UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

APR - 8 2022

The Honorable Jack Reed
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The Department's response to House Report 117-118, page 182, accompanying H.R. 4350, the National Defense Authorization Act for Fiscal Year 2022, which requests the Secretary of Defense to report on rare cancer treatment in the Military Health System (MHS), is enclosed.

The MHS provides molecular diagnostic testing services to Service members and beneficiaries as a vital component of comprehensive cancer care. This is true regardless of the incidence of the specific cancer and whether or not it is classified as "rare." The MHS conducts comprehensive molecular diagnostic testing through three routes: (1) internal; (2) research-based; and (3) send-out testing. In 2020, there were approximately 9,570,484 MHS-eligible beneficiaries. Of those, 8.1 percent had a diagnosis indicating current cancer or a personal history of cancer. Of the 8.1 percent, 5.8 percent received molecular diagnostic testing that may be cancer-applicable.

The Department of Defense (DoD) has detailed data-sharing policies to support relationships with various organizations and entities. It is feasible for DoD to form public-private partnerships to explore next-generation, precision-oncology platforms. The Department is establishing a Genomics Program, which will explore this potential further. The Air Force Medical Genetics Center at Keesler Air Force Base and the Joint Pathology Center provide information to DoD clinicians on the value of molecular diagnostic testing, including methods of reimbursement. The TRICARE Laboratory Developed Tests Demonstration Program also reimburses for multiple cancer-related tests.

Thank you for your continued strong support for the health and well-being of our Service members and families. I am sending a similar letter to the House Armed Services Committee.

Sincerely,

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable James M. Inhofe
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

APR - 8 2022

The Honorable Adam Smith
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

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Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable Mike D. Rogers
Ranking Member

Report to the Congressional Armed Services Committees

In Response to House Report 117-118, Page 182, Accompanying H.R. 4350, the National Defense Authorization Act for Fiscal Year 2022. on Rare Cancer Treatment

April 2022

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $27,000 in Fiscal Years 2021-2022. This includes $0 in expenses and $27,000 in DoD labor.
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EXECUTIVE SUMMARY

This report is in response to House Report 117-118, page 182, accompanying H.R. 4350, the National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2022, which requests that the Secretary of Defense submit a report to the Committees on Armed Services of the Senate and House of Representatives providing:

(1) A description of the specific types of molecular diagnostics, such as microarray, whole exome, and ribonucleic acid (RNA) sequencing, which the Department of Defense (DoD) is providing to beneficiaries diagnosed with cancer and their frequency of use;
(2) The Department's detailed policy for data-sharing practices for cancer cell lines and models with the external research community;
(3) The feasibility of the Department to engage in public-private partnerships to use a next-generation, precision-oncology platform that integrates bioinformatics, machine learning, and mathematics to unveil unprecedented insights into cancer and moves beyond a single-target-based approach. This approach should seek to identify complex and interconnected mechanisms responsible for drug response and resistance revealed in the human transcriptome to determine the best treatments and facilitate developing new ones and any potential costs associated with this; and
(4) The method by which the Department provides information to all clinicians treating TRICARE and Military Health System (MHS) patients on the value of using molecular diagnostics for all cancer patients and reimburses for these important diagnostics at the time of diagnosis.

The MHS provides comprehensive molecular diagnostic testing through three methods: (1) internal; (2) research-based; and (3) send-out testing routes. Specifically:

(1) **Internal Testing:** Conducted at the Joint Pathology Center (JPC) and Air Force Medical Genetics Center (AFMGC) at Keesler Air Force Base (AFB), these testing routes include both germline[1] and somatic testing[2].
(2) **Research-based Testing:** Research-based testing, such as full genome sequencing[3], germline sequencing, precision oncology, and clinical trial matching, occurs at military medical treatment facilities (MTFs) that participate in one or more of the following Institutional Review Board (IRB) research protocols: Applied Proteogenomic Organizational Learning Outcomes (APOLLO) Network, the Murtha Cancer Center (MCC) Bio-Bank, and/or Oncology Research Information Exchange Network (ORIEN).
(3) **Send-out Testing:** When internal capabilities are not available, testing is sent out to an external lab (e.g., Laboratory Corporation of America® [LabCorp®])[4]. This includes a program of clinical sequencing and clinical trial matching, as well as RNA testing.

[1] Germline testing looks at mutations, which are hereditary, that arise in germline cells and are inherited.
[2] Somatic testing looks for mutations, which are acquired changes restricted to an individual's specific cell and its progeny, and are not passed to children or siblings.
[3] Sequencing is a technique used in a laboratory that determines the exact sequence of bases (Adenine [A], Cytosine [C], Guanine [G], and Thymine [T]) in an individual's DNA.
[4] References to non-federal entities do not constitute an endorsement of those entities by DoD or any of its Components.

The MHS Data Repository (MDR) was used in this report to identify beneficiaries with a cancer diagnosis that received care through the MHS. Direct Care data (Comprehensive Ancillary Data Record Extract (CADRE) Laboratory, LabCorp®, and MHS GENESIS Laboratory) and Private Sector Care data (TRICARE Encounter Data (TED) Non-Institutional) were used to identify molecular tests performed within the respective FY. In FY 2020, the most recent year for which complete data is available, there were approximately 9,570,484 MHS-eligible beneficiaries. Of those, 775,164 (8.1 percent) had a diagnosis indicating current cancer or a personal history of cancer. In FY 2020, of the 775,164 beneficiaries with a diagnosis indicating cancer, 45,016 (5.8 percent) received molecular diagnostic testing that may be cancer-applicable. A similar trend was found for the prevalence of cancer among MHS-eligible beneficiaries in FY 2019. Among the 9,517,011 beneficiaries, 803,490 (8.4 percent) had a diagnosis indicating current cancer or a personal history of cancer. Of the 803,490 beneficiaries with a diagnosis indicating cancer in FY 2019, 48,551 (6 percent) received molecular diagnostic testing that may be cancer-applicable. Cancer prevalence, as well as molecular diagnostic testing frequency, are discussed in further detail later in this report.

Addressing the committee's concern over the prevalence of "rare" cancers in the Service member (SM) population, the MHS provides molecular diagnostic testing services to SMs as a vital component of comprehensive cancer care. This is true regardless of the incidence of the specific cancer and whether or not it is classified as "rare." As noted in this report, "rare" cancer is defined differently based on the source. By Federal regulation, TRICARE uses the following in determining a rare disease: "any disease or condition with a prevalence of less than 200,000 persons per year in the United States" (32 CFR § 199.2). Although the definitions vary, the MHS finds that molecular diagnostic testing is standard of care for most cancers, whether or not they are classified as "rare."

DoD has established data-sharing relationships with various organizations and entities, and has detailed policies and procedures for engaging in such relationships. The Department of Veterans Affairs (VA) and DoD collaborate at three APOLLO sites. APOLLO data are submitted to the National Institutes of Health's (NIH) National Cancer Institute (NCI) Genetic Data Commons (GDC) Portal; once in the GDC Portal, data are available to the public. The MHS has also stood up the MHS Information Platform (MIP) that serves as a data reporting and analysis repository, facilitating the integration and sharing of data.

It is feasible for DoD to form public-private partnership(s) to explore next-generation, precision-oncology platforms. The Defense Health Agency (DHA) is currently developing a new Genomics Program which, once established, will articulate its priorities, future state, gap analysis, and initiatives, including the feasibility of public-private partnerships relating to the integration of artificial intelligence, machine learning, deep learning, and quantum computing.

Molecular diagnostic treatment and research fulfills the requirements of the MHS Quadruple Aim (i.e., the ultimate goal for MHS which represents the MHS leadership's commitment to delivering value to all it serves and is aligned with the MHS strategic goals and value proposition) by: (1) ensuring that all cancer patients, including the thousands of active duty Service members (ADSMs) with cancer, have the best quality treatment at a lower cost to the Department compared to network care; and (2) ensuring access to precision cancer treatments

based on each individual's germline and somatic genetics, which results in higher cancer cure rates with lower side effects of treatment, all of which contribute to maintaining readiness of the Force.

Additional benefits from testing related to research and treatment include the following:

- Research testing builds important molecular expertise within the DoD. The MHS must have adequate knowledge about molecular medicine to provide current and best treatment to the Force.
- Testing within the DoD allows for standardization of the testing processes; this is associated with improved quality.
- Research testing goes beyond clinical testing: it can identify novel mutations that are linked to clinical trials. Access to clinical trials is associated with better outcomes.
- Research leads to discoveries that change the way medicine is practiced, leading to improved outcomes.
- DoD clinical and research testing permits for the analysis of data without the risk of sending samples to commercial reference labs, which can compromise national security by exposing SMs' private, personally identifiable genomic information, as well as information about lineage.

DoD supports clinicians treating TRICARE and MHS patients by providing information on the value of using molecular diagnostics for all cancer patients. Information on molecular diagnostics is provided to clinicians through various channels, including the Laboratory Developed Test (LDT) Demonstration and consultation with the AFMGC.

INTRODUCTION

Overview of Molecular Testing

The MHS provides excellent care to SMs and beneficiaries throughout the entire spectrum of cancer care. A culture of safety is promoted by engaging, educating, and equipping patient-care teams to put evidence-based leading practices in place across the organization. Within the world of cancer care, evidence-based leading practices are strongly tied to molecular diagnostic testing. Molecular testing, also referred to as molecular profiling throughout this report, is defined as "a laboratory test that checks for certain genes, proteins, or other molecules in a sample of tissue, blood, or other body fluid. Molecular tests also check for certain changes in a gene or chromosome that may cause or affect the chance of developing a specific disease or disorder, such as cancer. A molecular test may be done with other procedures, such as biopsies, to help diagnose some types of cancer. It may also be used to help plan treatment, find out how well treatment is working, or make a prognosis" (NCI, 2020).

Molecular testing provides a molecular profile, which refers to the assessment of deoxyribonucleic acid (DNA), RNA, and/or proteins within a patient's cancer cells. The world of molecular profiling has undergone revolutionary changes over the last few years as knowledge, technology, and standard clinical practice have evolved.

Comprehensive molecular profiling of patient tumors has been widely studied over the last few years in a variety of cancers, leading to the development of a new term: precision medicine (sometimes also referred to as "personal medicine"). Precision medicine is available to patients being treated by a medical oncologist in both Direct Care and Private Sector Care. Molecular profiling is standard practice for most patients with advanced disease, either as a large next-generation sequencing (NGS) panel or as specific mutation-focused testing based on national guideline recommendations, replacing the historical treatment paradigm of prescribing standard chemotherapy based upon the tumor's organ of origin, histology, and stage. If precision medicine is not recommended by the national guidelines, the individual oncologist can still determine if it is clinically warranted. This is usually considered when a patient has progressed on all standard therapies, or if the cancer is rare and no standard therapies are known. This approach allows oncologists to make treatment recommendations based upon genomic drivers of cancer.

The focus of molecular profiles has shifted from a small number of predictive, disease-specific, evidence-based tests chosen "a la carte," to broader panel testing that measures levels of or changes in genes or gene products. These genomic changes can be therapeutic targets or serve as biomarkers of both response prediction and a patient's prognosis.

The most useful biomarkers for predicting the efficacy of targeted therapy in advanced malignancies are somatic genome alterations known as molecular driver mutations. These mutations occur in cancer cells within genes encoding for proteins critical to cell growth and survival. Molecular driver mutations are typically transformative, meaning they initiate the evolution of a noncancerous cell to malignancy. An often used analogy is that a normally functioning cell may have a switch in its circuitry that is sometimes turned on and sometimes

turned off, but in general is regulated with feedback inhibition loops and stimulators. In an oncogene-driven cancer cell, the switch is stuck in the "on" position all the time and is no longer affected by regulation.

In many advanced malignancies, matching a specific targeted drug to the identified driver mutation for an individual patient results in improved therapeutic efficacy, often with decreased toxicity. Screening for molecular driver mutations is a necessity for high-quality treatment decisions for non-small cell lung cancer. Over the last few years, however, screening for molecular driver mutations in the advanced and/or metastatic setting has become recommended for many other malignancies, to include breast cancer, colorectal cancer, pancreatic cancer, and prostate cancer. Additionally, there are now Food and Drug Administration (FDA)-approved treatments for cancer based solely on the identification of a Neurotrophic Tropomyosin Receptor Kinase mutation or microsatellite instability (as two examples), and are not dependent on the organ from which the cancer emerged.

It remains important to distinguish between acquired somatic mutations and hereditary germline mutations in the rapidly evolving field of molecular testing. Somatic mutations are mutations, which are acquired changes restricted to a specific cell and its progeny and are not passed to children or siblings. Germline mutations are hereditary mutations that arise in germline cells and are inherited. Germline mutations are most commonly known for associations with breast and ovarian cancer but are increasingly being identified for their association in other malignancies, such as pancreatic and prostate cancers. A good example of this is the incorporation of Breast Cancer gene (BRCA) germline testing for all patients with pancreatic cancer. Germline testing involves an extensive coverage of BRCA, whereas current somatic testing covers only certain regions of that gene. As mutation analysis evolves into whole exome sequencing, coverage of germline and somatic testing will be similar if not identical. Given the increased need for somatic testing in patients with pancreatic cancer, it is possible that whole exome sequencing will replace germline testing in guidelines to come. Similar to somatic mutations, the FDA has approved drugs for the treatment of BRCA-mutated cancers of the breast, ovaries, prostate, and pancreas. Both somatic and germline testing have developed an increasingly significant role in cancer care. In summary, access to standard of care molecular tests for SMs and beneficiaries remains of utmost importance.

Relationship between Molecular Testing, Rare Cancer, and Cancer Incidence

As described above, the MHS provides molecular diagnostic testing services to SMs as a vital component of comprehensive cancer care. This is true regardless of the incidence of the specific cancer and whether or not it is classified as "rare."

House Report 117-118, page 182, accompanying H.R. 4350, the NDAA for FY 2022, states, "Over 60 cancers disproportionately impact those who have served in the military and most are rare cancers, defined as fewer than 6 new cases per 100,000 Americans per year."

Although the NDAA language defines rare cancer as fewer than 6 new cases per 100,000 people per year, it is important to note that rare cancer is defined differently based on the source:

1) NCI: Cancer that occurs in fewer than 15 out of 100,000 people each year.
2) American Cancer Society: Cancer with fewer than 6 cases per 100,000 people per year.
3) Cleveland Clinic Cancer Center: Rare cancer is defined as having an annual incidence of 2 new cases or less per 100,000 people.

TRICARE uses the following in determining a rare disease: "any disease or condition with a prevalence of less than 200,000 persons per year in the [U.S.]" (32 CFR § 199.2). Although the definitions vary, the MHS feels that molecular diagnostic testing is standard of care for most cancers, whether or not they are classified as "rare" by any of the definitions above.

Zhu, et al., (2009), compared the incidence of four cancers common in U.S. adults (lung, colorectum, prostate, and breast cancers) and two cancers more common in U.S. young adults (testicular and cervical cancers) in the military and general populations. The study analyzed data from DoD's Automated Central Tumor Registry (ACTUR) and the NCI's Surveillance, Epidemiology, and End Results (SEER) nine cancer registries for the years 1990-2004 for persons aged 20-59 years old. "Incidence rates were significantly lower in the military population for colorectal cancer in white men, lung cancer in white and black men and white women, and cervical cancer in black women. In contrast, incidence rates of breast and prostate cancers were significantly higher in the military among both whites and blacks. Incidence rates of testicular cancer did not differ between ACTUR and SEER." The authors summarized their findings by stating, "Overall, these results suggest that cancer patterns may differ between military and non-military populations. Further studies are needed to confirm these findings and explore contributing factors" (Zhu, 2009).

In a study completed by Lee, T., Williams, V., Taubman, S., and Clark, L. (2016), the authors found that of the six cancers that occur most commonly (by annual incidence) in ADSMs, none are classified as rare cancers. These cancers are: testis, melanoma, prostate, non-Hodgkin lymphoma, female breast, and colon/rectum (Figure 1). The study looked at 16 of the most common cancer types in the typical SM demographic (i.e., young, healthy), which make up approximately 60 percent of the cancer types among MHS beneficiaries with cancer.

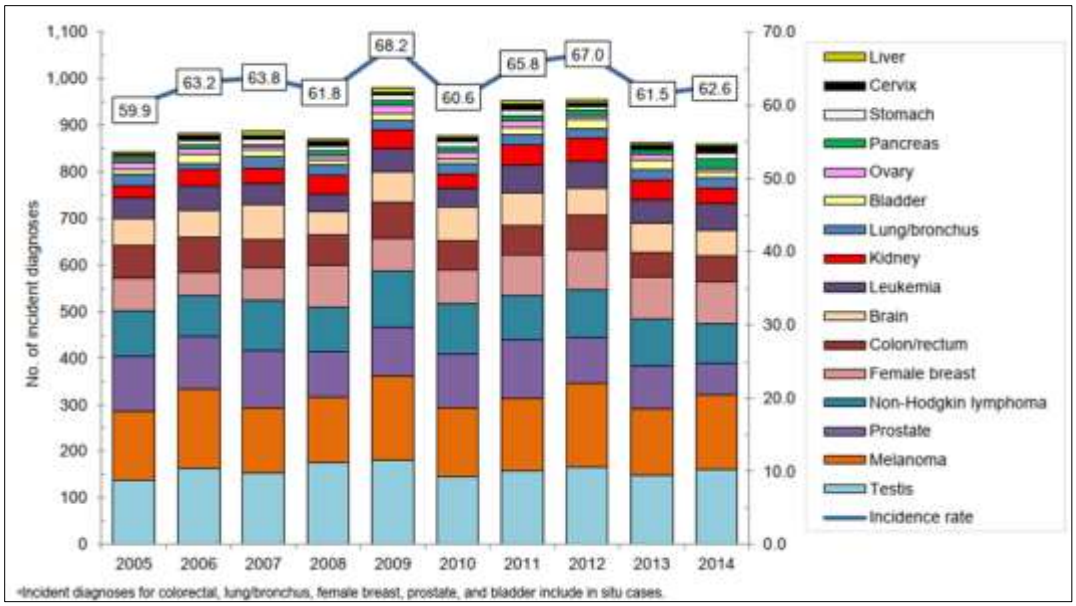

Figure 1. Incident Diagnosis of Selected Cancers and Total Incidence Rate, by Year (2005-2014) and Affected Anatomic Site/Cell Type, Active Component, U.S. Armed Forces

The information in this report outlines the work that the MHS is doing to provide excellent cancer care to SMs, which includes molecular diagnostic services as a standard of care for most cancers. Through excellent cancer care, the MHS affirms its unwavering commitment to quality health care and patient safety for SMs.

TYPES OF MOLECULAR DIAGNOSTICS

Molecular diagnostic testing is a vital aspect of cancer care within the MHS. SMs have access to comprehensive molecular diagnostic testing through: (1) internal, (2) research-based, and (3) send-out testing routes. The five main categories of molecular diagnostic testing available in the MHS are described below, with their sub-tests described in further detail in Appendix B.

All of the test methods listed below are designed to look for harmful disease-causing changes in genes. These harmful changes are termed "pathogenic mutations." Pathogenic mutations present in DNA that a person is born with are known as germline mutations, and are important in inherited types of cancer. Pathogenic mutations in DNA from malignant tumors, such as breast cancer and prostate cancer, are termed somatic mutations. All of the listed test methods can be performed on a variety of specimen types, such as peripheral blood, to look for germline mutations. They can also be performed on formalin-fixed paraffin embedded (FFPE) tumor tissue to look for somatic mutations.

1) DNA Arrays: Array technology is a type of hybridization analysis allowing simultaneous analysis of large numbers of genes or even an entire genome. The human genome is comprised of more than 30,000 genes that are neatly compacted in 23 pairs of chromosomes with one additional mitochondrial DNA. Genes are made of nucleic acids, specifically DNA and RNA. The current estimate of protein-coding genes is 20,000-30,000, while estimates for all genes, including protein coding genes, other functional DNA elements/non-coding genes, and those expressing regulatory RNAs, are 46,500. There are also an estimated 2,300 microRNA "genes." In DNA arrays, the word "array" means an orderly distribution of molecules on solid surfaces, such as glass or silicon. Synonyms for microarrays include gene chip, DNA chip, biochip, gene array, DNA array, and DNA microarray. These assays are used for detection of changes in genes such as loss or gain of genetic material. Targeted arrays are increasingly being used in the clinical laboratory for the diagnosis of both cancer and congenital conditions.

2) Epigenomic Studies: The expression of a gene can be altered when DNA is modified by natural processes known as methylation, phosphorylation, or acetylation. Through alterations in the form of DNA by exposure to toxins and medications, or by nutrition, these modifications can unwind and expose normally hidden parts of the DNA or roll up and hide normally exposed parts of the DNA. Epigenomic changes that cause short-term or sustained changes in gene expression include not only changes in chromatin structure [often partially mediated by non-coding RNAs (ncRNAs)], but also changes in transcriptional and post-transcriptional regulation mediated by other ncRNAs such as small interfering RNAs, microRNAs, piwi-interacting RNAs, etc. The interplay between structural elements of the chromosome and ncRNAs is a complex and active field of study. These epigenomic changes may affect the DNA of offspring. Such modifications do not change the underlying DNA sequence and are known as epigenetic changes. Methylation studies are the most common epigenetic studies performed in cancer. In some instances, methylation status is used to determine if the tumor analyzed is inherited or sporadic (not inherited). Additionally, methylation status is useful for prognosis in

some types of brain cancer. It is also useful for treatment guidance and genetic counseling in colon and endometrial cancers.

3) Fluorescence In Situ Hybridization (FISH): In FISH, fluorescently tagged probes are used to identify pathogenic mutations specific to a disease process. The major advantages of FISH are the utility for testing FFPE tumor tissue sections, and for identification of specific abnormalities when partnered with conventional cytogenetics. The number and location of the fluorescent signal(s) can identify genetic abnormalities, including gene amplification, gene deletion, or gene rearrangements (also known as translocations). FISH is used to aid in the diagnosis of solid tumors, such as soft tissue sarcomas, and blood tumors, such as leukemia and lymphoma. FISH is also used to guide treatment in specific solid tumors, such as breast cancer and lung cancer.

4) Polymerase Chain Reaction (PCR): This technique was developed in the mid-1980s and is deemed the most important "invention," giving rise to the field of molecular pathology. PCR exponentially amplifies specific sequences of DNA or RNA to produce enough nucleic acid for mutation analysis. Once these are amplified, the nucleic acid can be used for different purposes, including the diagnosis of minimal residual disease and engraftment studies in leukemia and lymphoma patients, as well as a guidance in treatment of melanoma, colon cancer, and lung cancer.

5) Sequencing: The ability to sequence DNA and RNA has been essential in the field of molecular pathology. Sequencing is a method used to map the order of nucleotides within nucleic acids and is extremely useful in identifying pathogenic mutations that serve to either confirm a cancer diagnosis or guide treatment decisions in many cancer types.

Internal Testing

Many molecular diagnostic tests are available internally in the MHS at the JPC Molecular Pathology Laboratory and the AFMGC at Keesler AFB.

Clinical tests are ordered by a health care provider for the purpose of diagnosis or treatment of an individual patient. These laboratories perform high complexity testing under a strict regulatory framework outlined by Clinical Laboratories Improvement Amendments (CLIA) and the College of American Pathologists. As part of the accreditation and certification process, clinical laboratories agree to participate in ongoing, continuous proficiency testing as a quality safeguard.

JPC

The JPC Molecular Pathology Laboratory in Silver Spring, Maryland, provides molecular testing for a variety of cancers in the setting of the JPC's pathology consultative service. Most of the samples tested at the JPC Molecular Pathology Laboratory represent patients with recurrent or advanced disease, or complex cases where diagnosis by traditional pathologic analysis may be difficult or uncertain. Currently, few (if any) samples obtained at primary diagnosis are received at the JPC Molecular Pathology Laboratory.

The JPC provides somatic (tumor tissue) molecular diagnostic capabilities within the MHS using various methodologies, including FISH, real-time PCR, fragment analysis, and first-generation sequencing techniques to detect somatic mutations and epigenetic alterations in solid tumor samples. The JPC currently uses 32 assays to provide information relevant to diagnosis, prognosis, therapeutic decisions, and disease monitoring for solid tumors. Other assays, including NGS-based, multi-gene, somatic tumor profiling assays, are in development.

AFMGC

The AFMGC at Keesler AFB in Biloxi, Mississippi, is the DHA-designated reference laboratory for all germline testing within the DoD. As part of the AFMGC's mission, it performs testing for rare genetic disorders, hereditary cancer syndromes, molecular autopsies, PGx testing, and carrier screening for genetic conditions.

The AFMGC provides several services to aid in the diagnosis, treatment, and prevention of rare cancers. These services have been available since 2016; in that time, over 5,000 beneficiaries suspected of having a hereditary cancer syndrome have been tested.

The molecular laboratory provides comprehensive testing for hereditary cancer syndromes, covering over 150 genes, with the ability to report on single nucleotide variations, insertions/deletions, and copy number variations (deletions/duplications). Specifically, the AFMGC provides germline (blood) molecular diagnostic capabilities, including testing for single gene disorders, as well as large panel testing covering the great majority of known hereditary cancer syndromes. This is achieved within an NGS core (comprised of Illumina Miseq, NextSeq and NovaSeq instruments, robotic handlers, and other instrumentation) and a custom-developed bioinformatics pipeline.

The molecular laboratory also offers PGx testing which can help guide the use of certain chemotherapeutic agents. Additionally, the cytogenetics laboratory provides testing support to selected MTFs for FISH and chromosomal microarray to aid in the diagnosis of solid tumors and leukemias.

Research-Based Testing

ADSMs and beneficiaries can receive molecular diagnostic testing through research-based protocols, including the APOLLO Network, ORIEN, and Bio-Bank. To preserve readiness, the first priority is to obtain consent from the over 1,000 ADSMs a year who are newly diagnosed with cancer in the MHS. Patients agree to participate in IRB-approved research at the time of diagnosis and are consented prior to surgery. The tumor sample is collected and sent for testing based on the specific protocol in which the patient is enrolled. Research-based testing approaches include full genome sequencing, germline sequencing, clinical trial matching, and precision oncology.

The MHS value proposition for this research is that it fulfills the requirements of the MHS Quadruple Aim (better care, better health, lower cost, increased readiness) by ensuring that all

cancer patients, including the thousands of ADSMs with cancer, have the best quality treatment at lower cost to the DoD compared to care in the civilian network. This also ensures precision cancer treatments based on each individual's tumor genetics, resulting in higher cancer cure rates with lower treatment side effects, all of which contribute to maintaining readiness of the Force. Additional benefits from testing related to research and treatment include:

(1) Building important molecular expertise within the DoD. These skills are necessary for DoD to maintain up-to-date knowledge;
(2) Standardizing testing within the DoD, which is associated with quality;
(3) Identifying novel mutations that are linked to clinical trials. Access to clinical trials is associated with better outcomes;
(4) Making discoveries that change the way medicine is practiced, leading to improved outcomes; and
(5) Ensuring biosecurity: DoD clinical and research testing allows for data analysis without the risk of compromising DoD data security by sending to commercial reference labs.

APOLLO Network

Patients at participating MTFs have the opportunity to be enrolled in the APOLLO Network and receive full genome sequencing. This allows for access to unique data, which includes germline sequencing. APOLLO's vision is to serve as a Federal cancer alliance that, through strong research collaborations and partnerships, optimizes Federal cancer resources, enhances cancer research and discoveries, decreases duplication, leverages technologies, enhances intellectual capital, and increases education and training opportunities. Using advanced methods in proteogenomics to characterize and compare tumors, the alliance develops a deeper understanding of cancer biology by identifying potential therapeutic targets and pathways for cancer prevention, detection, and intervention.

Eight MTFs currently participate in the APOLLO Network:

- Walter Reed National Military Medical Center (WRNMMC)
- San Antonio Military Medical Center (SAMMC)
- Madigan Army Medical Center (MAMC)
- Tripler Army Medical Center (TAMC)
- Womack Army Medical Center (WAMC)
- Keesler AFB
- Naval Medical Readiness and Training Command - San Diego (NMRTC-SD)
- Naval Medical Readiness and Training Command - Portsmouth (NMRTC-P)

The APOLLO Protocol consists of seven types of molecular analyses:

- Prior to analyzing the molecules, laser microdissection is used to separate the tumor cells from their supporting cellular matrix (stroma) to study those two elements in parallel.

- DNA sequencing (HiSeq X Ten system) of the tumor's whole genome looks for mutations within the tumor that can be treated with precision medications targeting the patient's specific tumor.
- DNA sequencing (HiSeq X Ten system) of the patient's blood looks for family-derived hereditary mutations that have resulted in the patient developing cancer or having a higher risk than average of doing so.
- RNA sequencing (Nova Seq system) of the tumor looks for the abnormalities in the connecting message between the DNA (instruction manual of the tumor) and proteins (action molecules that carry out the instructions from the DNA).
- Four types of protein analyses are also performed on all tumors sent through the APOLLO workflow:
    - Lumos Fusion Orbitraps
    - Exploris 480 Orbitrap
    - Q-Trap 6500 Triple Quadrupoles
    - Q-Exactive HF-Xs

Taken together, the above four protein analysis workflows enable evaluation of all known aspects of the protein functions in both the tumor cells and the stroma cells, to include high performance mass spectrometric identification of all peptides and proteins for patient management, the phosphoproteome that signals activation of protein cellular functions, and overall protein identifications.

The APOLLO Research Pathology Center (RPC) uses industrialized workflows and highly standardized operating procedures for preparation of cancer tissues for histopathology review by experts at the JPC, and credentialing of tissues for the multiple APOLLO molecular workflows. A hallmark of the APOLLO RPC is the laser microscopy core that represents one of the largest assemblies of laser microscopes in the world. This capability places APOLLO in a unique position to uncover profound new insights into the complex interactions within the tumor microenvironment and underpins the ability of the DoD to repurpose, advance, and deploy new therapeutic options for cancer patients.

At the Uniformed Services University of Health Sciences (USU) Center for Precision Medicine Initiative for Military Medical Education and Research (PRIMER) in Bethesda, Maryland, whole genome sequencing is performed for all APOLLO patients within The American Genome Center (TAGC) at a rate of 15,000 samples per year, yielding 45 billion base pairs (A, T, C, G). Integrated laboratory robotics and sequencers process, prepare, and sequence biospecimens in a highly parallelized workflow. These massive sequences are then analyzed to identify molecular markers for disease diagnosis and outcomes within the Data Science Core's secure, high-performance computing enclave. As a part of its role in PRIMER, the genetics team at USU/WRNMMC is involved in a collaborative effort with Baylor University and the Mayo Clinic to study use of pharmacogenetics in the MHS. This includes studying genes that are important for oncology-related medications. Specifically, all participants undergo CYP2D6 and CYP2C19 genotyping and next generation sequencing of a panel of genes that includes CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP2D6, VKORC1, TPMT, UGT1A1, SLCO1B1, and DPYD.

APOLLO supports the Federal Government's ongoing "Precision Oncology" initiative. The information gained through the APOLLO study will help foster development of early detection tests, prognostic panels, and companion diagnostics, as well as identify targets for prevention strategies or innovative interventions including precision oncology treatments.

The APOLLO Clinical Proteomics Platform (CPP) leverages its industry-leading standardized procedures and high-performance mass spectrometry to profile human cancer tissue to identify and validate protein biomarkers for personalized cancer patient management through improved early detection, patient stratification, and monitoring for therapeutic efficacy, outcome and recurrence.

ORIEN

ORIEN is a unique research partnership among North America's top cancer centers that recognizes collaboration and access to data as the keys to cancer discovery. ORIEN collects and shares data with the purpose of matching high-risk cancer patients to targeted treatments. Through ORIEN, detailed molecular data are generated through whole exome sequencing so patients can better understand their diagnoses and identify clinical trials early on in the treatment process, also known as clinical trial matching. This also allows for patients to be contacted and enrolled in new biomarker-driven clinical trials that arise, even after beginning or completing treatment. Additional elements of ORIEN include:

- Patient portal for self-reporting data;
- Real-time data capture at the source;
- Standardized process for tissue, data, and consenting;
- Biomarker-based pre-population of patients for clinical trials;
- Data aggregation and linkage across systems;
- Data concierge services; and
- Information platform options to access and use data.

There are 19 NCI-designated cancer centers in the United States that participate in ORIEN; USU/WRNMMC's MCC is the only DoD site (Figure 2). Across the network, there are over 600,000 patients enrolled in ORIEN, with over 30,000 having undergone sequencing.

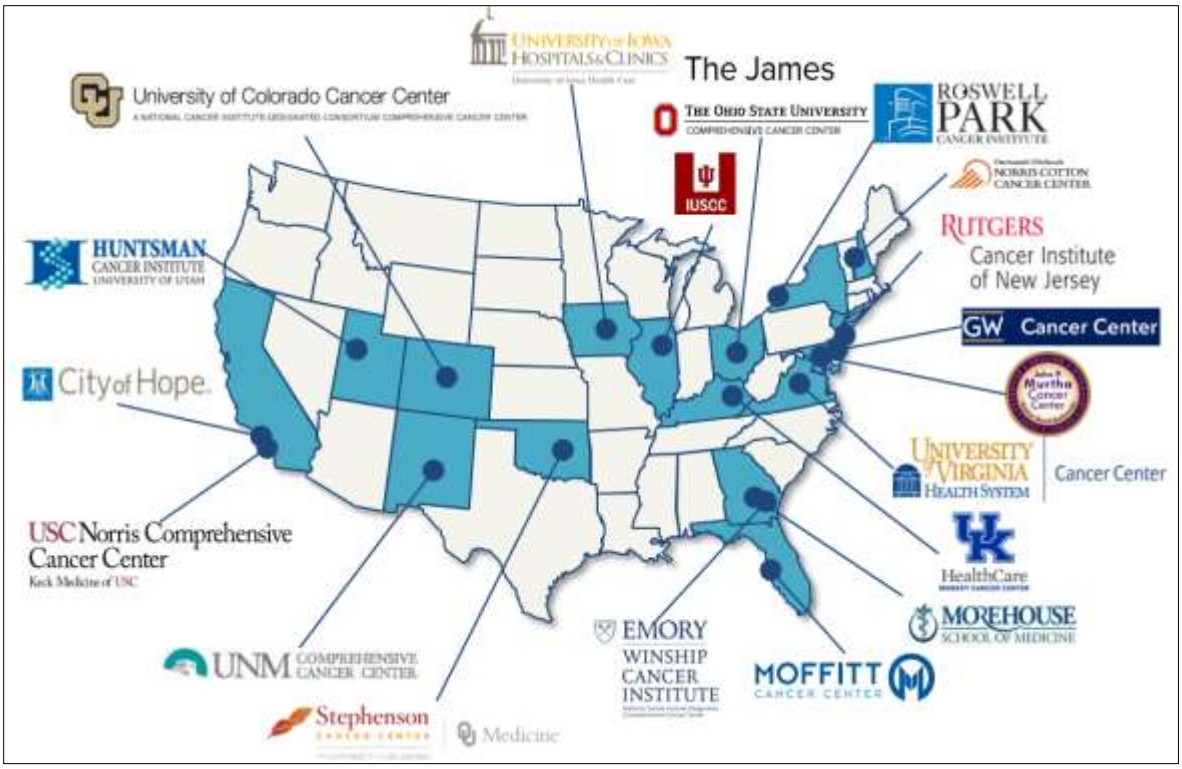

Figure 2. ORIEN Network Sites

Bio-Bank

USU, through DHA, funds the MCC's Bio-Bank program. The Bio-Bank operates through IRB-approved protocols by acquiring prospectively collected bio-specimens and associated clinical data from consented ADSMs and others treated for cancer at the eight participating APOLLO Network facilities (WRNMMC, SAMMC, MAMC, TAMC, WAMC, Keesler AFB, NMRTC-SD, and NMRTC-P). MCC's Bio-Bank program collects freshly obtained tissue (lesional as well as a non-lesional control), liquid specimens (e.g., blood, urine), and "dry" material (e.g., demographics, pathology information).

Seven types of molecular analyses (APOLLO protocol), including whole genome sequencing, are completed on the specimen. MCC identifies molecular targets for treatment on these patients, resulting in true "precision oncology" with improved outcomes and fewer side effects due to unnecessary treatments. This results, ultimately, in faster and higher return to duty rates.

Send-out Testing

While the AFMGC has extensive germline molecular testing capabilities for MTFs across the enterprise, molecular testing capabilities and resources for somatic cancer testing are limited to a handful of MTFs across the United States (e.g., WRNMMC in Bethesda, Maryland; SAMMC in San Antonio, Texas; and the JPC in Silver Spring, Maryland). For this reason, MTFs with limited or no internal molecular testing resources and capabilities refer thousands of molecular

tests to external labs and medical institutions in accordance with established standards of medical care. This is achieved through contracts granted by the DoD, primarily with LabCorp®.

As described in detail in the *Types of Molecular Diagnostics Testing* section above, there are many different molecular testing procedures used in the assessment of cancer that provide the information necessary for diagnosis, prognosis, minimal residual disease, and therapeutic guidance. It is important to note that the testing capabilities and repertoire of molecular testing modalities of LabCorp® are limited. These limitations can hinder the tumor's molecular profiling assessment, which ultimately could have a negative impact on the patient's outcome. If LabCorp,® through its subsidiaries, cannot provide the molecular testing needs for the spectrum of cancer cases observed in the MTFs, other external institutions and laboratories with the needed molecular testing and tumor profiling capabilities are identified and utilized (e.g., Memorial Sloan Kettering Cancer Center, Stanford University, Mayo Clinic, and University of Pittsburgh Medical Center).

PREVALENCE OF CANCER AMONG BENEFICIARIES

In FY 2020, the most recent year for which complete data is available, there were approximately 9,570,484 MHS eligible beneficiaries. Of those, 775,164 (8.1 percent) had a diagnosis indicating current cancer or a personal history of cancer (Figure 3). The prevalence (the rate of new and existing cases) of cancer among those eligible beneficiaries who were diagnosed with cancer was highest among retirees, who represented 50.1percent of the total beneficiaries diagnosed with cancer. Beneficiaries age 70 to 74 (18.3 percent) and age 75 to 79 (16.1 percent) had the highest prevalence of cancer by age (Appendix Table C1). The prevalence rates of types of cancer for the total beneficiary population can be found in Appendix Table C2.

A similar trend was found for the prevalence of cancer among MHS eligible beneficiaries in FY 2019. Among the 9,517,011 beneficiaries, 803,490 (8.4 percent) had a diagnosis indicating current cancer or a personal history of cancer (Figure 3). The prevalence (the rate of new and existing cases) of cancer among those eligible beneficiaries who were diagnosed with cancer was highest among retirees (49.9 percent) compared to other beneficiary types, and beneficiaries age 70 to 74 (17.6 percent) and age 75 to 79 (16.1 percent) had the highest prevalence of cancer among all other age groups. The prevalence of cancer was also high among beneficiaries who identified as "other" or whose race/ethnicity was unknown (62.6 percent), and those who identified as white, non-Hispanic (32.8 percent) (Appendix Table C1). The most predominant type of cancer in the beneficiary population for both FYs 2019 and 2020 was "other non-epithelial cancer of skin" (31.5 percent and 31.1 percent respectively), followed by breast cancer (10.2 percent and 10.3 percent, respectively), and prostate cancer (10.2 percent and 10.2 percent, respectively). The prevalence rates for types of cancer for the total beneficiary population are reported in Appendix Table C2.

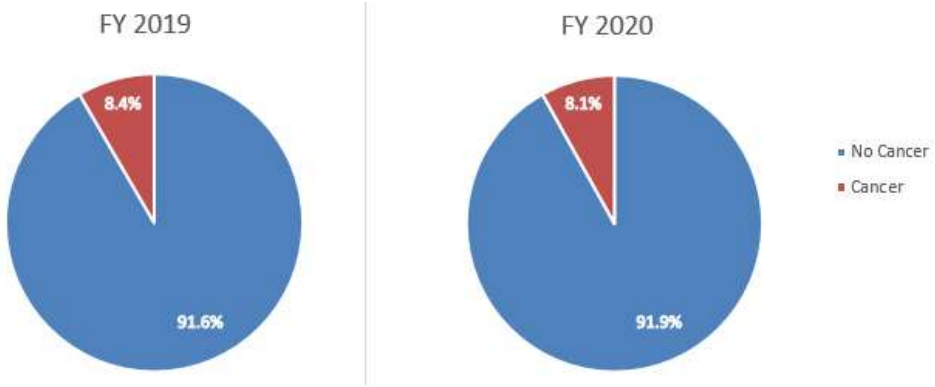

Figure 3. Prevalence of Cancer among Beneficiaries, FY 2019 and FY 2020

Table 1. Prevalence of Cancer Type among Beneficiaries Diagnosed with Cancer				
	FY 2019		FY 2020	
Cancer Type	**N**	**%**	**N**	**%**
Other non-epithelial cancer of skin	368,123	31.5%	350,546	31.1%
Cancer of breast	119,194	10.2%	115,645	10.3%
Cancer of prostate	118,958	10.2%	115,194	10.2%
Melanomas of skin	65,617	5.6%	63,853	5.7%
Maintenance chemotherapy; radiotherapy	52,049	4.5%	50,867	4.5%
Secondary malignancies	50,935	4.4%	50,745	4.5%
*Cancer of colon**	36,257	3.1%	33,621	3.0%
*Cancer of bronchus; lung**	35,186	3.0%	34,209	3.0%
Cancer of bladder	29,566	2.5%	28,615	2.5%
Cancer; other and unspecified primary	29,388	2.5%	27,219	2.4%
Neoplasms of unspecified nature or uncertain behavior	27,330	2.3%	26,979	2.4%
Non-Hodgkin`s lymphoma	27,307	2.3%	26,804	2.4%
*Cancer of kidney and renal pelvis**	20,522	1.8%	20,204	1.8%
*Leukemias**	20,511	1.8%	20,300	1.8%
Cancer of thyroid	20,306	1.7%	19,965	1.8%
Malignant neoplasm without specification of site	17,783	1.5%	17,575	1.6%
Cancer of head and neck	17,197	1.5%	16,595	1.5%
Cancer of uterus	13,833	1.2%	13,119	1.2%
*Cancer of cervix**	10,901	0.9%	9,788	0.9%
*Cancer of rectum and anus**	10,265	0.9%	9,884	0.9%
Cancer of other GI organs; peritoneum	9,700	0.8%	9,740	0.9%
Multiple myeloma	8,361	0.7%	8,406	0.7%
Cancer of ovary	8,211	0.7%	7,729	0.7%
Cancer of bone and connective tissue	7,411	0.6%	6,974	0.6%
Cancer of brain and nervous system	7,297	0.6%	6,951	0.6%
Cancer of liver and intrahepatic bile duct	5,930	0.5%	5,856	0.5%
Cancer of pancreas	5,288	0.5%	5,231	0.5%
Cancer of stomach	4,851	0.4%	4,768	0.4%
Cancer of other female genital organs	4,185	0.4%	3,921	0.3%
Cancer of esophagus	3,953	0.3%	3,842	0.3%
Hodgkin`s disease	3,885	0.3%	3,713	0.3%
Cancer of testis	3,127	0.3%	3,116	0.3%
Cancer of other urinary organs	3,046	0.3%	3,020	0.3%
Cancer; other respiratory and intrathoracic	1,727	0.1%	1,565	0.1%
Cancer of other male genital organs	928	0.1%	976	0.1%
Total**	**1,169,128**	100.0%	**1,127,535**	100.0%

***Cancer type in italics represents a change in rank order from FY 2019.
**One beneficiary can experience more than one cancer type.

PREVALENCE OF MOLECULAR TESTING AMONG BENEFICIARIES WITH CANCER

In FY 2020, of the 775,164 beneficiaries with cancer, 45,016 (5.8 percent) received molecular diagnostic testing that may be cancer applicable (Figure 4). In that same year, 69.5 percent of the cancer patients who were provided molecular testing were female. Looking at the beneficiary type classification, molecular testing was performed highest on dependents (64.1 percent), and the highest percentage of testing was done in beneficiaries between the ages of 70 to 74 (10.7 percent) (Appendix Table D1). Similarly, of the 803,490 beneficiaries with cancer in FY 2019, 48,551 (6 percent) received molecular diagnostic testing that may be cancer applicable (Figure 4). In FY 2019, similar molecular diagnostic testing trends were seen as in FY 2020. A larger percentage of female beneficiaries had tests performed (71.4 percent), dependents were the highest beneficiary type that received tests (65.7 percent), and those beneficiaries between the ages of 70 to 74 (9.8 percent) received more tests (Appendix Table D1).

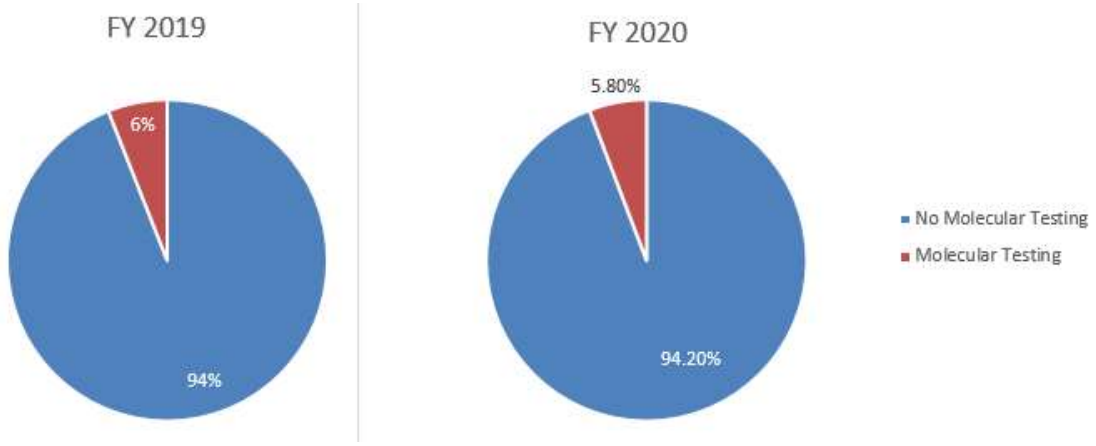

Figure 4. Prevalence of Molecular Diagnostic Testing Among Beneficiaries with Cancer, FY 2019 and FY 2020

FREQUENCY OF USE

In FY 2020, a total of 517,505 cancer-related molecular diagnostic tests were performed among beneficiaries compared to 585,170 cancer-related molecular diagnostic tests performed in FY 2019. Of those tests, 42 percent (218,616) were performed through Direct Care and 58 percent (298,889) were performed through Private Sector Care. There was a decrease in the number of tests from FY 2019 to 2020 overall, but more significantly in the tests performed through Direct Care (294,287) in FY 2019 and (218,616) in FY 2020. The number of tests performed in Private Sector Care were more consistent between the two years. Of the cancer-related tests in FY 2020, 24 percent of those performed in Direct Care were for beneficiaries with cancer associated diagnosis codes** and 56 percent of those performed in Private Sector Care were for beneficiaries with cancer associated diagnosis codes**. Those trends were similar in FY 2019 as well. Considering the cancer-related molecular tests that were part of a LDT Demonstration Project, 67 percent of those were for beneficiaries with cancer-associated diagnosis codes** in FY 2020 and 66 percent of those in FY 2019 (Table 2).

Table 2. Frequency of Use of Cancer Related Molecular Diagnostic Tests among the Beneficiary Population

	FY 2019		FY 2020	
	Direct Care	**Purchased Care**	**Direct Care**	**Purchased Care**
Cancer-related molecular tests	294,287	290,883*	218,616	298,889*
Cancer-related molecular tests performed for beneficiaries with cancer-associated diagnosis codes	68,725 (23% of total Direct Care cancer-related molecular tests)	160,559***** (55% of total Private Sector Care cancer-related molecular tests)	53,199 (24% of total Direct Care cancer-related molecular tests)	166,802***** (56% of total Private Sector Care cancer-related molecular tests)
Cancer-related molecular tests that were part of the LDT Demonstration	N/A	35,269*****	N/A	33,233*****
Cancer-related molecular tests that were part of the LDT Demonstration, performed for beneficiaries with cancer-associated diagnosis codes	N/A	23,248***** (66% of cancer related tests that were part of the LDT Demo)	N/A	22,385***** (67% of cancer related tests that were part of the LDT Demo)

*Counting private sector care cancer-related molecular tests requires making an estimate. See Appendix A.
**"Beneficiaries with cancer-associated diagnosis codes" are those with a diagnosis in the year indicating current cancer, a personal history of cancer, possible cancer, or another condition associated with cancer that makes the beneficiary a candidate for increased cancer-related molecular testing.

DATA SHARING PRACTICES

The Privacy Act of 1974 and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security rules require that certain privacy and security protections be met before sharing personally identifiable information (PII), including protected health information (PHI). These also require that specific privacy language be included in data sharing agreements (DSAs), depending on the data shared and the purpose for which it is shared. In addition, the Office of Management and Budget and National Institute of Standards and Technology (NIST) guidance outlines best privacy practices and provides specific security and privacy controls that must be met in sharing data through contracts.

The DHA Privacy Office receives various types of research and non-research requests for DHA data. Under its Data Sharing Program, the DHA Privacy Office reviews each request for compliance with applicable federal law and implementing DoD policies. Uses and disclosures of PHI are outlined in section 4 of DoD Manual 6025.18, "Implementation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in DOD Health Care Programs." In order to comply with this guidance, DHA uses DSAs/Data Use Agreements (DUAs). DHA uses the DSA as an administrative control measure, to:

- Confirm that DHA data will be used only as permitted or required;
- Exercise administrative, technical, and physical safeguards to protect the privacy and security of PHI, as required by HIPAA;
- Determine the HIPAA-defined category of data intended for use (i.e., PHI, a limited data set, or de-identified PHI); and
- Maintain records to confirm compliance in case of an investigation.

HIPAA also permits a covered entity to use or disclose a limited data set (LDS) for research, public health, or health care operations purposes if the covered entity enters into a DUA with the data recipient.

Data Sharing Agreement Applications

The DHA Privacy Office provides a DSA Application (DSAA) or Prerequisite Checklist (PRC) for the applicants and Government Sponsors (requestors) to complete when requesting DHA data. The DSAA requires the requestors to provide the purpose for the request, as well as specify the data elements required. The PRC requires requestors to provide compliance information to determine if a DSAA is needed for the request. The DHA Privacy Office uses the information provided in the DSAA or PRC to conduct all necessary compliance reviews and ensure that the requested data will be safeguarded in compliance with applicable Federal laws and DoD policies.

Data Evaluation Workgroup (DEW)

The DEW includes members of the DHA Privacy Office Data Sharing Compliance team, the DHA Privacy Board staff, and data experts. The DEW meets biweekly to review and discuss the progress of research DSAAs. The DEW mission is to determine the type of data requested

for research purposes based on the information provided in the DSAA.

DHA HIPAA Privacy Board

As required by HIPAA, the DHA Privacy Office established a DHA Privacy Board to provide HIPAA Privacy Rule reviews and documentation for researchers that seek to use and/or disclose PHI managed by DHA. The DHA Privacy Board has been critical for DHA's compliance with the HIPAA Privacy Rule (45 CFR Parts 160 and 164) and DoD Manual 6025.18.

The DHA Privacy Board reviews IRB-approved documentation of full or partial waivers of authorization and altered authorizations. The board also provides templates for researchers to complete in requesting data for several different types of research projects. These templates help researchers to obtain approved compliance documentation from the board for the following:

- HIPAA Authorizations;
- Altered Authorization;
- Full or Partial Waivers of Authorization;
- Required Representations for Review on Decedents' Information only; and
- Required Representations for Review Preparatory to Research.

In addition to board reviews and maintaining HIPAA compliance documentation of DHA PHI requests, the DHA Privacy Board meets quarterly to discuss the board metrics and current related topics. DHA Privacy Board staff also assists researchers and the research community by responding to questions related to HIPAA compliance requirements.

HIPAA Safeguard Reviews (HSR) of Non-Federal Systems

Occasionally, data requestors will seek to use, store, transmit, process, or otherwise maintain DHA PHI or LDS data obtained through the DSA process on an information system that has not been granted a Federal Authority to Operate (ATO) or Interim ATO. In those instances, the requestors are required to submit an HSR packet. The HSR is a template used to address the requirements of DoD Instruction 8580.02, "Security of Individually Identifiable Health Information in DoD Health Care Programs," NIST Special Publication 800-171, revision 2, ("NIST 800-171"), and DoD Instruction 8582.01, "Security of Non-DoD Information Systems Processing Unclassified Nonpublic DoD Information." To be compliant with NIST 800-171, the HSR packet includes a completed System Security Plan and Plan of Action and Milestones based on the NIST 800-171 controls.

DSA

After all compliance reviews are completed, the DHA Privacy Office Data Sharing Compliance team completes the execution of the DSA. Depending on the type of data requested and the required assurances for compliance standards, the requestors will sign one of

four template DSAs:

- De-identified data DSA;
- PII that is not PHI DSA;
- LDS; or
- PHI DSA.

The DSAs incorporate the DSAA into the agreement as further evidence of the data elements requested and the compliance requirements that the requestors must meet in receiving DHA data. A DSA is valid for no longer than one year and then it must be renewed or closed.

APOLLO Data Sharing

The APOLLO Network utilizes multiple sites for sample collection and data analyses. The APOLLO network of MCC consists of eight DHA medical facilities, seven VA hospitals, and one civilian medical center. Underpinning this vast DoD-enabled cancer research network are the regulatory-required IRB protocols, memoranda of agreement between agencies, and DSAs. All clinical and pathology data associated with APOLLO study subjects' samples collected under existing MCC bio-banking protocols and stored at MCC's biorepository at the Chan Soon-Shiong Institute of Molecular Medicine at Windber (CSSIMMW) in Windber, Pennsylvania, are given study identifier (ID) codes for internal primary APOLLO use, and a Global Unique Identifier (GUID) when distributed externally. The APOLLO Informatics Infrastructure team located at CSSIMMW generates the APOLLO study ID and GUID codes to label the study data and specimens. Clinical and sample data do not include PHI data elements as defined by HIPAA. The coded clinical and pathology data are accessible by the APOLLO study team for genomic and proteomic platform-specific analyses, integrative data analysis workflows, and association of proteogenomic profiles with longitudinally collected clinical outcomes in multiple cohorts.

Coded clinical, pathology, and sample data are collected under existing MCC and Clinical Breast Cancer Project (CBCP) data and sample collection protocols and extracted from the databases associated with these protocols. APOLLO study data elements that are not obtained from the existing MCC bio-banking databases are sought from the DoD tumor registry system (which utilizes OncoLog®, a commercially available tumor registry software solution) and/or from study participants' medical records by an APOLLO study team member. Broad data categories include such information as diagnosis, pathology, treatment, outcome, demographics, family history, and lifestyle factors. The frequency of data collection from the above data systems, including electronic medical records, is performed, as needed, based on individual study participant clinical case scenarios. Study participants' treatment and outcome data are collected on an ongoing basis. DoD tumor registry data usage for research purposes has the appropriate DHA data-sharing approval.

For APOLLO study cases, digital slides are created at CSSIMMW from samples collected or stored under the MCC Biobank and CBCP protocols. CSSIMMW study staff upload these

digital slides into the APOLLO Informatics Infrastructure system and transmit them to the Cancer Imaging Archive of the NCI.

Coded pathology data elements associated with each digital slide are entered into the APOLLO Informatics Infrastructure system. These pathology data elements are provided to JPC through the APOLLO Data Tracking System. JPC enters the results of its review and slide annotations in the system, where they are reviewed by the APOLLO study team prior to shipment to the participating laboratories. Data elements accompany samples to the participating laboratories. These data are sent electronically in spreadsheet form via secure file transmission.

Coded APOLLO clinical and pathology data are collected and organized in the MCC APOLLO Informatics Infrastructure system based on the elements listed in the APOLLO Clinical Data Dictionary. Clinical and sample data elements for external distribution and future secondary use are listed in the protocol. The informatics infrastructure team at CSSIMMW aggregates and prepares APOLLO data for transmission to the Jamboree site hosted by the NCI Center for Biomedical Informatics and Information Technology with the required Data-Sharing Agreement in place. The data are transmitted via secure file transfer protocol (SFTP) to the Jamboree site for research use by the project team. The APOLLO Informatics Infrastructure system also integrates such data with the processed genomic and proteomic molecular data generated from TAGC and MCC Clinical Proteomics Platform.

The APOLLO Jamboree site is a flat file storage site maintained by the NCI to enable encrypted data sharing by APOLLO data analysis teams. Access to the Jamboree site requires approval by the APOLLO leadership. All data transfer to and from the Jamboree site is via SFTP; during each SFTP session, the host and the client are validated through a host key and a client key cross-saved during the initial setup session. Thus, the APOLLO Jamboree site is a far more secure data storage and sharing site than any file transfer site. The NCI has used a similar system to support all The Cancer Genome Atlas studies.

Coded APOLLO clinicopathologic data and sample-level proteogenomic data pass quality assurance and are tracked in the APOLLO Informatics Infrastructure system. The CSSIMMW team managing the system generates data files and submits to the Jamboree site for sharing. Members of APOLLO data analysis teams then access the Jamboree site to obtain the data for analyses to generate publications and intellectual properties. Limited platform-specific raw data that needs to be shared are loaded to the Jamboree site by molecular centers directly due to the size of the files, and these activities are coordinated by the CSSIMMW team via the APOLLO Informatics Infrastructure system after generating corresponding manifests.

After the APOLLO study team has analyzed the data in the Jamboree site and has developed related publications, the data are transmitted to the GDC, Proteomic Data Commons (PDC), and Cancer Research Data Commons (CRDC) hosted and maintained by NCI. Data-Sharing Agreements and System Security Verifications are provided for all systems involved.

The raw genomic data (also referred to as Level 1 data) generated by TAGC are stored initially at TAGC and then transferred to GDC and CRDC, after required Institutional Certification and database of Genotypes and Phenotypes (dbGaP) registration, using the established GDC transfer

tool, coordinated by the APOLLO Informatics Infrastructure system, which generates submission manifests.

The raw proteomic data (also referred to as Level 1 data) generated by the MCC CPP consortium laboratories are initially stored at MCC CPP and then transferred to the PDC and CRDC using the same Institutional Certification and dbGaP registration process described.

Integrated, coded clinical, pathology, and molecular data for each study subject's case are transferred to the NIH GDC, PDC, and CRDC. This process follows the established guidelines and procedures outlined in the NIH Genomic Data Sharing Policy.

After all required data sharing agreements and system security verifications are approved, proteogenomic profiling data generated under APOLLO 5 are submitted to the NCI GDC, PDC, and CRDC for use in future approved research studies. The process for submitting data to GDC, PDC, and CRDC is described above. The APOLLO 5 protocol workflow is depicted below at Figure 5.

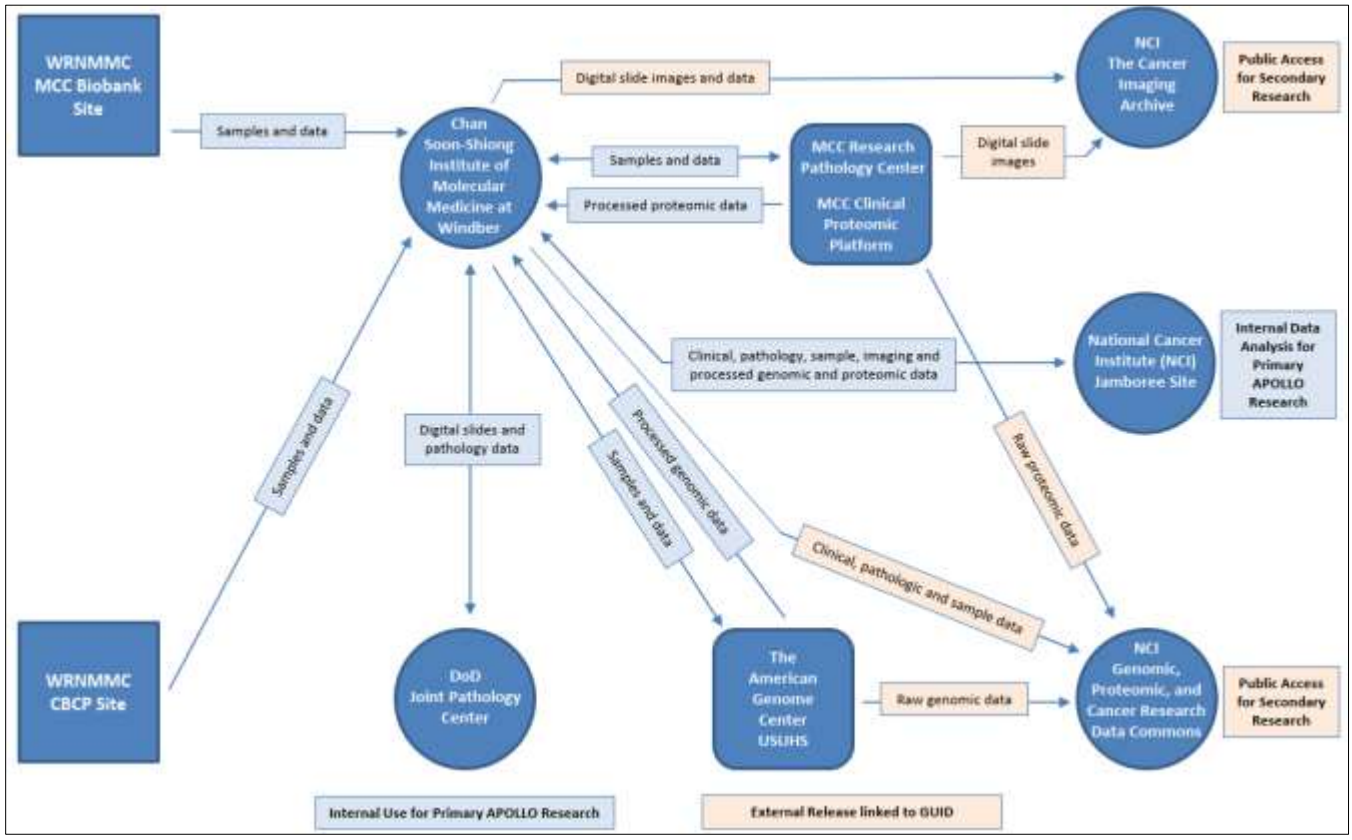

Figure 5. APOLLO 5 Protocol Workflow

ORIEN

All ORIEN members, whether DoD-affiliated or not, have access to data via the ORIEN portal. Similar to APOLLO, ORIEN data access is based on NIH standard federal requirements. One of ORIEN's key goals is to use data science to accelerate cancer-related discovery through data

sharing. DoD limits involvement with ORIEN to minimize ADSM enrollment, and all data on other patients is de-identified and involves honest broker arrangements.

MHS Information Platform

The MIP is a three-layer system (Figure 6) that integrates and shares all medical data that exists on systems used throughout the MHS, including molecular diagnostic testing. Input from several source systems is aggregated, rationalized, and normalized. This provides a range of capabilities for users, including near real-time reporting, deep-dive analytics, and statistical analysis, while also providing clinical information data warehousing modules. The MIP enables DHA to monitor, extract, and make available both clinical and business data from MTFs.

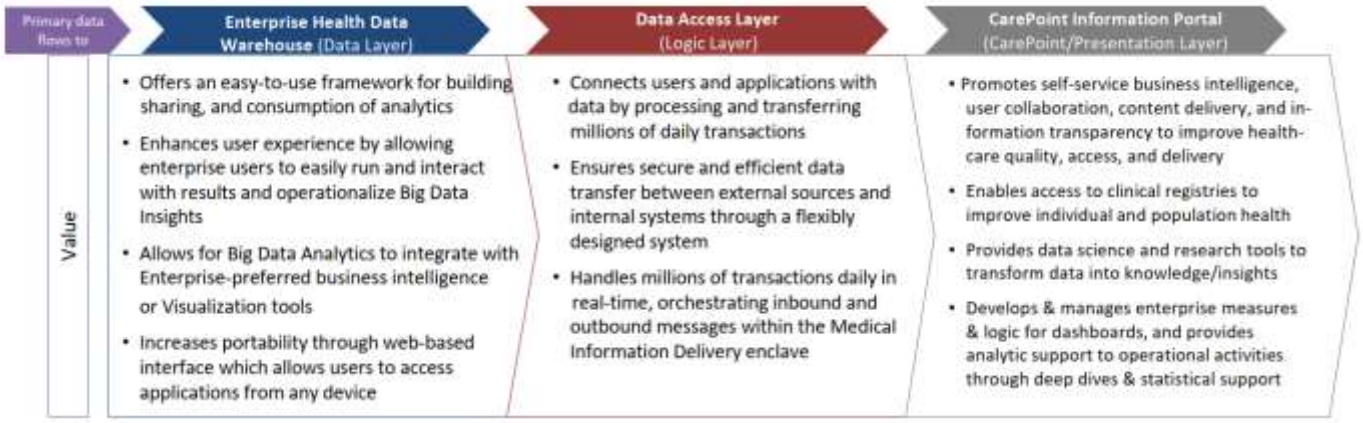

Figure 6. MIP's Three Layers (Maneval, 2018)

PUBLIC-PRIVATE PARTNERSHIPS FOR NEXT-GENERATION PRECISION-ONCOLOGY

It is feasible for DoD to form public-private partnerships to support integrative analysis with the intent of unveiling novel insights into the diagnosis, treatment and monitoring of cancers.

The DoD already has multiple efforts underway to generate high quality data that could be used to support public-private partnerships to support discoveries about cancer. The JPC is digitizing its microscopic slides and integrating the image data with other clinical data, including genomic data, in support of the development of machine learning algorithms that augment the ability to diagnose, monitor and determine the best treatments for ADSMs, beneficiaries, and veterans with cancer. The JPC is also generating comprehensive molecular data about some of the most prevalent cancers in ADSMs that will be used for research that involves machine learning and mathematics. The MCC is another example of a DoD organization that is generating high quality research data on cancers that could be used to support public-private partnerships. As previously noted, the MCC has established a network of biobanks to collect clinical samples that are comprehensively analyzed using a variety of next-generation molecular techniques to generate high quality data that are being used for integrative analysis. Data from the MCC's research has already resulted in novel discoveries about the most prevalent cancers in SMs. The formation of public-private partnerships could potentially leverage these data to make additional discoveries and capabilities in precision oncology that could further support SMs and veterans.

In addition, DHA is establishing a new Genomics Program and is hiring a Genomics Program Lead. Once established, DHA will develop priorities and initiatives, identify the future state, and complete a gap analysis. This will include further determining the feasibility of public-private partnerships, artificial intelligence, machine learning, deep learning, and quantum computing.

The public-private partnerships intended to use next-generation, precision-oncology platforms that integrate bioinformatics, machine learning, and mathematics must include these considerations to securely unveil unprecedented insights into cancer and move beyond a single-target-based approach.

PROVIDING INFORMATION TO CLINICIANS TREATING TRICARE AND MHS PATIENTS

DoD provides information to clinicians treating TRICARE and MHS patients on the value of using molecular diagnostics for cancer patients, as well as methods of reimbursements. Details on how information is provided are below.

TRICARE Patients

TRICARE Managed Care Support Contractors (MCSCs) encourage providers to use validated health information and guidance that constitutes reliable evidence. The MCSCs recognize the National Comprehensive Cancer Network (NCCN) Cancer Guidelines as a key example of such evidence-based validated practice guidance. Rather than promoting specific diagnostic or therapeutic practices, MCSCs expect providers to use reliable scientific evidence, experience, judgement, and shared decision-making in formulating their approaches to evaluation and treatment of TRICARE beneficiaries. Molecular diagnostic testing in the TRICARE program needs to factor in exclusion of non-FDA approved testing unless testing is covered under a Demonstration such as the LDT Demonstration. Many, but not all, molecular diagnostic tests are LDTs legally marketed under CLIA authority. Coverage determinations for molecular tests in panels can be particularly complex, making brief high-level communications broadly encouraging their use challenging. MCSCs defer to the NCCN and other clinically validated guidelines in shaping provider practice in evaluation and treatment of cancer, and support the utilization of molecular and diagnostic testing to the maximum extent that can be covered under current TRICARE policy.

Per the FDA, "A LDT is a type of in vitro diagnostic test (classified as a medical device) that is designed, manufactured, and used within a single laboratory. LDTs can be used to measure or detect a wide variety of analytes (substances such as proteins, chemical compounds like glucose or cholesterol, or DNA), in a sample taken from a human body. Some LDTs are relatively simple tests that measure single analytes, such as a test that measures the level of sodium. Other LDTs are complex and may measure or detect one or more analytes. For example, some tests can detect many DNA variations from a single blood sample, which can be used to help diagnose a genetic disease. While the uses of an LDT are often the same as the uses of FDA-cleared or approved in vitro diagnostic tests, some labs may choose to offer their own test. For example, a hospital lab may run its own vitamin D assay, even though there is an FDA-cleared test for vitamin D currently on the market."

According to 32 CFR § 199.4(g)(15)(i)(A), DHA may not cost-share medical devices, including LDTs, if the tests are non-FDA approved, that is, they have not received FDA marketing 510(k) clearance or premarket approval. LDTs with FDA approval are available for cost-sharing under the TRICARE Basic Program as long as they otherwise meet TRICARE criteria for coverage.

To provide TRICARE beneficiaries with access to LDTs that FDA has not approved, DHA initiated a demonstration project to review these tests to determine if they meet TRICARE requirements for safety and effectiveness according to the hierarchy of reliable evidence or TRICARE's rare disease policy (See reliable evidence and rare disease criteria below). When

the Demonstration was initiated the FDA claimed jurisdiction to review and approve LDTs as "devices." Under the previous administration, the FDA relinquished this authority, only to recently (November 2021) retake the authority to review and approve LDTs. Absent the LDT demonstration, DHA cannot provide access to these tests if they are not FDA approved under the regulation. Under the LDT Demonstration Program, over 100 LDTs are covered; a number of them are specifically for certain cancers.

Reliable evidence includes:

- Well-controlled studies of clinically meaningful endpoints, published in refereed medical literature;
- Published formal technology assessments;
- Published reports of national professional medical associations;
- Published national medical policy organization positions; and
- Published reports of national expert opinion organizations.

For rare diseases, the following sources of clinical literature may be used:

- Trials published in refereed medical literature;
- Formal technology assessments;
- National medical policy organization positions;
- National professional associations; and
- National expert opinion organizations.

Coverage of the non-FDA-approved LDTs under the Demonstration is addressed in the TRICARE Operations Manual, Chapter 18, Section 3, and FDA approved LDTs are addressed in the TRICARE Policy Manual, Chapter 6, Section 3.1. If there is a change/update to coverage of LDTs, it is placed in one of the two Sections of the manuals, and the contractors are notified during the manual change process when they are able to ask questions and provide comments.

MHS Patients

In addition to performing molecular and cytogenetic testing, the MHS provides outpatient and telegenetic consultations to ADSMs and their dependents primarily for consideration of germline testing for possible hereditary cancer syndromes. As the need for genetic testing far exceeds the capability of genetic providers within the MHS, primary and other specialty care providers must stay informed about and assist in coordinating genetic testing. The AFMGC employs three geneticists and one genetic counselor who, aside from clinical duties, are available to help educate providers about updates in genetic testing menus, when to consider testing, and results interpretation. Information via Frequently Asked Questions has been disseminated to the DHA Clinical Communities for wider distribution.

CONCLUSION

Approximately 8 percent of the 9.5 million beneficiaries served through the MHS have a cancer diagnosis. Of those beneficiaries diagnosed with cancer, approximately 6 percent receive molecular diagnostic testing within the given year.

Molecular diagnostic testing is available within the Direct Care system through internal, research-based, and send-out testing, although it is not currently supported by standardized coordination and overarching policy. Within Private Sector Care, genetic tests with FDA medical device 510(k) clearance or premarket approval are a TRICARE benefit if:

- They are medically necessary for the diagnosis and treatment of cancer; or
- They have demonstrated clinical utility.

Otherwise, genetic tests that meet the definition of a LDT but lack FDA approval are considered for coverage under the LDT Demonstration.

DoD continues to share data and collaborate with entities such as the VA, NIH, and the external research community. Data-sharing is guided by detailed policies and procedures for engaging in such relationships, as outlined in this report. It is feasible for DoD to form public-private partnership(s) to explore next-generation, precision-oncology platforms. The goal of these platforms would be to integrate bioinformatics, machine learning, and mathematics to reveal unprecedented insights into cancer. DHA is establishing a new Genomics Program that once established, will develop priorities, future state, gap analysis, and initiatives, including the feasibility of public-private partnerships, artificial intelligence, machine learning, deep learning, and quantum computing.

Information on molecular diagnostics is provided to clinicians treating TRICARE and MHS patients through various channels, including the LDT Demonstration and consultation with the AFMGC. The molecular diagnostic clinical and research field is rapidly changing, and the MHS has a duty to its ADSMs to provide excellent care throughout the entire spectrum of cancer, including molecular diagnostics.

APPENDIX A: METHODOLOGY OVERVIEW

Data Sources, Analysis, and Limitations

For the population cancer analysis and cancer-related molecular testing statistics generated specifically for this report, the following data sources were utilized. The MHS total eligible beneficiary population in the first month of FY 2019 (October 2018) and FY 2020 (October 2019) was identified in the MDR Defense Enrollment Eligibility Reporting System VM6BEN data source. The MDR Direct Care (Comprehensive Ambulatory/Professional Encounter Record, Standard Inpatient Data Record, MHS GENESIS Encounter, and MHS GENESIS Admission) and Private Sector Care (TED Non-Institutional and TED Institutional) health care data sources were then searched to identify which population members from the first month received health care during the associated FY where a cancer-related diagnosis code was recorded as a primary or secondary diagnosis. These diagnosis searches were conducted using several different International Classification of Diseases (ICD-10) diagnosis lists and concepts determined by subject matter experts, such as codes used to identify cancer prevalence and codes used to identify beneficiaries with cancer-related diagnoses that make them likely candidates for increased cancer-related molecular testing. Clinical Classifications Software (CCS) categories were then used to group diagnosis codes into broader types/classifications of cancer. A beneficiary can appear under multiple classifications if their records contained diagnosis codes for multiple CCS categories. The prevalence statistics are estimates produced by identifying the MHS beneficiary population in the first month of the FY and then analyzing the MHS health care records for these beneficiaries over the following 1-year period to identify and categorize beneficiaries receiving health care in the MHS where recorded diagnosis codes indicate that the patient has current cancer or a personal history of cancer. These "estimates of prevalence" are more precisely described as beneficiaries receiving health care in the MHS where diagnosis codes recorded within the FY indicate current cancer or a personal history of cancer. If any beneficiaries with current or past cancer were not represented in MHS health care records as described, then the methodology would not include them in the prevalence statistics.

Molecular tests for the FYs were identified in the MDR Direct Care (CADRE Laboratory and MHS GENESIS Laboratory) and Private Sector Care (TED Non-Institutional) sources. The Direct Care records were identified by matching either a subject-matter-expert-determined procedure code or lab test name. The procedure codes represented cancer-related molecular tests, with the exception of some "generic" codes, which may identify cancer-related molecular tests or molecular tests not related to cancer. The lab test names represented cancer-related molecular tests. The Private Sector Care records were only identified by a match to one of the procedure codes, as a lab test name variable does not exist in the Private Sector Care source. For the "generic" procedure code Direct Care tests, the lab test names were analyzed for matches to the list, to determine which of these tests were confirmed to be cancer-related. This Direct Care "generic" analysis was then applied to Private Sector Care to estimate the number of cancer-related "generic" procedure tests. This application of "generic" findings from Direct Care to Private Sector Care is based on the assumption that the true underlying percentages of the "generic" codes that are in actuality cancer-related molecular tests are the same in Direct Care and Private Sector Care. In reality, these true ratios may vary. Non-standardized lab test naming conventions introduce some uncertainty to the comprehensive capture, identification, and

categorization of all relevant records, especially records without procedure codes. Tests sent out to private external labs, such as LabCorp®, are analyzed through Direct Care records generated by the MTFs sending out the tests. MTF record quality and consistency may vary between MTFs and send-out tests, depending on which private external lab the test is used. Different data capture and recording systems used by the MTFs may also produce variations.

The "PREVALENCE OF MOLECULAR TESTING AMONG BENEFICIARIES WITH CANCER" section and Figure 4 utilize all "generic" molecular testing procedure code records, which may identify cancer-related molecular tests. Beneficiaries with a cancer diagnosis that received molecular diagnostic testing that may be cancer related are identified, even though some of these molecular tests may not be able to be confirmed as cancer-specific tests through procedure code and lab test name analysis.

Effects from coronavirus disease 2019 on health care delivery likely materially impacted the identification, diagnosis, and recording of current and personal history of cancer, as well as cancer-related molecular testing, during FY 2020, relative to other fiscal years. The ethnicity demographic information is unreliable and may often be unknown, especially for non-sponsors.

Based on the limitations discussed above, it is possible that the molecular testing frequencies may not be exact or entirely comprehensive, and cancer prevalence estimates may deviate from true underlying prevalence in the ways described above.

APPENDIX B: TYPES OF MOLECULAR DIAGNOSTIC TESTS

DNA Arrays	
Name	**Description**
Single Nucleotide Polymorphism (SNP) Array	Data from the Human Genome Project revealed that the human nucleotide sequence differs every 1,000 to 1,500 bases from one individual to another. The majority of these sequence differences are variations of single nucleotides, or SNPs. The traditional definition of polymorphism requires that the genetic variation be present at a frequency of at least one percent of the population. The International SNP Map Working Group observed that two haploid genomes differ at one nucleotide per 1,331 base pair (bp). This rate, along with the theory of neutral changes expected in the human population, predicts 11 million sites in a genome of three billion bp that vary in at least one percent of the world's population. In other words, each individual has 11 million SNPs. So far, approximately 5 million SNPs have been identified in the human genome. Applications of SNP arrays include genome-wide association studies, determination of heterozygosity, and molecular karyotyping of clinical samples. SNP arrays are commonly used for leukemias, myelodysplastic diseases, multiple myeloma, and solid tumors.
Expression Arrays	These are powerful tools for comparing complex RNA populations. These techniques are used as a means of defining clinical subtypes of cancer that could be correlated with clinical outcomes and therapy response. The majority of these commercially available expression arrays are for prognostic testing in breast cancer.
aCGH	Array Comparative Genomic Hybridization or Genomic Microarrays. This is a technique developed for genome-wide characterization of copy number changes. aCGH has a higher resolution than conventional karyotyping. Occasionally referred to as molecular karyotyping, the International Standard Cytogenomic Array Consortium recommended aCGH as the first-tier clinical diagnostic test for individuals with multiple congenital anomalies and developmental delay. In addition, the ability to detect copy number variants (CNVs) have led to diagnostically significant subgroup classification of cancer (e.g., diffuse large B-cell lymphoma, etc.). As a result, targeted arrays are used in the clinical laboratory for both cancer and congenital conditions.
Epigenomic Studies	
Name	**Description**
MLH1 promoter hypermethylation	MLH1 is a DNA-repair gene. Methylated DNA can be distinguished from unmethylated DNA using different techniques that include restriction endonuclease digestion with methylation-sensitive enzymes, sequencing, and methylation-specific PCR. These techniques are useful in the detection of abnormal methylation in neoplastic processes to include colon cancer in the setting of Lynch Syndrome and in glioblastoma.
FISH	
Name	**Description**
Human Epidermal Growth Factor Receptor 2 (HER2) FISH	HER2 is an important predictive marker in breast cancer, which is a cell-surface membrane glycoprotein involved in cell proliferation control. HER2 gene amplification, leading to protein overexpression, is found in approximately 15-20 percent of invasive breast cancer. Early research showed that patients with HER2-amplified breast cancers had higher recurrence and death rates that those with HER2-normal cancers. Testing is performed to identify patients who are likely to benefit from anti-HER2-targeted treatment (e.g., trastuzumab, etc.) or those with breast cancers that overexpress HER2 protein and/or have HER2 gene amplification by In Situ Hybridization.
HER2 Chromogenic In Situ Hybridization (CISH)	Similar to HER2 FISH, this technique assesses HER2 gene amplification. Testing is performed to identify patients who are likely to benefit from anti-HER2-targeted treatment (e.g., trastuzumab, etc.). FISH probes are generally labelled with a variety of different fluorescent tags and can only be detected under a fluorescence microscope, whereas CISH probes are labelled with biotin or digoxigenin, and can be detected using a bright-field microscope. CISH has some advantages over FISH: 1) CISH is much cheaper and is easier to use because it uses bright-field microscopes instead of fluorescence microscopes; 2) CISH reagents are more stable than the FISH reagents; 3) FISH also requires a high-

	resolution digital camera to capture micrographs of the sample before the fluorescence fades; and 4) by using bright-field microscopy the tissue or cell sample as a whole can be visualized through CISH whereas cell morphology is difficult to assess using FISH. The concordance rate between FISH and CISH was 94.8 percent, showing CISH to be a comparable technique to FISH. However, sometimes CISH shows lower sensitivity for low level amplifications.
BCR-ABL FISH	This is a dual-colored FISH that employs two probes with different fluorescence wavelengths to identify a BCR-ABL structural rearrangement (fusion) in the diagnosis of chronic myelogenous leukemia and acute lymphoblastic leukemias.
PCR	
Name	**Description**
Microsatellite Instability (MSI)	Represents an indirect functional assay of mismatch repair (MMR) proteins. Instability is defined by a change in the length of a microsatellite in tumor DNA when compared to non-tumor ("normal") DNA from the same patient. Deficiency in MMR and MSI in a tumor may be associated with inherited cancer syndromes (e.g., Lynch Syndrome, etc.).
Reverse Transcription-PCR	This technique can be seen as an RNA-based PCR. RNA analysis is virtually as rapid and sensitive as PCR-based DNA investigation. One of the most widespread applications is for the detection of *BCR-ABL* translocation of chronic myelogenous leukemia.
Real-Time (quantitative) PCR	This technique is based on the generation of a fluorescent signal by the PCR process, which is detected during PCR cycling in real time, and reflects the amount of PCR product made. Multiple applications exist today in the clinical molecular laboratory (e.g., diagnostic, monitoring).
Multiplex PCR	This is a technique used for amplification of several discrete genetic loci with multiple PCR primer pairs in a single reaction. This technique simultaneously answers several related questions about a specimen without the need for multiple individual PCR reactions. Examples of applications of multiplex PCR include the analysis of multiple *BRCA1* loci in breast cancer patients and bone marrow engraftment analysis.
Nested PCR	Two pairs of PCR primers with one set internal to the other (nested) are used to sequentially amplify a single locus. The first pair is used to amplify the locus as any PCR assay. A dilution of the first PCR reaction then is amplified with nested primers. This technique enhances sensitivity and specificity.
Pyrosequencing	Amplified targets are sequenced by adding and detecting incorporation of nucleotides one at a time. This is particularly useful when analytical sensitivity is of particular concern, such as in detection of somatic mutations in tumor specimens which yield both non-variant and variant DNA. Pyrosequencing is best suited for detection of variants within a targeted region. Kirsten Rat Sarcoma Viral Oncogene and B-Raf Proto-Oncogene (BRAF) mutation detection in multiple tumor types (e.g., lung cancer, colon cancer, thyroid cancer) are some pyrosequencing applications in the clinical molecular laboratory.
Digital Droplet PCR (ddPCR)	ddPCR is used to directly quantify and clonally amplify nucleic acids strands, including DNA, complementary DNA, or RNA. This method carries out a single reaction within a sample; however, the sample is separated into a large number of partitions, and the reaction is carried out in each partition individually. This leads to more reliable collection and sensitive measurement of nucleic acid amounts and is very useful for studying point mutations. Detection of single point mutations in hairy cell leukemia (e.g., BRAF) and gliomas (e.g., Isocitrate Dehydrogenase 1 [IDH1] and Isocitrate Dehydrogenase 2) are some applications for this PCR technique.
Sequencing	
Name	**Description**
Sanger Sequencing	The Sanger sequencing reaction uses a single DNA primer and DNA polymerase resulting in linear, rather than the exponential, PCR amplification. Sanger components include: 1) DNA template; 2) sequence-specific primers, complementary to the opposite strands and ends of the DNA region to be sequenced; 3) small proportions of dideoxynucleoside triphosphates, in addition to the conventional deoxyribonucleoside triphosphates used in DNA sequencing reaction; and 4) an electrophoresis technique capable of clearly distinguishing single nucleotide length differences in DNA strands. When a

	dideoxynucleoside triphosphate is incorporated into the elongating strand, no additional deoxyribonucleoside triphosphates can be incorporated and the reaction stops. The end result is a set of newly synthesized DNA chains that are complementary to the template DNA, but that vary in length. Detection of mutations in BRCA1 (breast cancer), acute myeloid leukemia, and IDH1 (gliomas) are some applications for Sanger sequencing.
NGS	This method is also known as massively parallel sequencing. It is designed to sequence large numbers of templates simultaneously, yielding not just one, but hundreds of thousands of sequences in a run that only takes a few hours to complete. The principle of NGS sequencing methodologies include sequencing by synthesis and sequencing by ligation. All platforms require the incorporation of adapters to target DNA and subsequent PCR-based generation of clonally amplified and clustered DNA. Advances in enrichment and capture technologies have enabled the development of cost-effective gene panels or exome sequencing for inherited disorders. These technologies can be used not only to sequence multiple whole genomes but also to investigate populations of small genomes, such as microbial diversity. Genetic material from different patients can be deferentially labeled using unique short sequence tags, multiplexed, and sequenced in the same sequencing run, which reduces sequencing costs. High throughput NGS platforms have made sequencing of an individual human genome in a reasonable timeframe and at a reasonable cost a reality. Multiple platforms and panels exist for DNA sequencing, RNA sequencing, cell-free tumor DNA detection, and cell-free messenger RNA detection. Ultimately, NGS aids in the diagnosis of germline mutations, in tumor profiling for the identification of specific therapeutic targets, and in the detection of mutations already known in patient's plasma for determination of relapse or progression.
Whole Exome Sequencing	This technique can be used for gene discovery and also for gene panel or pathways analysis. Because the human exome is roughly 1.5 percent of the human genome, bioinformatic analysis is not as daunting as genome analysis. Exomes from different patients can be labeled separately using unique short sequence tags, multiplexed, and sequenced in the same sequencing run, which reduces sequencing costs.
Whole Genome Sequencing	Often applied to the study of cancer as a discovery tool in the investigative setting. It is helpful for detection of CNVs and is especially well-suited to detect structural variants, which often involve noncoding DNA breakpoints.

APPENDIX C: CANCER PREVALENCE IN BENEFICIARY POPULATION

Table C1. Demographics of Beneficiaries with a Cancer Diagnosis				
	FY 2019		FY 2020	
	N	%	N	%
Total	**803,490**	**100%**	**775,164**	**100%**
Beneficiary Type				
Active Duty	11,517	1.4%	10,861	1.4%
Dependents	385,422	48.0%	370,197	47.8%
Guard/Reserve	5,246	0.7%	5,317	0.7%
Retirees	400,806	49.9%	388,316	50.1%
Other/Unknown	499	0.1%	473	0.1%
Sex				
Female	396,992	49.4%	381,769	49.3%
Male	406,495	50.5%	393,392	50.7%
Unknown	3	0.00%	3	0.00%
Age				
0 to 4	835	0.1%	810	0.1%
5 to 14	2,088	0.3%	2,057	0.3%
15 to 17	923	0.1%	897	0.1%
18 to 24	3,652	0.5%	3,386	0.4%
25 to 34	12,124	1.5%	11,148	1.4%
35 to 44	22,418	2.8%	21,881	2.8%
45 to 64	175,409	21.8%	166,326	21.5%
65 to 69	109,709	13.7%	101,910	13.1%
70 to 74	141,728	17.6%	141,640	18.3%
75 to 79	128,969	16.1%	125,181	16.1%
80 to 84	109,406	13.6%	105,235	13.6%
85+	96,229	12.0%	94,693	12.2%
Race/Ethnicity				
American Indian/ Alaskan Native	2,517	0.3%	2,541	0.3%
Asian/Pacific Islander	7,881	1.0%	8,093	1.0%
Black, non-Hispanic	29,322	3.6%	29,752	3.8%
Hispanic	5,315	0.7%	5,468	0.7%
White, non-Hispanic	255,650	31.8%	257,152	33.2%
Other/unknown	502,805	62.6%	472,158	60.9%

*Includes Active and Inactive Guard/Reserve
**Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees

Table C2. Prevalence Rates of Cancer Type in the Total Beneficiary Population				
	FY 2019 N = 9,517,011		FY 2020 N = 9,570,484	
Cancer Type	**N**	*Rate per 10,000*	**N**	*Rate per 10,000*
Other non-epithelial cancer of skin	368,123	386.8	350,546	366.3
Cancer of breast	119,194	125.2	115,645	120.8
Cancer of prostate	118,958	125.0	115,194	120.4
Melanomas of skin	65,617	68.9	63,853	66.7
Maintenance chemotherapy; radiotherapy	52,049	54.7	50,867	53.1
Secondary malignancies	50,935	53.5	50,745	53.0
*Cancer of colon**	36,257	38.1	33,621	35.1
*Cancer of bronchus; lung**	35,186	37.0	34,209	35.7
Cancer of bladder	29,566	31.1	28,615	29.9
Cancer; other and unspecified primary	29,388	30.9	27,219	28.4
Neoplasms of unspecified nature or uncertain behavior	27,330	28.7	26,979	28.2
Non-Hodgkin`s lymphoma	27,307	28.7	26,804	28.0
*Cancer of kidney and renal pelvis**	20,522	21.6	20,204	21.1
*Leukemias**	20,511	21.6	20,300	21.2
Cancer of thyroid	20,306	21.3	19,965	20.9
Malignant neoplasm without specification of site	17,783	18.7	17,575	18.4
Cancer of head and neck	17,197	18.1	16,595	17.3
Cancer of uterus	13,833	14.5	13,119	13.7
*Cancer of cervix**	10,901	11.5	9,788	10.2
*Cancer of rectum and anus**	10,265	10.8	9,884	10.3
Cancer of other GI organs; peritoneum	9,700	10.2	9,740	10.2
Multiple myeloma	8,361	8.8	8,406	8.8
Cancer of ovary	8,211	8.6	7,729	8.1
Cancer of bone and connective tissue	7,411	7.8	6,974	7.3
Cancer of brain and nervous system	7,297	7.7	6,951	7.3
Cancer of liver and intrahepatic bile duct	5,930	6.2	5,856	6.1
Cancer of pancreas	5,288	5.6	5,231	5.5
Cancer of stomach	4,851	5.1	4,768	5.0
Cancer of other female genital organs	4,185	4.4	3,921	4.1
Cancer of esophagus	3,953	4.2	3,842	4.0
Hodgkin`s disease	3,885	4.1	3,713	3.9
Cancer of testis	3,127	3.3	3,116	3.3
Cancer of other urinary organs	3,046	3.2	3,020	3.2
Cancer; other respiratory and intrathoracic	1,727	1.8	1,565	1.6
Cancer of other male genital organs	928	1.0	976	1.0

*****Cancer type in italics represents a change in rank from FY2019

**One beneficiary can experience more than one cancer type

APPENDIX D: PREVALENCE OF MOLECULAR TESTING AMONG BENEFICIARIES WITH CANCER

Table D1. Molecular Testing Among Beneficiaries with Cancer				
	FY 2019		FY 2020	
	N	%	N	%
Total	**48,551**	**100%**	**45,016**	**100%**
Beneficiary Type				
Active Duty	1,736	3.6%	1,532	3.4%
Dependents*	31,909	65.7%	28,833	64.1%
Guard/Reserve**	683	1.4%	657	1.5%
Retirees	14,178	29.2%	13,951	31.0%
Other/Unknown	45	0.1%	43	0.1%
Sex				
Female	34,673	71.4%	31,284	69.5%
Male	13,878	28.6%	13,732	30.5%
Age				
0 to 4	144	0.3%	151	0.3%
5 to 14	209	0.4%	229	0.5%
15 to 17	80	0.2%	99	0.2%
18 to 24	551	1.1%	478	1.1%
25 to 34	3,065	6.3%	2,604	5.8%
35 to 44	4,896	10.1%	4,441	9.9%
45 to 64	20,608	42.4%	18,522	41.1%
65 to 69	4,235	8.7%	3,985	8.9%
70 to 74	4,780	9.8%	4,833	10.7%
75 to 79	4,296	8.8%	4,183	9.3%
80 to 84	3,309	6.8%	3,226	7.2%
85+	2,378	4.9%	2,265	5.0%
Race/Ethnicity				
American Indian/ Alaskan Native	172	0.4%	170	0.4%
Asian/Pacific Islander	800	1.6%	802	1.8%
Black, non-Hispanic	2,478	5.1%	2,388	5.3%
Hispanic	602	1.2%	565	1.3%
White, non-Hispanic	12,284	25.3%	11,989	26.6%
Other/unknown	32,215	66.4%	29,102	64.6%

*Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees
**Includes Active and Inactive Guard/Reserve

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