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

PERSONNEL AND READINESS

SEP 17 2021

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

Dear Mr. Chairman:

The Department's response to House Report 116-442, page 153, accompanying H.R. 6395, the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021, which requests a report on rare cancer research and treatment in the Military Health System (MHS), is enclosed.

The MHS provides molecular diagnostic testing services to Service members 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. Approximately nine percent of the nine million MHS beneficiaries have a cancer diagnosis, of which approximately six percent receive molecular diagnostic testing within the given year. Each year, approximately 125,000 molecular diagnostic tests are performed among beneficiaries with cancer for a total cost of approximately $17M. The Department of Defense has established data-sharing relationships with various organizations and entities, including the Department of Veterans Affairs and National Institutes of Health.

Thank you for your continued strong support for our Service members, veterans, and their families. I am sending a similar letter to the Senate Armed Services Committee.

Sincerely,

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable Mike D. Rogers
Ranking Member

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

PERSONNEL AND READINESS

SEP 17 2021

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

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Sincerely,

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable James M. Inhofe
Ranking Member

Report to the Congressional Armed Services Committees

RARE CANCER RESEARCH AND TREATMENT

Requested by: House Report 116-142, page 153, accompanying H.R. 6395, the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $194,000 in Fiscal Years 2020-2021.
This includes $102,000 in expenses and $93,000 in DoD labor.
Generated on December 09, 2020

Contents

EXECUTIVE SUMMARY

This report responds to the request in the House Report 116-442, page 153, accompanying H.R. 6395, the William M. (Mac) Thornberry National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2021 for a report to the Committees on Armed Services of the Senate and the House of Representatives describing:

1) specific types of molecular diagnostics, such as micro-array, whole exome, and ribonucleic acid (RNA) sequencing that the Department is providing to cancer patients;

2) frequency of use, cost of treatment, and recommendations on providing molecular diagnostic testing for all Service members (SMs) with cancer at first diagnosis; and

3) data-sharing practices across the Services and with the Department of Veterans Affairs (VA) and the National Institutes of Health (NIH) for cancer cell lines and models with the external research community.

The Military Health System (MHS) provides comprehensive molecular diagnostic testing through three routes: (1) internal, (2) research-based, and (3) send-out testing.

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, 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]). This includes a program of clinical sequencing and clinical trial matching, as well as RNA testing.

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 2019 (the most recent year for which complete data is available), of the 9,517,011 beneficiaries that received MHS care, 897,504 (9.4

[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.

percent) had a cancer diagnosis. Of those beneficiaries, 54,137 (6.0 percent) received molecular diagnostic testing within the year. A total of 125,544 molecular diagnostic tests were performed among beneficiaries with cancer at a total cost of $17,832,174. Similarly, in 2018, of the 9,401,659 MHS beneficiaries, 878,597 (9.3 percent) had a cancer diagnosis. Of those beneficiaries, 51,290 (5.8 percent) received molecular diagnostic testing within the year. A total of 125,132 molecular diagnostic tests were performed among beneficiaries with cancer in both direct and private sector care at a total cost of $17,412,217. Cancer prevalence, as well as molecular diagnostic testing frequency and cost are discussed in further detail later this report.

DoD has established data-sharing relationships with various organizations and entities, including the VA and NIH. VA and DoD collaborate at three APOLLO sites. APOLLO data are submitted to the NIH's 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 and allows for integration and sharing of data.

Molecular diagnostic treatment and research fulfills the requirements of the MHS Quadruple Aim 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, and 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 service members' private, personally identifiable, genomic information, as well as information about lineage.

The MHS is composed of skilled clinicians who are committed to patient safety and clinical quality through the provision of the best cancer care available. The continued support from the Committees on Armed Services of the Senate and the House of Representatives is a vital and important aspect of continuing to ensure safe, reliable, high-quality cancer care for every patient, every time.

INTRODUCTION

Overview of Molecular Testing

The MHS provides excellent care to SMs 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, personalized or precision 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 United States (U.S.) 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."

The NDAA for FY 2021 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." (United States, 2020).

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.

By federal regulation, TRICARE uses the following in determining a rare disease: "A rare disease is defined as any disease or condition with a prevalence of less than 200,000 persons per year [in the U.S.]" (NIH, 2020). 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.

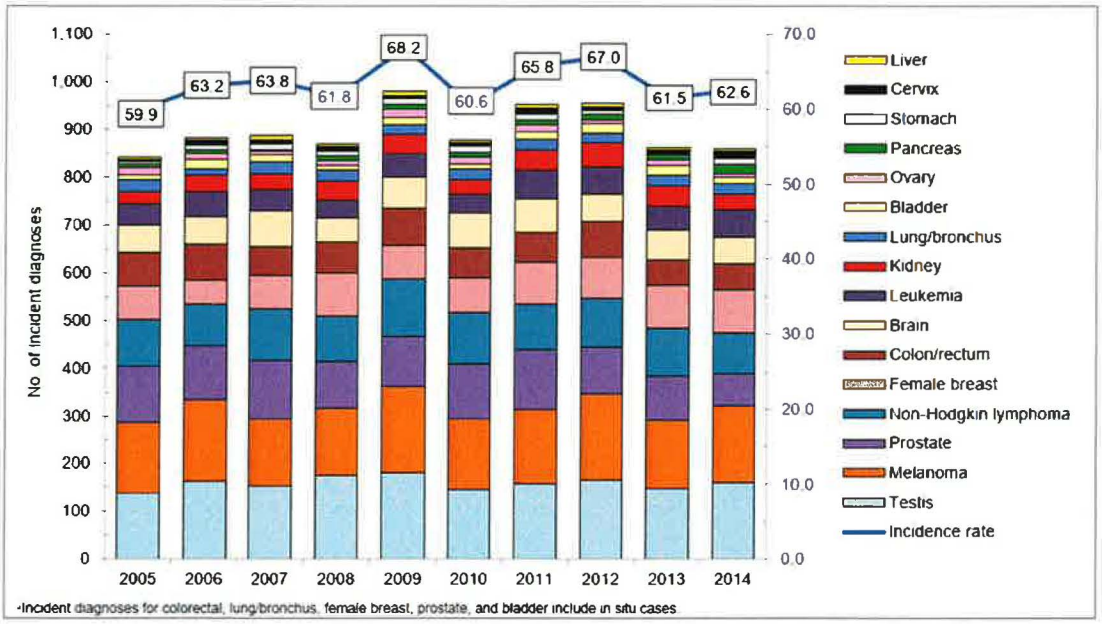

Figure 1. Incident Diagnosis of Selected Cancers and Total Incidence Rate, by Year and Affected Anatomic Site/Cell Type, Active Component, U.S. Armed Forces, 2005-2014

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 healthcare 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 composed of more than 30,000 genes that are neatly compacted in 23 pairs of chromosomes with one additional mitochondrial DNA (mtDNA). 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, is 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 complex and an 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 so as to produce enough nucleic acid for mutation analysis. Once these are amplified, the nucleic acid can be used for different purposes to include aiding in diagnosis of minimal residual disease and engraftment studies in leukemia and lymphoma patients, and also for 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.

Precision Medicine Approach

Genomic instability is a hallmark of cancer. Consequently, as a tumor grows and metastasizes, tumor cells accumulate genomic changes. Different populations/subsets of cells within a tumor can accumulate different sets of changes, at different rates. Even cancer of the same type in different individuals and/or metastatic derivatives of a primary tumor are quite variable at the genomic level (tumor heterogeneity). High levels of tumor heterogeneity predispose patients to differential levels of sensitivity to treatment, resistance to treatment, and different clinical outcomes. Over the last decade, a fuller understanding of these concepts and our steadily increasing knowledge regarding the relationship between specific mutations found in tumors (biomarkers), disease prognosis, and response to therapy has shifted treatment paradigms in oncology. A more precision (or personalized) medicine approach, where the selection of therapeutic agent(s) are guided by and targeted for relevant biomarkers detected in a patient's tumor, is rapidly replacing the historical "one-size-fits-all" approach of prescribing standard chemotherapy based upon the tumor's organ of origin, histology, and stage.

Tumor mutation status is assessed by 1) somatic tumor profiling using targeted, first-generation tests that detect a few known and specific changes; or 2) second-generation, large panel, or genomic-scale techniques based on NGS. Both first and second-generation tumor profiling tests have comparable sensitivity and specificity, and are currently used, in conjunction with clinico-pathological parameters, to provide information on disease diagnosis, prognosis, risk of recurrence, and for optimization of therapy. However, unlike first generation tests (FISH, PCR, Immunohistochemistry [IHC]), currently deployed NGS-based profiling assays (assessing up to 500 genes) can detect a much larger number and variety of changes in a tumor, including unexpected or novel ones. This expedites more comprehensive, molecular/biological characterization and sub-grouping of disease; facilitates individualized, biomarker-driven treatment; and increases enrollment of patients in genomically-driven, umbrella clinical trials. NGS-based tumor profiling studies have shown that some actionable mutations in some driver genes are shared across multiple tumor types. This led to the development and FDA-approved implementation of "pan-cancer" approaches for selection of targeted therapies. NGS-based testing can also provide an economical alternative to serial or parallel testing with multiple highly targeted assays. Tumor profiling assays are also being used for the non-invasive detection of tumor biomarkers in biological fluids, including blood plasma or serum, saliva, urine, etc. NGS-based detection of circulating tumor DNA (ctDNA) can detect tumor-specific mutations and epigenetic changes, and can help to guide treatment by identifying targetable somatic mutations in the tumor, as well as to monitor disease progression, and response to therapy.

The larger NGS profiling panels will often detect clinically relevant germline mutations in patients undergoing tumor genomic profiling. The assessment and reporting of such variations is especially important for cancers with a large inherited component, such as breast, ovarian, and colorectal cancers. These results are not only important in terms of providing information that enables better management of disease, including choice of therapies, but also have implications for the health of family members. As panels grow larger, the importance of germline-focused analysis of selected genes of relevance will increase. When appropriate, referral to genetic subspecialties for familial management and long-term follow-up should be included.

Germline Pharmacogenomics for Cancer Care

Patients vary in their response to medications, and the same doses of many medications can exhibit significant dissimilarities in efficacy and toxicity in different individuals. These differences can be partially explained by genetic variation in gene-encoding drug receptors, downstream effectors, detoxifying enzymes, proteins and transporters, "pharmacogenes" that affect the pharmacokinetics (absorption, distribution, metabolism, elimination), or pharmacodynamics (pharmacologic effects) of specific drugs. Genetic variations that affect the impact of cancer treatment drugs can result in new somatic tumor cells or be tied to pre-existing germline variations. Both types of variation must be taken into account for a more complete understanding of patient and tumor drug response. Clinical pharmacogenomic (PGx) testing utilizing high-level information can play an important role in identifying responders and non-responders to medications, helping to choose the right drug, optimize drug dosage, and minimize adverse events, including for some commonly used chemotherapeutic agents and drugs used to alleviate the side-effects of chemotherapy. This can potentially reduce morbidity and mortality due to these events, thereby reducing costs. Multiple health systems in the United States have implemented PGx testing for patients. Limited PGx testing is available in accordance with FDA

guidance at the AFMGC at Keesler AFB for the two most common genes (CYP2D6 and CYP2C19). Other genes are available, but are generally ordered as special send-out tests.

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 healthcare 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 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.

The Joint Pathology Center

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 30 assays to provide information relevant to diagnosis, prognosis, therapeutic decisions, and disease monitoring for solid tumors. An additional (10+) assays are in development and are expected to be available for clinical use in 2021. In addition, several NGS-based, multi-gene, somatic tumor profiling assays are in development, and are slated for clinical deployment by mid-year 2021.

The Air Force Medical Genetics Center

The AFMGC at Keesler AFB in Biloxi, Mississippi, is the Defense Health Agency (DHA)-designated reference laboratory for all germline testing taking place within the DoD. As part of the AFMGC's mission, they perform 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 (composed 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 consent 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 as 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.
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.

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 in 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 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.

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 are the keys to cancer discovery. ORIEN collects and shares data with the purpose of matching high-risk cancer patients with targeted treatments. Through ORIEN, detailed molecular data are generated through whole exome sequencing so that 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; WRNMMC's MCC is the only DoD site (Figure 2). Across the network, there are over 500,000 patients enrolled in ORIEN, with 20,000 having undergone sequencing.

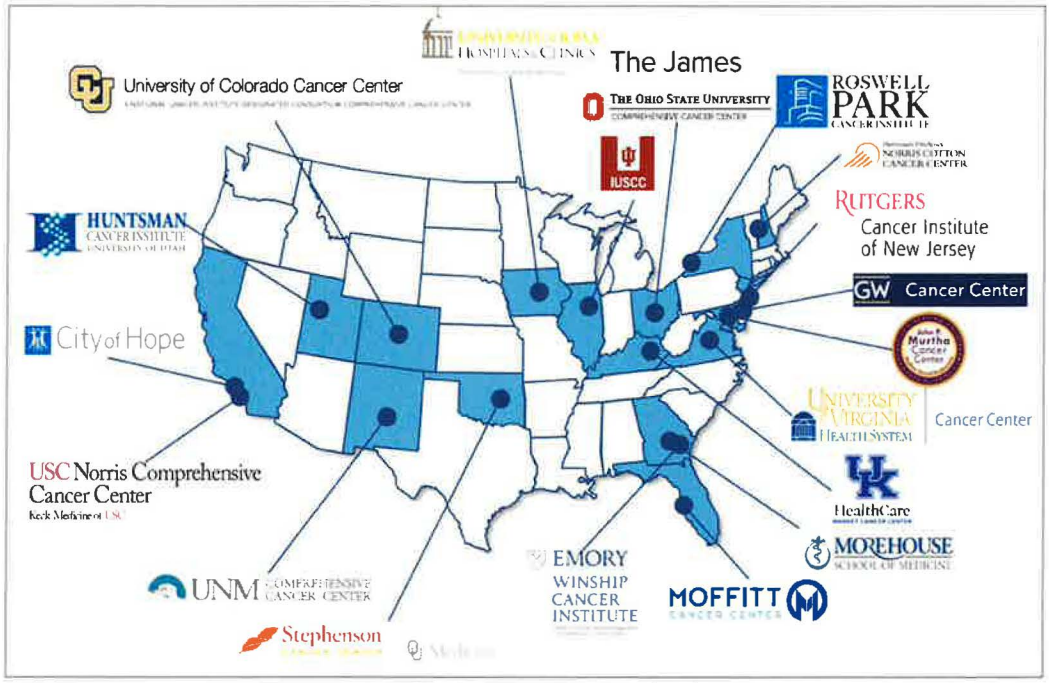

Figure 2. ORIEN Network Sites

Bio-Bank

USU, through the 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).

Private Sector Care Testing

By federal regulation, TRICARE covers only those medical devices, including laboratories, which have received FDA medical device 510(k) clearance or premarket approval. Under TRICARE, FDA-approved tests must also be medically necessary for the diagnosis and treatment of an illness such as cancer and have demonstrated clinical utility.

Per the FDA, "A laboratory developed test (LDT) is a type of in vitro diagnostic test 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."

To provide access to these tests for TRICARE beneficiaries, DHA initiated a demonstration project to review non-FDA approved LDTs to determine if they meet TRICARE requirements for safety and effectiveness according to the hierarchy of reliable evidence or TRICARE's rare disease policy. 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
- 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
- national expert opinion organizations

PREVALENCE OF CANCER AMONG BENEFICIARIES

In 2019, the most recent year for which complete data is available, approximately 9,517,011 beneficiaries were served through the MHS. Of those, 897,504 (9.4 percent) had a cancer diagnosis (Figure 3). The prevalence (the rate of new and existing cases) of cancer was highest among retirees (19.1 percent) compared to other beneficiary types. Beneficiaries ages 75 to 79 (31.6 percent) and ages 80 to 84 (33.7 percent) had the highest prevalence by age. Beneficiaries who identified as "other" or whose race/ethnicity was unknown (9.9 percent), and those who identified as White (10.9 percent), led prevalence by race (Appendix Table C1). A similar trend was seen in cancer prevalence among beneficiaries served through the MHS in 2018. Among the 9,401,659 beneficiaries, 878,597 (9.3 percent) had a cancer diagnosis (Figure 3). The prevalence of cancer was highest among retirees (19.0 percent) compared to other beneficiary types, and beneficiaries ages 75 to 79 (31.2 percent) and ages 80 to 84 (33.1 percent) led all age groups. Beneficiaries who identified as "other" or whose race/ethnicity was unknown (10.5 percent), and those who identified as White, non-Hispanic (9.2 percent) had the highest prevalence by race (Appendix Table C2).

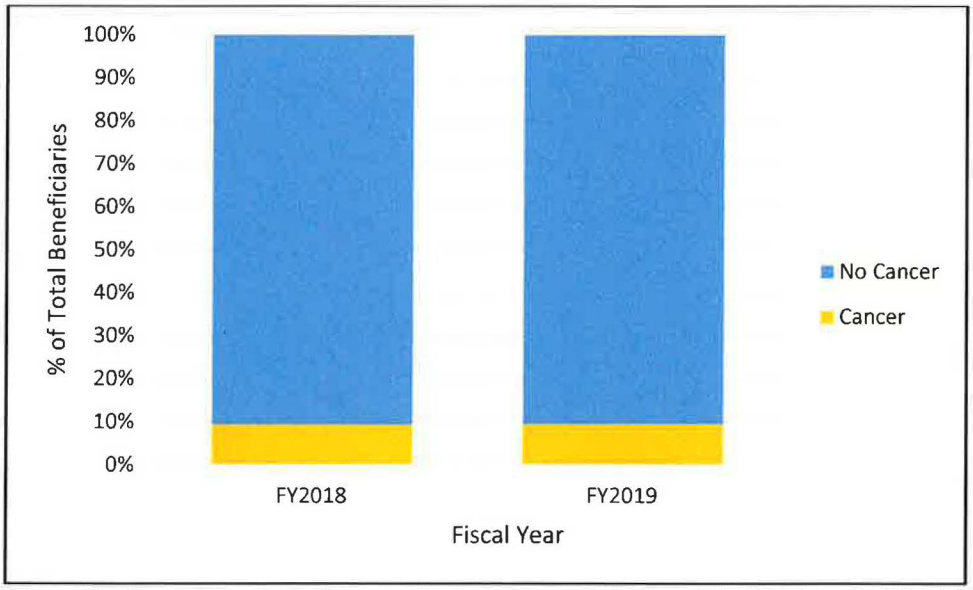

Figure 3. Prevalence of Cancer Among Beneficiaries, FY 2018 and FY 2019

In 2019, the most common cancer among beneficiaries was "other non-epithelial cancer of skin" (3.8 percent), followed by "neoplasms of unspecified nature or uncertain behavior" (1.8 percent), cancer of the breast (1.3 percent), and cancer of the prostate (1.2 percent) (Table 1).

Table 1. Prevalence of Cancer Cases Among Beneficiaries, FY 2019			
	FY 2019 Beneficiary Population with Cancer = 897,504		
	N	Rate+	%^
Cancer Type			
Cancer of head and neck	17,190	1,915	1.9%
Cancer of esophagus	3,953	440	0.4%
Cancer of stomach	4,850	540	0.5%
Cancer of colon	36,235	4,037	4.0%
Cancer of rectum and anus	10,811	1,205	1.2%
Cancer of liver and intrahepatic bile duct	5,934	661	0.7%
Cancer of pancreas	5,283	589	0.6%
Cancer of other GI organs; peritoneum	9,698	1,081	1.1%
Cancer of bronchus; lung	35,181	3,920	3.9%
Cancer; other respiratory and intrathoracic	1,726	192	0.2%
Cancer of bone and connective tissue	7,403	825	0.8%
Melanomas of skin	65,612	7,310	7.3%
Other non-epithelial cancer of skin	361,605	40,290	40.3%
Cancer of breast	119,160	13,277	13.3%
Cancer of uterus	13,816	1,539	1.5%
Cancer of cervix	31,653	3,527	3.5%
Cancer of ovary	8,205	914	0.9%
Cancer of other female genital organs	6,206	691	0.7%
Cancer of prostate	118,847	13,242	13.2%
Cancer of testis	3,121	348	0.3%
Cancer of other male genital organs	930	104	0.1%
Cancer of bladder	29,553	3,293	3.3%
Cancer of kidney and renal pelvis	20,514	2,286	2.3%
Cancer of other urinary organs	3,044	339	0.3%
Cancer of brain and nervous system	7,292	812	0.8%
Cancer of thyroid	20,305	2,262	2.3%
Hodgkin`s disease	3,885	433	0.4%
Non-Hodgkin`s lymphoma	27,301	3,042	3.0%
Leukemias	20,509	2,285	2.3%
Multiple myeloma	8,359	931	0.9%
Cancer; other and unspecified primary	43,297	4,824	4.8%
Secondary malignancies	50,925	5,674	5.7%
Neoplasms of unspecified nature or uncertain behavior	175,214	19,522	19.5%

[1]Includes Active and Inactive Guard/Reserve [2] Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees

+ Rate per 100,000 Beneficiaries with Cancer

^ Number of cases identified divided by total beneficiary population with cancer in the period and multiplied by 100 as a standard percentage

SOURCE: See Appendix A for data sources, methodology, and limitations

Similarly, in 2018, the most common cancer among beneficiaries was "other non-epithelial cancer of skin" (3.7 percent), followed cancer of the breast (1.2 percent), and cancer of the prostate (1.2 percent) (Table 2).

Table 2. Prevalence of Cancer Cases Among Beneficiaries, FY 2018

	FY 2018 Beneficiary Population with Cancer = 878,597		
	N	Rate+	%^
Cancer Type			
Cancer of head and neck	16,992	1,934	1.9%
Cancer of esophagus	3,999	455	0.5%
Cancer of stomach	4,714	537	0.5%
Cancer of colon	36,153	4,115	4.1%
Cancer of rectum and anus	10,779	1,227	1.2%
Cancer of liver and intrahepatic bile duct	5,726	652	0.7%
Cancer of pancreas	5,092	580	0.6%
Cancer of other GI organs; peritoneum	9,439	1,074	1.1%
Cancer of bronchus; lung	34,640	3,943	3.9%
Cancer; other respiratory and intrathoracic	1,768	201	0.2%
Cancer of bone and connective tissue	7,356	837	0.8%
Melanomas of skin	62,120	7,070	7.1%
Other non-epithelial cancer of skin	346,896	39,483	39.5%
Cancer of breast	116,084	13,212	13.2%
Cancer of uterus	13,245	1,508	1.5%
Cancer of cervix	32,048	3,648	3.6%
Cancer of ovary	8,157	928	0.9%
Cancer of other female genital organs	6,091	693	0.7%
Cancer of prostate	116,884	13,303	13.3%
Cancer of testis	3,165	360	0.4%
Cancer of other male genital organs	973	111	0.1%
Cancer of bladder	29,191	3,322	3.3%
Cancer of kidney and renal pelvis	19,678	2,240	2.2%
Cancer of other urinary organs	2,965	337	0.3%
Cancer of brain and nervous system	7,316	833	0.8%
Cancer of thyroid	19,532	2,223	2.2%
Hodgkin`s disease	3,949	449	0.4%
Non-Hodgkin`s lymphoma	26,484	3,014	3.0%
Leukemias	19,869	2,261	2.3%
Multiple myeloma	8,004	911	0.9%
Cancer; other and unspecified primary	40,070	4,561	4.6%
Secondary malignancies	49,443	5,627	5.6%
Neoplasms of unspecified nature or uncertain behavior	17,310	1,970	2.0%

[1] Includes Active and Inactive Guard/Reserve [2] Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees

Rate per 100,000 Beneficiaries with Cancer

^Number of cases identified divided by total beneficiary population with cancer in the period and multiplied by 100 as a standard percentage

SOURCE: See Appendix A for data sources, methodology, and limitations

PREVALENCE OF MOLECULAR TESTING AMONG BENEFICIARIES WITH CANCER

In 2019, of the 897,504 beneficiaries with cancer, 54,137 (6.0 percent) received molecular diagnostic testing (Figure 4). Molecular diagnostic testing was most common among ADSMs (18.0 percent), Female (9.7 percent), those ages 25 to 34 (29.3 percent), and Hispanic (14.3 percent) beneficiaries (Appendix Table D1). Similarly, of the 878,597 beneficiaries with cancer in 2018, 51,290 (5.8 percent) received molecular diagnostic testing (Figure 4). Molecular diagnostic testing was most common among ADSMs (16.9 percent), Female (9.4 percent), those ages 25 to 34 (27.9 percent), and Hispanic (13.8 percent) beneficiaries (Appendix Table D2).

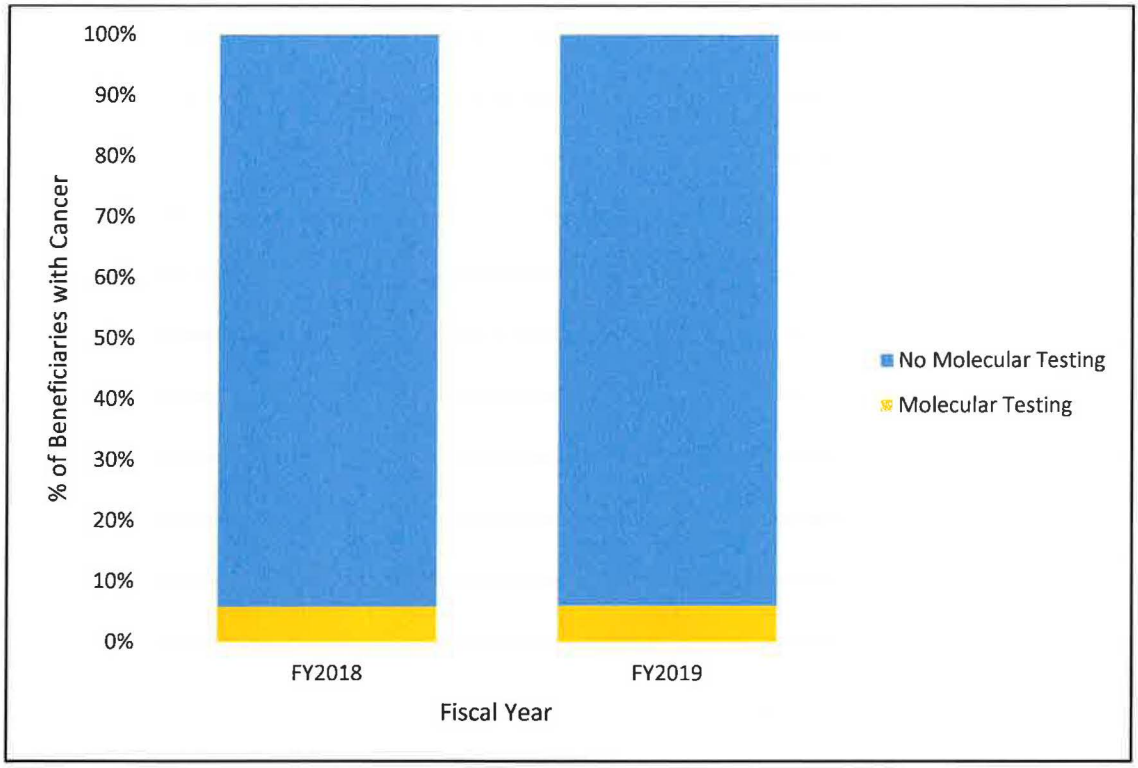

Figure 4. Prevalence of Molecular Diagnostic Testing Among Beneficiaries with Cancer, FY 2018 and FY 2019

FREQUENCY OF USE

In 2019, a total of 125,544 molecular diagnostic tests were performed among beneficiaries with cancer. Of molecular diagnostic tests performed, 91,609 (73.0 percent) were administered through private sector care and 33,934 (27.0 percent) were administered through direct care. FISH was the most administered test across both care settings, accounting for more than 40 percent of all tests administered (Table 3).

Table 3. Frequency of Molecular Diagnostic Testing Among Beneficiaries with Cancer, FY 2019

	FY 2019 Total = 125,544			
	Private Sector Care		Direct Care	
	N	% of Total N	N	% of Total N
Total	**91,609**	**73.0%**	**33,934**	**27.0%**
Type of Test				
Chromosomal Microarray	28	0.0%	241	0.7%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	16,138	17.6%	291	0.9%
Epigenomics	50	0.1%	-	0.0%
FISH	36,974	40.4%	20,965	61.8%
FISH/PCR	-	0.0%	2	0.0%
PCR	21,680	23.7%	9,283	27.4%
Sequencing	486	0.5%	625	1.8%
Sequencing/Epigenomic Studies	-	0.0%	3	0.0%
Sequencing/PCR	13,669	14.9%	507	1.5%
Unknown/Other	2,584	2.8%	2,017	5.9%

In 2018, a similar trend was seen with a total of 125,132 molecular diagnostic tests being performed among beneficiaries with cancer. Of molecular diagnostic tests performed, 87,513 (69.9 percent) were administered through private sector care and 37,619 (30.1 percent) were administered through direct care. FISH was the most administered test across both care settings, accounting for more than 39 percent of all tests administered (Table 4).

Table 4. Frequency of Molecular Diagnostic Testing Among Beneficiaries with Cancer, FY 2018				
	FY 2018 Total = 125,132			
	Private Sector Care		Direct Care	
	N	% of Total N	N	% of Total N
Total	**87,513**	**69.9%**	**37,619**	**30.1%**
Type of Test				
Chromosomal Microarray	41	0.0%	321	0.9%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	16,366	18.7%	317	0.8%
Epigenomics	49	0.1%	1	0.0%
FISH	34,657	39.6%	24,439	65.0%
FISH/PCR	-	0.0%	8	0.0%
PCR	19,128	21.9%	9,432	25.1%
Sequencing	159	0.2%	607	1.6%
Sequencing/Epigenomic Studies	-	0.0%	-	0.0%
Sequencing/PCR	14,162	16.2%	596	1.6%
Unknown/Other	2,951	3.4%	1,899	5.0%

Within the private sector care setting, 21,193 (23.1 percent) of the molecular diagnostic tests were administered through the LDT Demonstration Program in 2019, and 22,906 (26.2 percent) in 2018 (Figure 5). For both years, Sequencing/PCR accounted for the majority (over 51.8 percent) of the tests performed through the LDT Demonstration Program (Appendix Table E1 and E2).

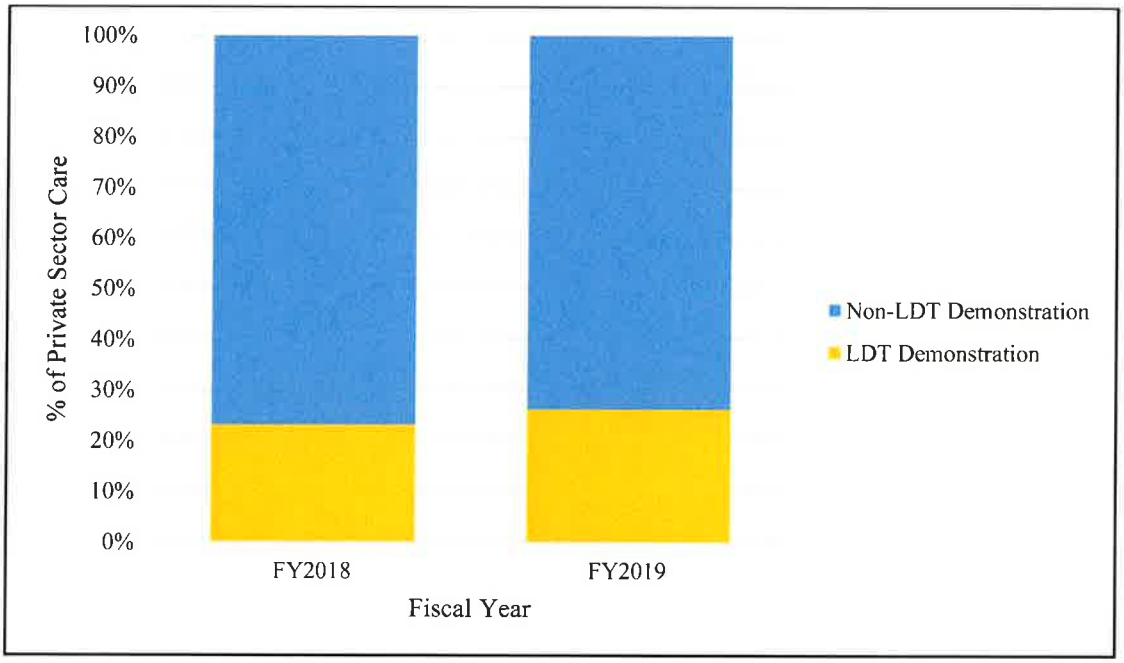

Figure 5. Frequency of Molecular Diagnostic Testing by Private Sector Care Type, Among Beneficiaries with Cancer, FY 2018 and FY 2019

COST OF TREATMENT

In FY 2019, a total of $17,832,174 was spent on molecular diagnostic tests performed for beneficiaries with cancer. Private sector care accounted for 82.9 percent of total molecular test cost, while direct care accounted for 17.1 percent. Sequencing/PCR accounted for the majority (11.3 percent) of the private sector care cost, while FISH accounted for the majority (5.3 percent) of the direct care costs (Table 5).

Table 5. Cost of Molecular Diagnostic Testing Among Beneficiaries with Cancer, FY 2019

	FY 2019 Total = $17,832,174			
	Private Sector Care		Direct Care	
	$	% of Total $	$	% of Total $
Total	**14,784,567**	**82.9%**	**3,047,608**	**17.1%**
Type of Test				
Chromosomal Microarray	69,621	0.2%	419,230	2.3%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	529,524	1.1%	8,320	0.0%
Epigenomics	6,111	0.0%	-	0.0%
FISH	1,891,186	4.1%	964,661	5.3%
FISH/PCR	-	0.0%	2,656	0.0%
PCR	963,145	2.1%	593,340	3.3%
Sequencing	1,784,705	3.9%	328,457	1.8%
Sequencing/Epigenomic Studies	-	0.0%	96	0.0%
Sequencing/PCR	5,229,544	11.3%	470,038	2.6%
Unknown/Other	4,310,731	9.3%	260,808	1.4%

In FY 2018, a similar trend was seen with a total of $17,412,217 spent on molecular diagnostic tests performed for beneficiaries with cancer. Private sector care accounted for 80.1 percent of total molecular test cost, while direct care accounted for 19.9 percent. Sequencing/PCR accounted for the majority (15.8 percent) of the private sector care cost, while FISH accounted for the majority (6.0 percent) of the direct care cost (Table 6).

Table 6. Cost of Molecular Diagnostic Testing Among Beneficiaries with Cancer, FY 2018				
	FY 2018 Total = $17,412,217			
	Private Sector Care		Direct Care	
	$	% of Total $	$	% of Total $
Total	**13,941,343**	**80.1%**	**3,470,874**	**19.9%**
Type of Test				
Chromosomal Microarray	94,170	0.3%	618,756	3.3%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	578,523	1.5%	10,983	0.1%
Epigenomics	4,523	0.0%	9	0.0%
FISH	1,778,043	4.8%	1,120,491	6.0%
FISH/PCR	-	0.0%	10,625	0.1%
PCR	956,644	2.6%	609,195	3.2%
Sequencing	704,287	1.9%	552,371	2.9%
Sequencing/Epigenomic Studies	-	0.0%	-	0.0%
Sequencing/PCR	5,890,689	15.8%	483,250	2.6%
Unknown/Other	3,934,463	10.5%	65,194	0.3%

Within the private sector care setting, while fewer molecular diagnostic tests were administered through the LDT Demonstration Program (23.1 percent versus 76.9 percent in 2019, and 26.2 percent versus 73.8 percent in 2018), it accounted for the majority of the cost. In 2019, $9,076,626 (61.4 percent) of the molecular diagnostic tests were administered through the LDT Demonstration Program and $9,750,979 (69.9 percent) in 2018. For both years, Sequencing/PCR accounted for the majority (over 56.4 percent) of the tests performed through the LDT Demonstration Program (Figure 6, Appendix Table F1 and F2).

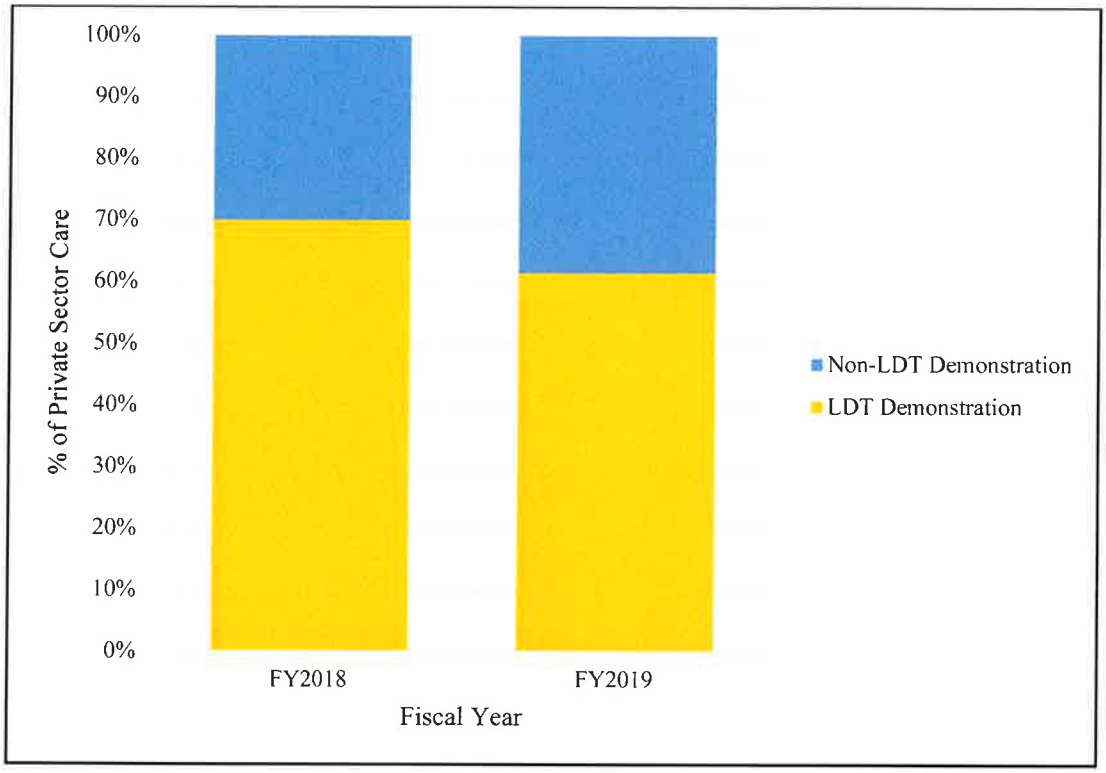

Figure 6. Cost of Molecular Diagnostic Testing by Private Sector Care Type, Among Beneficiaries with Cancer, FY 2018 and FY 2019

DATA-SHARING PRACTICES

DoD shares data with the VA, NIH, and the external research community through various programs and channels. Data-sharing with the VA occurs through collaboration at three VA APOLLO sites: VA Palo Alto Health Care System, Durham VA Health Care System, and VA Puget Sound Health Care System. APOLLO data from these and all other DoD APOLLO sites are entered into the NCI's GDC. Once in GDC, data are only available to approved researchers, using limited, de-identified datasets (i.e., without protected health information [PHI]). Data-sharing agreements for APOLLO are based on NIH's standard federal requirements and are supported through a Memorandum of Agreement between DoD, VA, and NCI.

APOLLO Data Sharing

The APOLLO Network utilizes multiple sites for sample collection and data analyses. 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 the Health Insurance Portability and Accountability Act. 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 ACTUR 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 the 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. ACTUR 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 Bio-Bank and CBCP protocols. CSSIMMW study staff upload these digital slides into the APOLLO Informatics Infrastructure system and transmit them to The Cancer Imaging Archive.

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 TAGC studies.

Coded APOLLO clinicopathologic data and sample-level proteogenomic data passes 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 7.

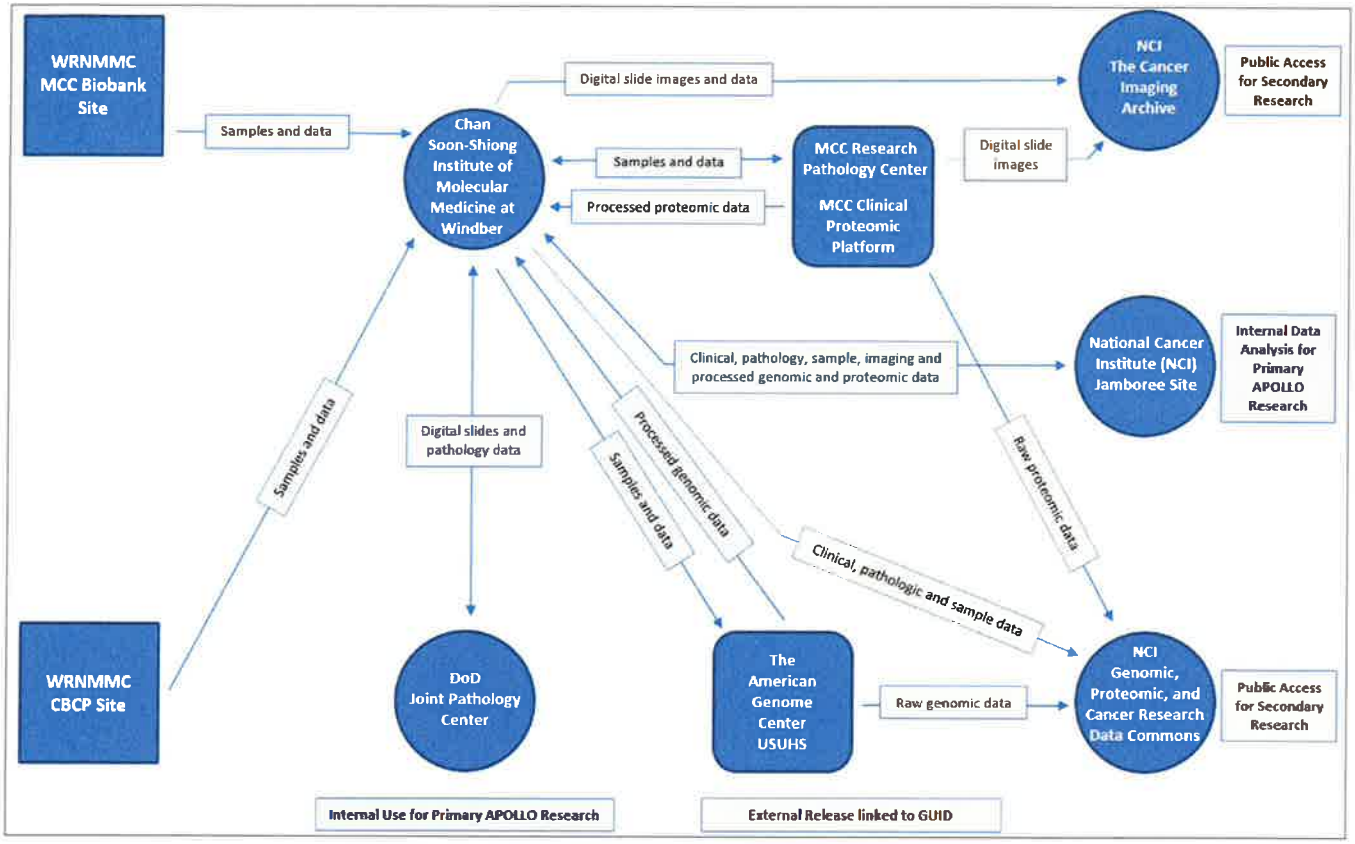

Figure 7. APOLLO 5 Protocol Workflow

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 8) 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.

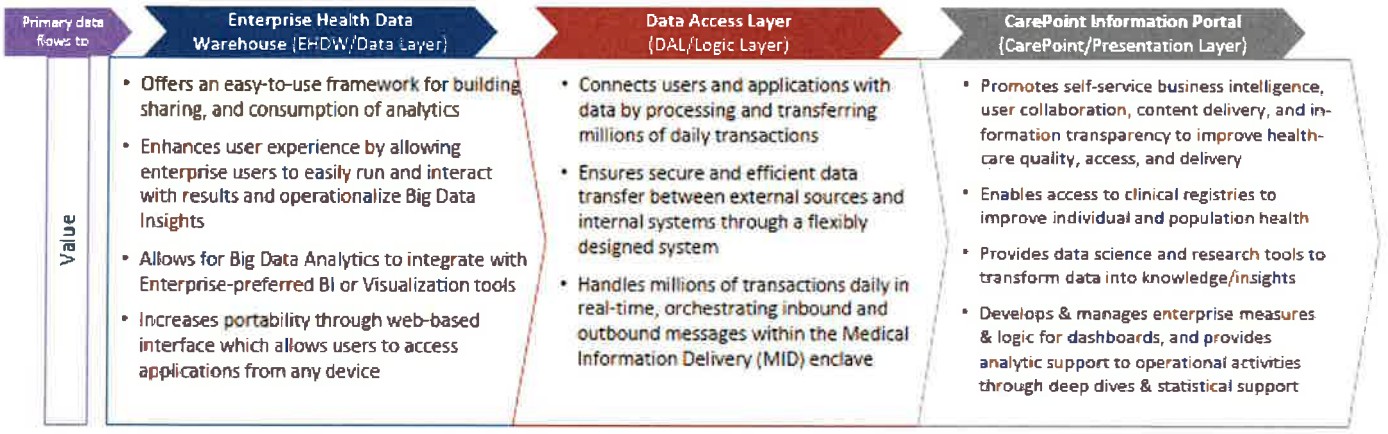

Figure 8. MIP's Three Layers (Maneval, 2018)

The future state of the MIP is to fully connect with other federal partners, such as the VA and NIH, using a hub and spoke model to share data (within the framework of policy and legal statutes), such as pathology results and genomic data.

CONCLUSION

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
- They have demonstrated clinical utility

Approximately 9 percent of the 9 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. Each year, approximately 125,000 molecular diagnostic tests are performed among beneficiaries with cancer for a total cost of approximately $17M.

DoD continues to share data and collaborate with entities such as the VA, NIH, and the external research community. Data-sharing and collaboration between organizations would continue to be prioritized with the development of a standardized comprehensive MHS molecular diagnostic testing program.

The molecular diagnostic clinical and research field is rapidly changing, and the MHS has a duty to its SMs to provide excellent care throughout the entire spectrum of cancer, including molecular diagnostics. A comprehensive MHS standardization effort has direct and immediate clinical applicability. This is best accomplished through the establishment of an adequately resourced molecular testing program centralized at the JPC.

Appendix A: Methodology Overview

Data Source and Methodology

For this report, the MDR Defense Enrollment Eligibility Reporting System (DEERS) VM6BEN was used to identify the total beneficiary population in the first month of FY 2018 (October 2017) and FY 2019 (October 2018). The MDR direct care data sources (Comprehensive Ambulatory/Professional Encounter Record [CAPER], Standard Inpatient Data Record [SIDR], MHS GENESIS Encounter, and MHS GENESIS Admission) and private sector care data sources (TED Non-Institutional and TED Institutional) were then searched to identify beneficiaries with a healthcare record that included a cancer diagnosis within the FY (October 2017-September 2018 and October 2018-September 2019, respectively). Cancer classification type was determined using the International Classification of Diseases (ICD)-10 cancer diagnosis codes. A beneficiary can appear under multiple classifications, if their records contained multiple Clinical Classification Software categories or diagnosis codes, respectively.

Direct care sources (CADRE Laboratory and MHS GENESIS Laboratory) and private sector care source (TED Non-Institutional) were used to identify beneficiaries that had any molecular test completed within the FY. The direct care records were identified by matching records using either a Current Procedural Terminology (CPT) code or lab test name. The private sector care records were only identified by matching one of the procedure codes, as a lab test name variable does not exist within the private sector care source. All CPT codes and lab test names indicating molecular diagnosis testing were identified and reviewed by subject matter experts. Direct care lab records include tests sent out to private external labs, such as LabCorp, but these records do not generally record the cost to the private lab to perform the test or the amount paid to the lab under a contract. Instead, they only contain the cost representing the MTF workload associated with the sent-out test, such as collecting the specimen and documenting results. Thus, supplementary data was obtained from LabCorp to determine the frequency and cost of tests completed within the FY. In comparing direct care costs with private sector care costs, differences in cost accounting must be considered. Private sector care "costs" are not real costs; rather, they include what was paid by TRICARE. Unlike direct care costs, private sector care costs do not capture the cost of the production of health services. Thus, comparisons between direct care and private sector care costs should be made with caution.

Based on the limitations discussed in further detail below, it is possible that the frequency of use and cost of molecular testing in both direct and private sector care are not exact, and may be either under or over reported.

Limitations

<u>Differences in Data Sources</u>

The direct care lab records came from a data source that does have a variable for a lab test name; however, this variable does not exist within private sector care records. This creates inconsistency between the direct care and private sector care data; therefore, private sector care records included non-molecular testing and molecular testing for beneficiaries who were not yet

diagnosed with cancer. Various test names can be grouped under a CPT code (both molecular and non-molecular), and in some cases a generic description is given for the lab test name and the CPT code, making it difficult to make a clear distinction on whether records should be consider molecular testing (i.e., CPT codes 81400 – 81401 are only described as Molecular Pathology Procedure[4]). Furthermore, the exact names of certain tests varied from the LabCorp data to other direct care sources and even within the direct care system. Fuzzy matching was used, where certain keywords for the tests were searched for and exact keywords and specifications of matching were provided and reviewed by the subject matter experts. However, not all test names were able to be matched across systems and data sources, thus causing some inconsistencies in how test names were categorized and summarized for reporting.

Direct Care versus Private Sector Care Cost

In comparing direct care costs with private sector care costs, differences in cost accounting must be considered. Direct care encounter records do not capture billing/claims data, but they instead capture patient-level clinical (limited) and workload data. Private sector care "costs" are not real costs; rather, they include what was paid by TRICARE. Unlike direct care costs, private sector care costs do not attempt to capture the cost of the production of health services. Instead, they are billing data for facility use and service line items. Thus, caution should be used when making comparisons of private sector care versus direct care costs.

[4] For these particular CPT codes, an inference was made to determine the percentage of molecular pathology test were 'true' molecular test in private sector care. These was done by calculating the % of records in the direct care data had a generic pathology CPT test code that also had a matching lab test name and applying that percentage to the total records of Molecular Pathology CPT test codes. For FY 2019, 1% of the total frequency of molecular pathology records had a matching lab test name, and 3% of the total cost of molecular pathology records had a matching lab test name. For FY 2018, 24% of the total frequency of molecular pathology records had a matching lab test name, and 20% of the total cost of molecular pathology records had a matching lab test name.

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 (GWAS), 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	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	Methylated DNA can be distinguished from unmethylated DNA using different techniques that include restriction endonuclease digestion with methylation-sensitive enzymes, sequencing, and methylation-specific Polymerase Chain Reaction (PCR, MSP). 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.
Fluorescent In Situ Hybridization (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.).
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.
Polymerase Chain Reaction (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, etc.).
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. 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 (KRAS) 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	This is used to directly quantify and clonally amplify nucleic acids strands including DNA, complimentary 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 [IDH2]) 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), *CEBPA* (acute myeloid leukemia), and *IDH1* (gliomas) are some applications for Sanger sequencing.
Next Generation 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 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 copy number variations (CNVs) and is especially well-suited to detect structural variants (SVs), which often involve noncoding DNA breakpoints.

Appendix C: Cancer Prevalence in Beneficiary Population

Table C1. Prevalence of Cancer by Demographics, FY 2019			
	FY 2019 Beneficiary Population = 9,517,011		
	N	Rate+	%
Total	**897,504**	**9,431**	**9.4%**
Beneficiary Type			
Active Duty	23,868	1,731	1.7%
Guard/Reserve[1]	8,440	2,333	2.3%
Dependents[2]	441,092	7,989	8.0%
Other/Unknown	616	1,480	1.5%
Retirees	423,488	19,132	19.1%
Sex			
Female	461,272	9,878	9.9%
Male	436,229	9,000	9.0%
Unknown	3	1,224	1.2%
Age			
0 to 4	1,434	253	0.3%
5 to 14	3,532	326	0.3%
15 to 17	1,758	560	0.6%
18 to 24	13,303	1,139	1.1%
25 to 34	27,129	2,286	2.3%
35 to 44	33,433	3,812	3.8%
45 to 64	201,717	10,000	10.0%
65 to 69	118,245	19,027	19.0%
70 to 74	149,774	26,029	26.0%
75 to 79	134,721	31,593	31.6%
80 to 84	113,523	33,733	33.7%
85+	98,935	28,884	28.9%
Race/Ethnicity			
American Indian/ Alaskan Native	2,991	6,304	6.3%
Asian/Pacific Islander	10,143	4,449	4.4%
Black, non-Hispanic	36,576	5,555	5.6%
Hispanic	8,620	2,358	2.4%
Other/unknown	556,764	9,883	9.9%
White, non-Hispanic	282,410	10,930	10.9%

[1]Includes Active and Inactive Guard/Reserve
[2]Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees
Rate per 100,000 Beneficiaries with Cancer
^Number of cases identified divided by total beneficiary population with cancer in the period and multiplied by 100 as a standard percentage

Table C2. Prevalence of Cancer by Demographics, FY 2018			
	FY 2018 Beneficiary Population = 9,401,659		
	N	Rate+	%^
Total	**878,597**	**9,345**	**9.3%**
Beneficiary Type			
Active Duty	24,494	1,790	1.8%
Guard/Reserve[1]	8,125	2,399	2.4%
Dependents[2]	426,782	7,809	7.8%
Other/Unknown	624	2,480	2.5%
Retirees	418,572	18,989	19.0%
Sex			
Female	448,664	9,721	9.7%
Male	429,932	8,983	9.0%
Unknown	1	518	0.5%
Age			
0 to 4	1,396	248	0.2%
5 to 14	3,544	331	0.3%
15 to 17	1,733	555	0.6%
18 to 24	13,415	1,176	1.2%
25 to 34	27,688	2,352	2.4%
35 to 44	32,914	3,869	3.9%
45 to 64	201,552	9,905	9.9%
65 to 69	120,737	19,117	19.1%
70 to 74	142,904	26,178	26.2%
75 to 79	129,031	31,166	31.2%
80 to 84	109,442	33,053	33.1%
85+	94,241	28,617	28.6%
Race/Ethnicity			
American Indian/ Alaskan Native	2,472	5,490	5.5%
Asian/Pacific Islander	9,402	4,323	4.3%
Black, non-Hispanic	30,524	5,029	5.0%
Hispanic	8,118	2,408	2.4%
Other/unknown	612,372	10,466	10.5%
White, non-Hispanic	215,709	9,203	9.2%

[1]Includes Active and Inactive Guard/Reserve
[2]Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees
+Rate per 100,000 Beneficiaries with Cancer
^Number of cases identified divided by total beneficiary population with cancer in the period and multiplied by 100 as a standard percentage

Appendix D: Prevalence of Molecular Testing Among Beneficiaries with Cancer

Table D1. Molecular Testing Among Beneficiaries with Cancer, FY 2019			
	FY 2019 Beneficiary Population with Cancer = 897,504		
	N	Rate+	%^
Total	**54,137**	**60.3**	**6.0%**
Beneficiary Type			
Active Duty	4,303	180.3	18.0%
Guard/Reserve+	1,218	144.3	14.4%
Dependents++	38,132	86.4	8.6%
Other/Unknown	60	97.4	9.7%
Retirees	10,424	24.6	2.5%
Sex			
Female	44,624	96.7	9.7%
Male	9,513	21.8	2.2%
Age			
0 to 4	107	74.6	7.5%
5 to 14	146	41.3	4.1%
15 to 17	71	40.4	4.0%
18 to 24	1,776	133.5	13.4%
25 to 34	7,952	293.1	29.3%
35 to 44	7,969	238.4	23.8%
45 to 64	22,577	111.9	11.2%
65 to 69	3,265	27.6	2.8%
70 to 74	3,477	23.2	2.3%
75 to 79	3,039	22.6	2.3%
80 to 84	2,218	19.5	2.0%
85+	1,540	15.6	1.6%
Race/Ethnicity			
American Indian/ Alaskan Native	227	75.9	7.6%
Asian/Pacific Islander	1,234	121.7	12.2%
Black, non-Hispanic	3,322	90.8	9.1%
Hispanic	1,233	143.0	14.3%
Other/unknown	35,469	63.7	6.4%
White, non-Hispanic	12,652	44.8	4.5%

[1]Includes Active and Inactive Guard/Reserve
[2]Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees
+ Rate per 100,000 Beneficiaries with Cancer
^Number of cases identified divided by total beneficiary population with cancer in the period and multiplied by 100 as a standard percentage

Table D2. Molecular Testing Among Beneficiaries with Cancer, FY 2018			
	FY 2018 Beneficiary Population with Cancer = 878,597		
	N	Rate+	%^
Total	**54,137**	**61.6**	**6.2%**
Beneficiary Type			
Active Duty	4,133	168.7	16.9%
Guard/Reserve+	1,108	136.4	13.6%
Dependents++	35,904	84.1	8.4%
Other/Unknown	48	76.9	7.7%
Retirees	10,097	24.1	2.4%
Sex			
Female	42,363	94.4	9.4%
Male	8,927	20.8	2.1%
Age			
0 to 4	101	72.3	7.2%
5 to 14	126	35.6	3.6%
15 to 17	76	43.9	4.4%
18 to 24	1,808	134.8	13.5%
25 to 34	7,734	279.3	27.9%
35 to 44	7,644	232.2	23.2%
45 to 64	21,192	105.1	10.5%
65 to 69	3,069	25.4	2.5%
70 to 74	3,180	22.3	2.2%
75 to 79	2,786	21.6	2.2%
80 to 84	2,162	19.8	2.0%
85+	1,412	15.0	1.5%
Race/Ethnicity			
American Indian/ Alaskan Native	212	85.8	8.6%
Asian/Pacific Islander	1,174	124.9	12.5%
Black, non-Hispanic	3,156	103.4	10.3%
Hispanic	1,117	137.6	13.8%
Other/unknown	35,062	57.3	5.7%
White, non-Hispanic	10,569	49.0	4.9%

[1]Includes Active and Inactive Guard/Reserve
[2]Includes Dependent Survivor and Dependent of Active Duty, Guard/Reserve, and Retirees
Rate per 100,000 Beneficiaries with Cancer
^Number of cases identified divided by total beneficiary population with cancer in the period and multiplied by 100 as a standard percentage

Appendix E: Frequency of Private Sector Care Molecular Testing

Table E1. Frequency of Molecular Diagnostic Testing by Private Sector Care Type, Among Beneficiaries, FY 2019				
	FY 2019 Private Sector Care Total = 91,609			
	Non-LDT Demonstration Program		LDT Demonstration Program	
	N	% of Total	N	% of Total
Total	**70,417**	**76.9%**	**21,193**	**23.1%**
Type of Test				
Chromosomal Microarray	-	0.0%	28	0.1%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	9,019	12.8%	7,119	33.6%
Epigenomics	1	0.0%	49	0.2%
Fluorescent in situ hybridization (FISH)	36,974	52.5%	-	0.0%
Fluorescent in situ hybridization (FISH)/Polymerase Chain Reaction (PCR)	-	0.0%	-	0.0%
Polymerase Chain Reaction (PCR)	19,538	27.7%	2,142	10.1%
Sequencing	476	0.7%	10	0.0%
Sequencing/Epigenomic Studies	-	0.0%	-	0.0%
Sequencing/Polymerase Chain Reaction (PCR)	2,848	4.0%	10,821	51.1%
Unknown/Other	1,561	2.2%	1,024	4.8%

Table E2. Frequency of Molecular Diagnostic Testing by Private Sector Care Type, Among Beneficiaries, FY 2018				
	FY 2018 Private Sector Care Total = 87,513			
	Non-LDT Demonstration Program		LDT Demonstration Program	
	N	% of Total	N	% of Total
Total	**64,607**	**73.8%**	**22,906**	**26.2%**
Type of Test				
Chromosomal Microarray	1	0.0%	40	0.2%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	9,510	14.7%	6,856	29.9%
Epigenomics	1	0.0%	48	0.2%
Fluorescent in situ hybridization (FISH)	34,647	53.6%	10	0.0%
Fluorescent in situ hybridization (FISH)/Polymerase Chain Reaction (PCR)	-	0.0%	-	0.0%
Polymerase Chain Reaction (PCR)	17,134	26.5%	1,994	8.7%
Sequencing	158	0.2%	1	0.0%
Sequencing/Epigenomic Studies	-	0.0%	-	0.0%
Sequencing/Polymerase Chain Reaction (PCR)	2,306	3.6%	11,856	51.8%
Unknown/Other	850	1.3%	2,101	9.2%

Appendix F: Cost of Private Sector Care Molecular Testing

Table F1. Cost of Molecular Diagnostic Testing by Private Sector Care Type, Among Beneficiaries, FY 2019				
	FY 2019 Private Sector Care Total = $14,784,567			
	Non-LDT Demonstration Program		LDT Demonstration Program	
	$	% of total $	$	% of total $
Total	**5,707,941**	**38.6%**	**9,076,626**	**61.4%**
Type of Test				
Chromosomal Microarray	-	0.0%	69,621	0.8%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	462,128	8.1%	67,396	0.7%
Epigenomics	135	0.0%	5,976	0.1%
Fluorescent in situ hybridization (FISH)	1,891,186	33.1%	-	0.0%
Fluorescent in situ hybridization (FISH)/Polymerase Chain Reaction (PCR)	-	0.0%	-	0.0%
Polymerase Chain Reaction (PCR)	635,949	11.1%	327,196	3.6%
Sequencing	1,774,464	31.1%	10,240	0.1%
Sequencing/Epigenomic Studies	-	0.0%	-	0.0%
Sequencing/Polymerase Chain Reaction (PCR)	114,395	2.0%	5,115,148	56.4%
Unknown/Other	829,684	14.5%	3,481,048	38.4%

Table F2. Cost of Molecular Diagnostic Testing by Private Sector Care Type, Among Beneficiaries, FY 2018				
	FY 2018 Private Sector Care Total = $13,941,343			
	Non-LDT Demonstration Program		LDT Demonstration Program	
	$	% of total $	$	% of total $
Total	**4,190,364**	**30.1%**	**9,750,979**	**69.9%**
Type of Test				
Chromosomal Microarray	920	0.0%	93,250	1.0%
Chromosomal Microarray/Sequencing	-	0.0%	-	0.0%
Cytogenetics	511,293	12.2%	67,230	0.7%
Epigenomics	128	0.0%	4,396	0.0%
Fluorescent in situ hybridization (FISH)	1,776,842	42.4%	1,201	0.0%
Fluorescent in situ hybridization (FISH)/Polymerase Chain Reaction (PCR)	-	0.0%	-	0.0%
Polymerase Chain Reaction (PCR)	622,155	14.8%	334,489	3.4%
Sequencing	703,774	16.8%	513	0.0%
Sequencing/Epigenomic Studies	-	0.0%	-	0.0%
Sequencing/Polymerase Chain Reaction (PCR)	92,432	2.2%	5,798,257	59.5%
Unknown/Other	482,821	11.5%	3,451,643	35.4%

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