

# Exploration of Modern Military Research Resources

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## PRACTICE POINTS

- Large patient databases and tissue repositories are increasingly being used to improve patient care through the use of clinical data, genomics, proteomics, and metabolomics.
- The US Military has an established electronic medical record as well as tissue and serum repositories that can be leveraged to study melanoma and other dermatologic diseases.

*This article outlines the unique resources available in the US Military to investigate epidemiologic trends, disease pathology, and clinical outcomes. These resources are available to military researchers and civilian collaborators and provide an invaluable research platform.*

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Advances in medical biotechnologies, data-gathering techniques, and -omics technologies have resulted in the broader understanding of disease pathology and treatment and have facilitated the individualization of health care plans to meet the unique needs of each patient. Military medicine often has been on the forefront of medical technology, disease understanding, and clinical care both on and off the battlefield, in

large part due to the unique resources available in the military health care system. These resources allow investigators the ability to integrate vast amounts of epidemiologic data with an extensive biological sample database of its service members, which in the modern age has translated into advances in the understanding of melanoma and the treatment of scars.

## History of Research in the Military

Starting in the 1950s, the US Department of Defense (DoD) started to collect serum samples of its service members for the purpose of research.<sup>1</sup> It was not until 1985 that the DoD implemented a long-term frozen storage system for serum samples obtained through mandatory screening for human immunodeficiency virus (HIV) in service members.<sup>2</sup> Subsequently, the Department of Defense Serum Repository (DoDSR) was officially established in 1989 as a central archive for the long-term storage of serum obtained from active-duty and reserve service members in the US Navy, Army, and Marines.<sup>2,3</sup> In the mid-1990s, the DoDSR expanded its capabilities to include the storage of serum samples from all military members, including the US Air Force, obtained predeployment and postdeployment.<sup>3,4</sup> At that time, a records-keeping system was established, now known as the Defense Medical Surveillance System (DMSS). The creation of the DMSS provided an extensive epidemiologic database that provided valuable information such as demographic data,

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service records, deployment data, reportable medical events, exposure history, and vaccination records, which could be linked to the serum samples of each service member.<sup>2-4</sup> Since 2008, the responsibilities of maintaining the DoDSR and the DMSS were transferred to the Armed Forces Health Surveillance Center (AFHSC).<sup>5</sup>

There have been several other databases created over the years that provide additional support and resources to military investigators. The Automated Central Tumor Registry and Department of Pathology and Area Laboratory Services both help investigators to track the incidence of specific cancers in the military population and provide them with pathologic specimens. Additionally, electronic medical records including the composite health care system and the Armed Forces Health Longitudinal Technology Application supplemented with insurance claims data accessible from the Military Health System Management and Reporting Tool (M2) database have made it possible to track patient data.

### Utilization of Military Research Resources

Today, the DoDSR is a secure facility that maintains more than 56 million serum specimens from more than 11 million individuals in  $-30^{\circ}\text{C}$  freezers, making it one of the largest repositories in the world.<sup>3,6</sup> Each serum sample is linked with an individual's DMSS record, providing a way for investigators to study how external factors such as deployment history, occupation, and exposure history relate to an individual's unique genetic and physiological makeup. Furthermore, these data can be used for seroepidemiologic investigations that contribute to all facets of clinical care. The AFHSC routinely publishes findings related to notifiable diseases, disease outbreaks, and disease trends in a monthly report.<sup>7</sup>

There are strict guidelines in place that limit access to the DoDSR and service members' data. Use of the repository for information directly related to a patient's health care is one reason for access, such as analyzing serum for antibodies and seroconversion to assist in the diagnosis of a disease such as HIV. Another reason would be to obtain information needed for criminal investigations and prosecution. Typically, these types of requests require a judge-issued court order and approval by the Assistant Secretary of Defense for Health Affairs.<sup>4</sup> The DoDSR also is used to study force health protection issues, such as infectious disease incidence and disease prevalence in the military population.

Obtaining access to the DoDSR and service members' data for research purposes requires that the principal investigator be a DoD employee. Each research proposal is reviewed by members of

the AFHSC to determine if the DoDSR is able to meet the demands of the project, including having the appropriate number of serum samples and supporting epidemiologic data available. The AFHSC provides a letter of support if it deems the project to be in line with its current resources and capabilities. Each research proposal is then sent to an institutional review board (IRB) to determine if the study is exempt or needs to go through a full IRB review process. A study might be exempt if the investigators are not obtaining data through interaction with living individuals or not having access to any identifiable protected health information associated with the samples.<sup>6</sup> Regardless of whether the study is exempt or not exempt, the AFHSC will de-identify each sample before releasing the samples to the investigators by using a coding system to shield the patient's identity from the investigator.

Resources within the military medical research system provide investigators with access to an extensive biorepository of serum and linked epidemiological data. Samples from the DoDSR have been used in no less than 75 peer-reviewed publications since 1985.<sup>8,9</sup> Several of these studies have been influential in expanding knowledge about conditions seen more commonly in the military population such as stress fractures, traumatic brain injuries, posttraumatic stress disorder, and suicide.<sup>8</sup> Additionally, DoDSR samples have been used to form military vaccination policies and track both infectious and noninfectious conditions in the military; for example, during the H1N1 influenza virus outbreak of 2009, AFHSC was essential in helping to limit the spread of the virus within the military community by using its data and collaborating with groups such as the Centers for Disease Control and Prevention to develop a plan for disease surveillance and control.<sup>5</sup>

Several military research resources are currently being used for a melanoma study that aims to assess if specific phenotypic features, melanoma risk alleles, and environmental factors (eg, duty station location, occupation, amount of UV exposure) can be used to develop better screening models to identify individuals who are at risk for developing melanoma. Secondarily, the study aims to determine if recently developed multimarker diagnostic and prognostic assays for melanoma will prove useful in the diagnostic and prognostic assessment of melanocytic neoplasms in the military population. For this study, one of the authors (J.H.M) is utilizing DoDSR serum from 1700 retrospective cases of invasive melanoma and 1700 matched controls. Additionally, the Automated Central Tumor Registry and Department of Pathology and Area Laboratory Services databases are being used to obtain tissue from more than 300 melanoma cases and nevi controls.

### Limitations of the Current System

Despite the impressive capabilities of the current system, there are some issues that limit its potential. One such limitation is associated with the way that the serum samples at the DoDSR are utilized. Through 2012, the DoDSR had 54,542,658 serum specimens available, of which only 228,610 (0.42%) had ever been accessed for study.<sup>8</sup> With such a wealth of information and relative availability, why are the serum samples not being accessed more frequently for studies? The inherent nature of the DoDSR being a restricted facility and only accessible to DoD-affiliated investigators may contribute, which allows the DoDSR to fulfill its primary purpose of contributing to military-relevant investigations but at the same time limits the number and type of investigations that can be performed. One idea that has been proposed is allowing civilian investigator access to the DoDSR if it can be proven that the research is targeted toward military-relevant issues.<sup>8</sup> However, the current AFHSC access guidelines would need revision and would require additional safeguards to ensure that military-protected health information is not compromised. Nonetheless, such a change may result in more extensive use of DoDSR resources in the future.

An ethical issue that needs to be addressed pertains to how the DoDSR permits use of human serum samples for research purposes without getting consent from the individuals being studied. The serum samples are collected as part of mandatory predeployment and postdeployment examinations for HIV screening of all military members. These individuals are not informed of potential use of their serum specimens for research purposes and no consent forms or opt-out options are provided. Although it is true that military members must comply with specific requirements pertaining to military readiness (eg, receiving appropriate vaccinations, drug testing, regular medical screening), it is debated whether they still retain the right as patients to refuse participating in research and clinical trials.<sup>10</sup> The AFHSC does have several regulatory steps in place to ensure that military members' samples are used in an appropriate manner, including requiring a DoD primary investigator, IRB review of every research proposal, and de-identification of samples. At a minimum, giving military members the ability to provide informed consent would ensure that the military system is adhering to evolving human research standards.

The current lack of biological specimens other than serum in the DoDSR is another limitation of the current system. Recent advances in molecular analyses are impacted by expanding

-omics techniques, such as epigenomics, transcriptomics, and proteomics. The field of epigenomics is the study of reversible changes to DNA (eg, methylation) associated with specific disease states or following specific environmental exposures.<sup>9,11</sup> Transcriptomics, which analyzes messenger RNA transcript levels of expressed genes, and proteomics, which uses expression of proteins, are 2 techniques being used to develop biomarkers associated with specific diseases and environmental exposures.<sup>9,11</sup> Serum alone does not provide the high-quality nucleic acids needed for many of these studies to take place. Adding whole-blood specimens or blood spot samples of military service members to the DoDSR would allow researchers to use these techniques to investigate many new biomarkers associated with military-relevant diseases and exposures. These techniques also can be used in the expanding field of personalized medicine so that health care providers are able to tailor all phases of care, including diagnosis and treatment, to an individual's genetic profile.

### Conclusion

The history of research in military medicine has been built on achieving the primary goal of serving those men and women who put their lives in danger to protect this country. In an evolving environment of new technologies that have led to changes in service members' injuries, exposures, and diseases, military medicine also must adapt. Resources such as the DoDSR and DMSS, which provide investigators with the unique ability to link epidemiological data with serum samples, have been invaluable contributors to this overall mission. As with any large system, there are always improvements that can be made. Improving access to the DoDSR serum samples, educating and obtaining consent from military service members to use their samples in research, and adding specimens to the DoDSR that can be used for -omics techniques are 3 changes that should be considered to maximize the potential of the military medical research system.

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