procedures and provide additional data on longitudinal findings of deployment-related lung disease.

THE MILLION VETERAN PROGRAM: THE VETERANS AFFAIRS OFFICE OF RESEARCH AND DEVELOPMENT MEGACOHORT

Background

The ability to perform excellent large-scale research requires collection of a variety of elements, including well-annotated medical record data, lifestyle/epidemiological data, and genomic data. Although some large biorepositories and centers have begun such ventures—including the Iceland Biobank, United Kingdom Biobank, and Kaiser Biobank—one was not available that would adequately serve the needs of US veterans.²⁷⁻²⁹ Fulfilling this need, combined

with the efforts of the Veterans Health Administration (VHA) of propelling veteran's genomic healthcare into the 21st century, required the establishment of a Genomics Medicine Program (GMP) within the Office of Research and Development (ORD).

Initially, the ORD established the GMP Advisory Committee (GMPAC) to help guide and advise the Secretary of VA in establishment, directions, assessment, and progress of the GMP and other related genomic initiatives within the VA. The GMPAC is comprised of private and public health;

TABLE 31-4
STAMPEDE PULMONARY FUNCTION STUDIES

PFT Values	Mean ± SD
FEV ₁ (% predicted)	87.8 ± 12.9
FVC (% predicted)	91.3 ± 13.5
FEV ₁ / FVC	79.5 ± 5.9
FEV ₁ post-BD (% predicted)	91.1 ± 11.7
Total lung capacity (% predicted)	90.9 ± 13.3
Residual volume (% predicted)	82.9 ± 34.7
DLCO (% predicted)	83.5 ± 19.8

BD: bronchodilator; DLCO: diffusing capacity for carbon monoxide; FEV₁: forced expiratory volume at 1 sec; FVC: forced vital capacity; PFT: pulmonary function testing; SD: standard deviation; STAMPEDE: Study of Active-Duty Military for Pulmonary Disease Related to Environmental Deployment Exposure

scientific; ethical; and legal experts in the field of genetics and veteran representatives, and partners, including but not limited to veterans service organizations, the DoD, and the National Institutes of Health (Bethesda, MD).

Poised against an evolving technological base, an increasing ability to improve healthcare using genomic testing, and an ever-present need to maintain patient privacy concerns, the GMPAC proposed that the VA review the attitudes of veterans toward the use of genomics in research.

Veterans' Attitudes Toward Genomic Research

A pivotal component of the development of the GMP and MVP required the VA to address the attitudes and concerns of veterans toward genomic research. The Johns Hopkins Genetic and Public Policy Center (Baltimore, MD) conducted a survey of veterans that spanned various demographic profiles. The study revealed that 83% of the VHA using veterans supported such a program, and 71% would participate in such program if available.³⁰ Willingness to participate was correlated with altruistic behavior, such as being a blood or organ donor. Three quarters of the veterans surveyed supported a key linking the individual's findings with their medical record data and themselves. Importantly, 93% revealed concern regarding information privacy and security. Lastly, the survey showed 96% felt that receiving information about their health was important.

The same group was requested to conduct a second survey of veterans to explore the veterans' attitudes pertaining to enrollment models, including opt-in (voluntary participation and enrollment into model) vs opt-out (automatic participation and enrollment model) enrollment. Interestingly, the majority of veterans were comfortable with either

enrollment model, with 80% favoring an opt-in and 69% favoring an opt-out approach.³¹ Nearly 80% of veterans were also comfortable with the VA using residual clinical samples for research purposes. Overall, both studies reveal strong support for establishment of a GMP program, a biobank for research needs, and support for genomic research.

The Million Veteran Program

Launched in May 2011 by VA Chief of Staff John R. Gingrich, the MVP now includes 50 of the 107 VA medical centers (VAMCs) that have the capacity for research (of 152 VAMCs total). The ultimate goal is to enroll 1 million veterans who use VHA for their healthcare over a 5- to 7-year timeframe. The overarching goal of the MVP is to unite genetic, health and lifestyle, and military exposure data, together within a single database called the Genomic Information System for Integrated Sciences (GenISIS). The VA is ideally poised for such a venture, that is, the VA—one of the largest healthcare systems within the United States—has more than 8.5 million enrollees as of 2012. Any given veteran enrollee has, on average, 15 years of electronic healthcare record data. Further, the VA has embedded within its healthcare system a world-class research program (ORD) with four research services:

- preclinical sciences,
- clinical sciences,
- rehabilitation sciences, and
- health implementation sciences.

ORD has a unifying VA Central Institutional Review Board overseeing large-scale research further streamlining approval from numerous research sites. Embedding the GMP within ORD enables the interdigitation of genomics between the four services, thereby addressing a multitude of questions at various research levels. Importantly, the MVP has strong support by VA leadership. Among the participants within MVP are VA Secretary Eric K. Shinseki, Deputy Secretary W. Scott Gould, and Chief of Staff John R. Gingrich.

Enrollment of veterans into the MVP begins with veterans receiving a letter asking if they would like to join the program. They may either opt into the program, or if they choose not to be asked again, opt out from further being contacted. If they opt in, they fill out a brief health survey and make an appointment at the VAMC to accompany their next medical visit. During this visit, they are educated about the program and given the opportunity to consent to be in the database and to make their medical records available for future unspecified studies. Also during this visit, they have blood drawn. Of note, the participants are identified with a unique number identifier. The GenISIS system provides this unique identifier, which tags all subsequent survey and

sample data in a chain of custody. In no way are any Health Insurance Portability and Accountability Act (HIPAA) identifiers available to anyone except for a limited set of individuals who maintain and oversee the database processes.

In addressing the veteran's concerns of data privacy, several safeguards into the MVP and GenISIS have been introduced. For example, all blood samples and products isolated from them (buffy coat, DNA [deoxyribonucleic acid], etc) are stored in a secure manner using bar code technology as the primary identifier. The interlinking of medical record data and genomic data are performed in a similar manner. Access to data for research, when it becomes available, will be provided only to authorized researchers within the VA, other federal health agencies, and academic institutions within the US, in a secure manner. This will entail the use of a computer portal into the GenISIS computing environment. The VA Central Institutional Review Board and the peer-reviewed proposals for these studies will dictate appropriate restrictions and limitations of data access as required. Such a portal will provide a virtual "sandbox" to perform one's research work with specific and limited access to genotypic and phenotypic data, as well as statistical tools to enable the performance of a sound analysis of the research question at hand. Importantly, in no way will the researcher have access to a veteran participant's name, address, social security number, or date of birth at any time. Therefore, data security is upheld.

The goal is for the researcher to work, through the GenISIS secure environment, on relationships of genotypic, phenotypic, and epidemiological data to identify relationships between any combinations of the aforementioned areas. In addition, having access to updated data longitudinally—both genomic as well as health record data—thereby enables the researcher to perform research on the level of epigenetics, microRNA (ribonucleic acid), and the like.

Further, the research environment will also allow future repurposing of data points identified in any given study once it is completed and/or published. Additional sampling will be limited to the researcher's ability to implement secondary phenotypic survey requests and the ORD's/GMP's ability to perform genomic-level analytics. Ultimately, associations between genes and health could lead to improved approaches of disease screening, prognosis, diagnosis, and truly personalized care.

Of those responding to the request letter, more than 20% of all mailings (1.3 million recipients) have responded in favor of opting into the MVP, with approximately 10% directly responding not to participate at all. The remaining 70% have neither responded for nor against participation. As of December 7, 2012, the MVP had 114,638 enrollees, with periods of service spanning from World War II to the current conflicts. Remarkably, nearly 14% of the enrollees were veterans who had not received a letter, but who had heard about the program and opted in/enrolled on their own. The program is enrolling in relative alignment to the population seen using the VHA,³² with more than 7% women participants, and approximately 13% and 6% African Americans and Hispanics participating, respectively. The ability to identify unique subpopulations within the MVP, including the use of additional survey tools and the like to enable additional data gathering (eg, respiratory questionnaire), is a potential strength of the program. Further data on VA sites participating in the MVP, our data security measures,³³ and study status may be seen at the ORD MVP website.³³

Thus, the VA is uniquely set to succeed with the GMP and MVP because of the altruistic patient and workforce populations. The VA ORD has had a long history of unique, game-changing discoveries that have improved veteran and national healthcare. By using the large longitudinal megacohort MVP, the VA can further improve veterans' healthcare.

SUMMARY

Concerns regarding respiratory symptoms and outcomes have arisen over the past decade—a time in which >2 million service members deployed to Iraq, Afghanistan, and neighboring countries. Several important studies have been initiated by the DoD and VA to provide critical information on the health outcomes, including respiratory conditions, of US military service members and veterans. These include a large epidemiological study consisting of >200,000 service members and veterans with planned longitudinal follow-up over the course of their lifetimes (the MCS); a

clinical study among military members returning from deployments with respiratory symptoms (the STAMPEDE); a large ongoing collection of genetic, health, and lifestyle data among approximately 1 million veterans (the MVP); and a 10-year longitudinal study of recent veterans (National Health Study for a New Generation of US Veterans). These research studies represent an invaluable resource for understanding emerging health conditions, including respiratory symptoms and conditions, among US military personnel and veterans.

REFERENCES

1. Institute of Medicine, Committee on Measuring the Health of Gulf War Veterans, Division of Health Promotion and Disease Prevention. *Gulf War Veterans: Measuring Health*. In: Hernandez LM, Durch JS, Blazer DG II, Hoverman IV, eds. Washington, DC: National Academy Press; 1999.
2. Knoke JD, Gray GC. Hospitalizations for unexplained illnesses among U.S. veterans of the Persian Gulf War. *Emerg Infect Dis*. 1998;4:211–219.
3. Secretary of Defense. *Report to the Committee on National Security, House of Representatives and the Armed Services Committee, and the U.S. Senate on the Effectiveness of Medical Research Initiatives Regarding Gulf War Illnesses*. Washington, DC: Department of Defense; 1998.
4. House of Representatives, 105th Congress-2nd Session. *Strom Thurmond National Defense Authorization Act for Fiscal Year 1999 (Conference Report to Accompany H.R. 3616)*. Washington, DC: Government Printing Office; 1998. Report 105-736.
5. Gray GC, Chesbrough KB, Ryan MAK, et al. The Millennium Cohort Study: a 21-year prospective cohort study of 140,000 military personnel. *Mil Med*. 2002;167:483–488.
6. Ryan MA, Smith TC, Smith B, et al. Millennium Cohort: enrollment begins a 21-year contribution to understanding the impact of military service. *J Clin Epidemiol*. 2007;60:181–191.
7. Dillman DA. *Mail and Telephone Surveys: The Total Design Method*. New York, NY: Wiley & Sons; 1978.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association, 1994.
9. Weathers FW, Huska JA, Keane TM. *The PTSD Checklist—Civilian Version*. Boston, MA: National Center for PTSD; 1991.
10. Terhakopian A, Sinaii N, Engel CC, Schnurr PP, Hoge CW. Estimating population prevalence of posttraumatic stress disorder: an example using the PTSD checklist. *J Traumatic Stress*. 2008;21:290–300.
11. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
12. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA*. 1999;282:1737–1744.
13. Ware JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36): conceptual framework and item selection. *Med Care*. 1992;30:473–483.
14. Ware JE, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Lincoln, RI: Quality Metric Incorporated; 2000.
15. Smith B, Wingard DL, Ryan MAK, et al. US military deployment during 2001–2006: comparison of subjective and objective data sources in a large prospective health study. *Ann Epidemiol*. 2007;17:976–982.
16. Smith TC, Smith B, Jacobson IG, et al. Reliability of standard health assessment instruments in a large, population-based cohort study. *Ann Epidemiol*. 2007;17:525–532.
17. Smith TC, Jacobson IG, Smith B, Hooper TI, et al. The occupational role of women in military service: validation of occupation and prevalence of exposures in the Millennium Cohort Study. *Int J Environ Health Res*. 2007;17:271–284.
18. Smith B, Chu LK, Smith TC, et al. Challenges of self-reported medical conditions and electronic medical records among members of a large military cohort. *BMC Med Res Methodol*. 2008;8:37.

19. Smith B, Leard CA, Smith TC, et al. Anthrax vaccination in the Millennium Cohort: validation and measures of health. *Am J Prev Med.* 2007;32:347–353.
20. Smith B, Smith TC, Gray GC, et al. When epidemiology meets the Internet: web-based surveys in the Millennium Cohort Study. *Am J Epidemiol.* 2007;166:1345–1354.
21. LeardMann CA, Smith B, Smith TC, Wells TS, Ryan MAK. Smallpox vaccination: comparison of self-reported and electronic vaccine records in the millennium cohort study. *Hum Vaccin.* 2007;3:245–251.
22. Cunradi CB, Moore R, Killoran M, Ames G. Survey nonresponse bias among young adults: the role of alcohol, tobacco, and drugs. *Subst Use Misuse.* 2005;40:171–185.
23. Littman AJ, Boyko EJ, Jacobson IG, et al. Assessing nonresponse bias at follow-up in a large prospective cohort of relatively young and mobile military service member. *BMC Med Res Methodol.* 2010;10:99.
24. Wells TS, Jacobson IG, Smith TC, et al. Prior health care utilization as a determinant to enrollment in a 22-year prospective study, the Millennium Cohort Study. *Eur J Epidemiol.* 2008;23:79-87.
25. Smith B, Wong CA, Smith TC, et al. Newly reported respiratory symptoms and conditions among military personnel deployed to Iraq and Afghanistan: a prospective population-based study. *Am J Epidemiol.* 2009;170:1433–1442.
26. Smith B, Wong CA, Boyko EJ, et al. The effects of exposure to documented open-air burn pits on respiratory health among deployers of the Millennium Cohort Study. *J Occup Environ Med.* 2012;54:708–716.
27. Office of Science Policy and Planning, Office of Science Policy, and the National Institutes of Health. *Iceland's Research Resources: The Health Sector Database, Genealogy Databases, and Biobanks.* Bethesda, MD: NIH; 2004.
28. UK Biobank. UK Biobank Website. <http://www.ukbiobank.ac.uk/about-biobank-uk/>. Accessed February 5, 2014.
29. Kaiser Permanente, Division of Research. *The Research Program on Genes, Environment, & Health: Building a Biobank.* <http://www.dor.kaiser.org/external/DORExternal/rpgeh/index.aspx>. Accessed February 5, 2014.
30. Kaufman D, Murphy J, Erby L, Hudson K, Scott J. Veterans' attitudes regarding a database for genomic research. *Genet Med.* 2009;11:329–337.
31. Kaufman D, Bollinger J, Dvoskin R, Scott J. Preferences for opt-in and opt-out enrollment and consent models in biobank research: a national survey of Veterans Administration patients. *Genet Med.* 2012;14:787–794.
32. US Department of Veterans Affairs. *National Center for Veterans Analysis and Statistics.* https://www.va.gov/vetdata/Veteran_Population.asp. Accessed February 5, 2014.
33. US Department of Veterans Affairs. *Office of Research & Development: Million Veteran Program—A Partnership With Veterans.* <http://www.research.va.gov/MVP>. Accessed February 5, 2014.

