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CANCER DATA TRENDS 2025

In collaboration with

AVAHO
ASSOCIATION OF VA HEMATOLOGY/ONCOLOGY

FEDERAL PRACTITIONER®

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The following abbreviations are used frequently throughout this issue:
FDA, US Food and Drug Administration; SEER, Surveillance, Epidemiology, and End Results Program; VA, Veterans Affairs; VHA, Veterans Health Administration

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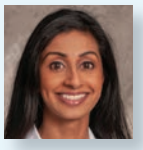

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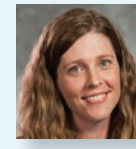

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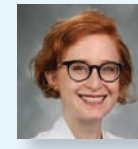

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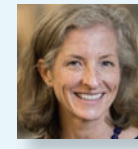

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Access, Race, and "Colon Age": Improving CRC Screening

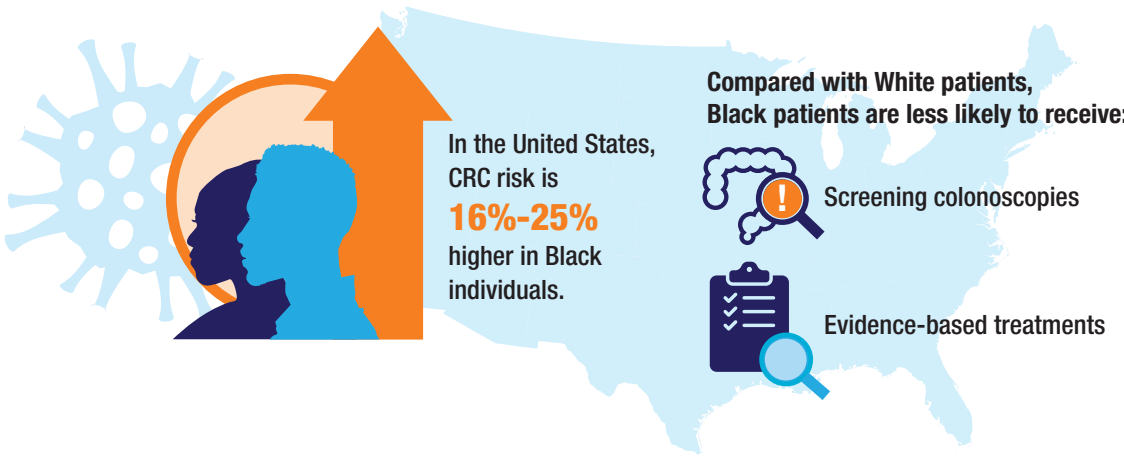
Divya B. Bhatt, MD, MA

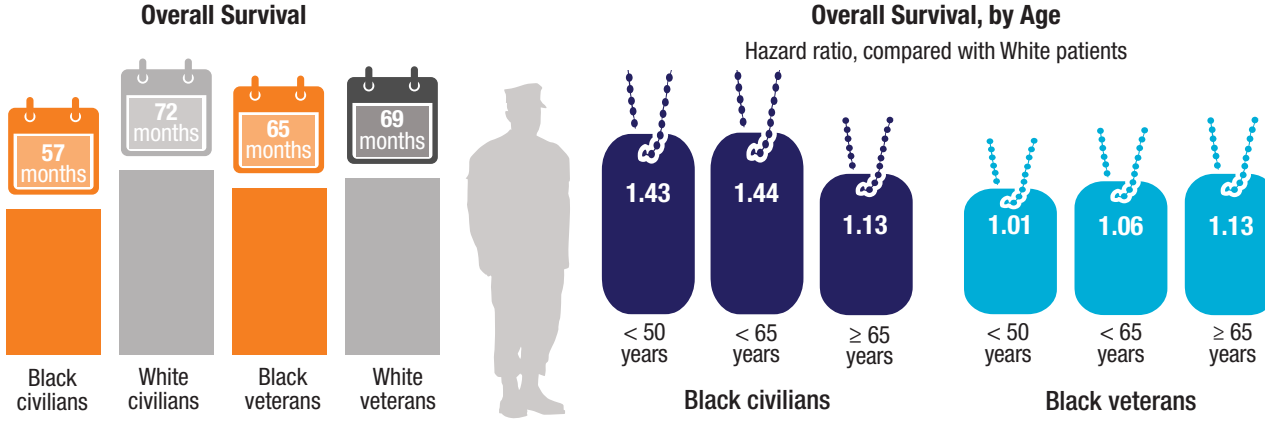
Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States, with an estimated 53,010 deaths and 152,810 new diagnoses in 2024.[1]

Incidence of CRC is higher in Black patients than in White patients, and racial disparities in survival persist in the general population[1] until individuals reach Medicare eligibility.[2] Interestingly, data published in 2024 have shown that this trend does not appear in the VHA system, indicating that access to care may play a more crucial role than racial contributions in influencing outcomes among non-Hispanic Black and White individuals.[2]

CRC rates and deaths are steadily decreasing among those aged 50 years or older but are rising in individuals under age 50. Early-onset colorectal cancer (EOCRC)—cases diagnosed before age 50—now represent 10% to 11% of all CRC. Of these cases, 75% occur in people aged 40 to 49, whereas about 50% affect individuals younger than 45. A novel measure, "colon age," quantifies EOCRC risk by taking biological factors into account. This metric can help VHA providers clarify CRC risk and help patients better grasp their screening options before age 45 or 50.[3]

CRC Racial Disparities: VHA vs US Population[1,2]





Colon Age: Estimating Risk for Early-Onset CRC[3]

With EOCRC cases on the rise, a greater understanding of risk factors in US veterans is needed to establish recommendations for earlier screening. Imperiale, et al., recently sought to develop a new metric for estimating CRC risk in veterans based on "colon age." This model still needs to be validated before it is ready for primetime, however.

Objective:

✔ Develop a metric to guide screening decisions for veterans aged < 50 years in a way that can simplify the discussion between health care providers and patients. Explicitly state that specific symptoms (eg, rectal bleeding) increase the person's calculated risk.

"Based on your risk factor profile, you have the colon age of an X-year-old patient."

Method:

Risk prediction models, validated on male veterans, were used to calculate relative risks (RRs) for 6 scenarios.

Models:

15 variables: Higher complexity, slightly more accurate
7 variables: Simplified, easier for clinical use

Scenarios:

1 Low risk (no risk factors)
4 Intermediate risk (some risk factors)
1 High risk (all risk factors)

Age Groups:

By incorporating risk factors for early-onset colorectal cancer with incidence rates, "colon age" may facilitate shared decision-making regarding screening for male veterans aged 50 years or younger. For individuals aged 45 to 49, a 7-variable model might be more favorable for VHA patients, providers, and the overall health care system because the highest risk scenario warrants noninvasive screening if the decision threshold is based on the SEER rate for this age group.[3]

Process for Each Scenario:

1. **Estimate 5-Year Absolute Risk**
   Using SEER CRC incidence rates and scenario-specific RRs
2. **Estimate Revised SEER rate**
   Revised SEER rate = Baseline SEER rate x (1 – attributable risk) x RR
3. **Identify "Colon Age"**
   a. Compare revised SEER rate to SEER age-group rates
   b. Identify the midpoint of the closest age group

Key Recommendations:

General Screening: When colon age is ≥ 50-54 years old

Colonoscopy: When colon age is ≥ 70-74 years old

Recommendations By Age Group:

35-39 years:
✔ **15-variable model:** Screening for high-risk patients

40-44 years:
✔ **15-variable model:** Colonoscopy for high-risk patients
✔ **7-variable model:** Noninvasive tests for high-risk patients

45-49 years:
Both models recommend:
✔ Colonoscopy for high-risk patients
✔ Noninvasive tests for some intermediate-risk scenarios

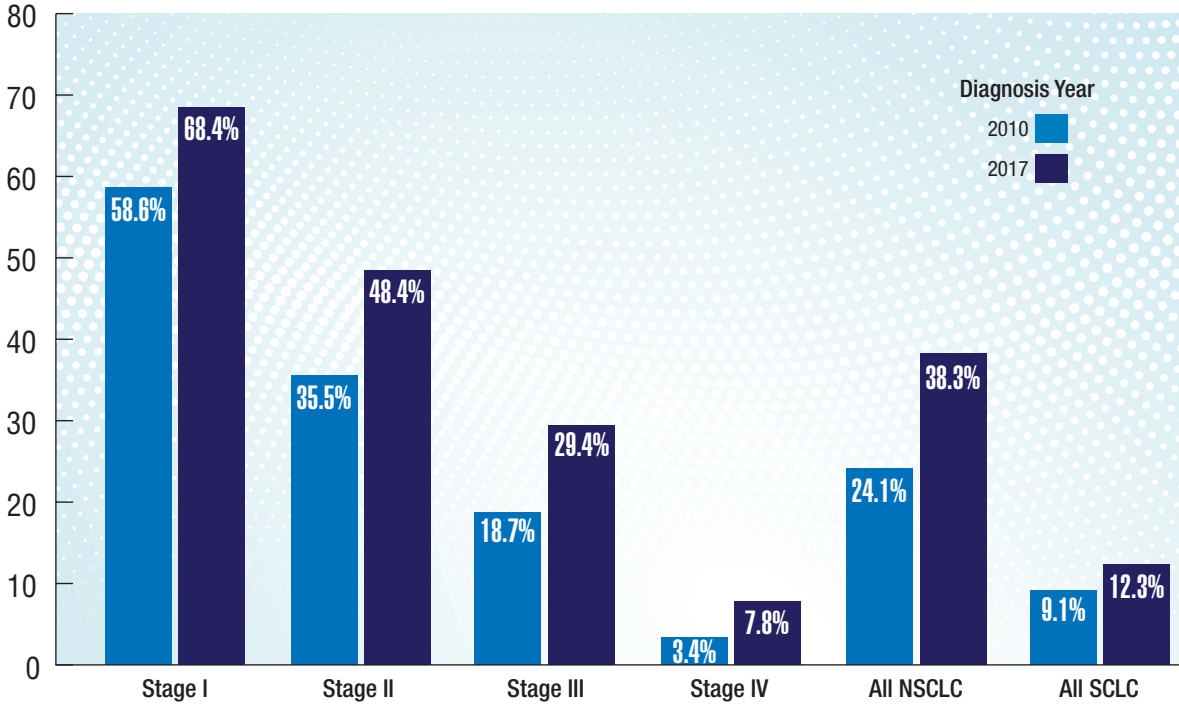
Lung Cancer: Mortality Trends in Veterans and New Treatments

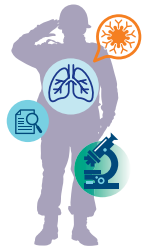
Millie Das, MD

The annual incidence rate of lung cancer among veterans is substantial and increasing, tripling from 2000 to 2017; historically, it was largely due to higher rates of smoking.[1] In recent years, the VHA has aimed to improve survival rates of patients with lung cancer across all disease stages and racial/ethnic groups.[2] These efforts include providing increased screening, molecular testing, and access to targeted therapies; adopting advanced surgical and biopsy techniques; and implementing nurse navigators to guide care.[2]

Veterans often have lung cancers that are strongly associated with smoking, which are less likely to harbor specific driver mutations such as *EGFR* or *ALK* alterations. This can limit the use of targeted therapies specifically designed for these mutations.[1,3] However, newly developed immunotherapy agents, which do not rely on the presence of driver mutations, have shown significant efficacy in patients with non-small cell lung cancer (NSCLC), particularly in cases with high PD-L1 expression.[4-6]

3-Year Overall Survival Trends in Veterans[2]

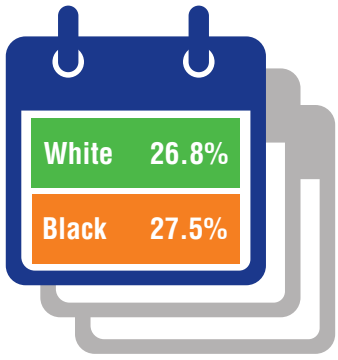




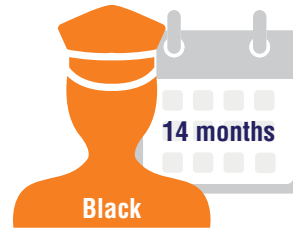
A 2024 study of more than 50,000 veterans with lung cancer diagnosed through the VHA demonstrated improved survival trends regardless of disease stage or type of lung cancer (NSCLC or small cell lung cancer [SCLC]). This finding could be due in part to an observed 68% increase in stage I diagnoses and 11% decrease in stage IV diagnoses, underscoring the positive impact of increased screening and early detection.

Survival Trends by Race in Veterans[2]

3-Year Overall Survival by Race



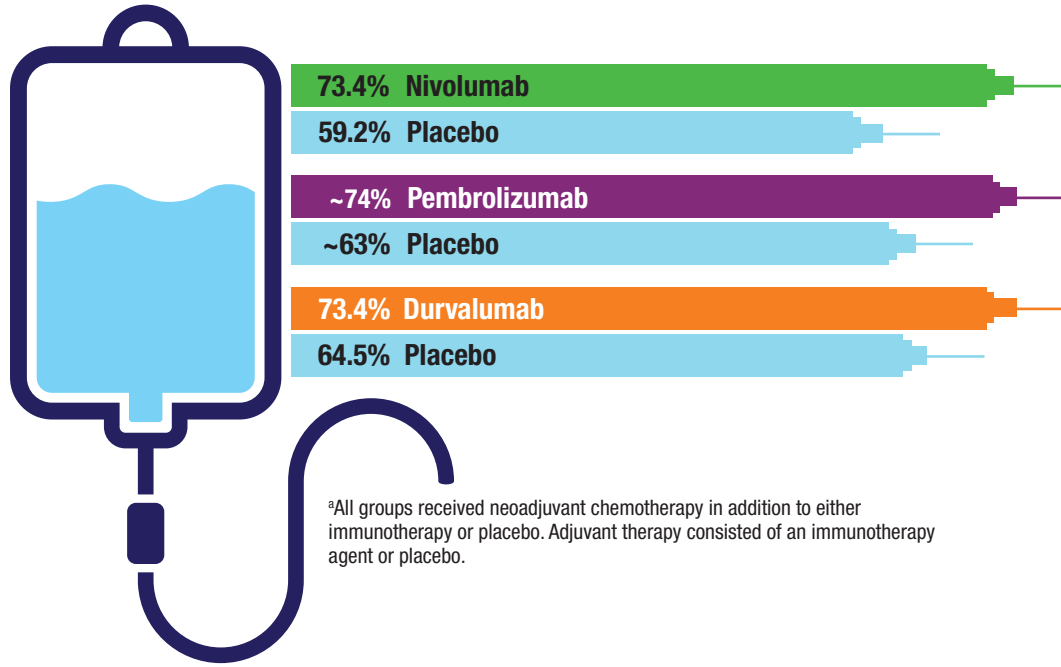
Median Overall Survival by Race



Black veterans had slightly higher lung cancer survival rates, which could be due to equity policy interventions in the VHA compared to those in other health care systems.[2] Black veterans also had higher overall survival specifically for SCLC when subtypes were compared. These trends differ from national trends outside the VA, which usually show worse outcomes for Black patients.[7]

Immunotherapy in Resectable NSCLC[4-6,a]

12-Month Event-Free Survival



[a]All groups received neoadjuvant chemotherapy in addition to either immunotherapy or placebo. Adjuvant therapy consisted of an immunotherapy agent or placebo.

Immune checkpoint inhibitors, such as nivolumab, pembrolizumab, and durvalumab, have demonstrated efficacy in patients with early-stage resectable NSCLC, and their use should be considered in eligible veterans. In particular, the perioperative trials have indicated higher rates of complete pathological response (defined as ≤ 10% residual viable tumor cells in the primary tumor after surgery). For example, nivolumab showed a **25.3% complete pathological response** compared to **4.7% with placebo** and higher rates of event-free survival among patients receiving immunotherapy as part of neoadjuvant and adjuvant treatment vs chemotherapy alone.

Racial Disparities, Germline Testing, and Improved Overall Survival in Prostate Cancer

Michael Goodman, MD

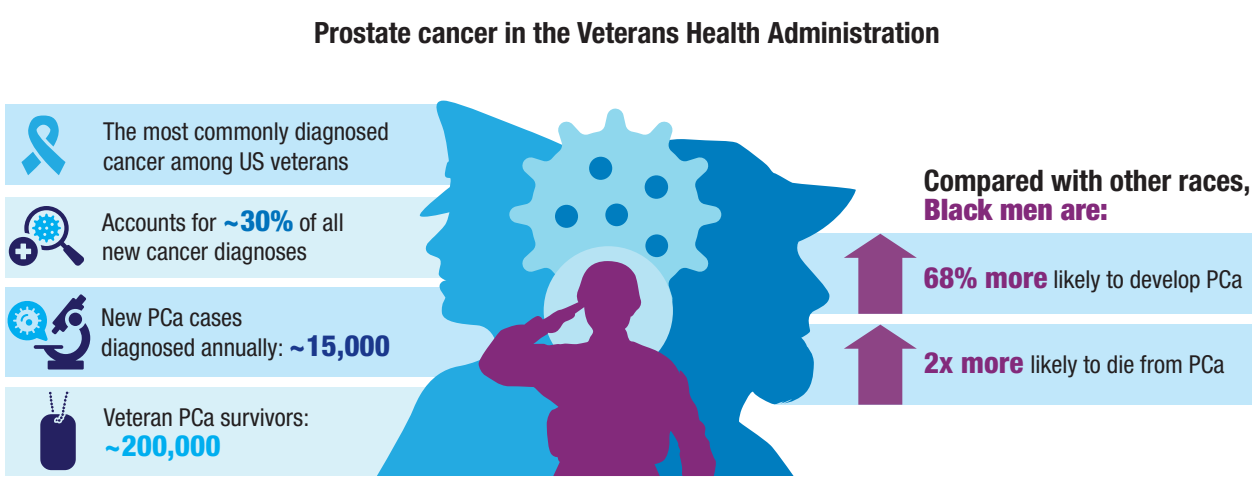
The incidence of prostate cancer (PCa) has been rising[1]; this increase is particularly evident in more aggressive, advanced stages of PCa. Metastatic castration-resistant PCa has a median overall survival (OS) of up to about 2 years and is the second leading cause of cancer-related deaths among men in the United States.[2]

Black men face a significantly higher risk for PCa compared with White men.[1] Researchers have identified variations in the genomic profiles of metastatic PCa cells among US veterans that are potentially linked to race and ethnicity. Study findings represent a significant advancement in understanding genomic alterations in metastatic prostate cancer.[1] This is especially noteworthy for Black men, who have been historically underrepresented in precision oncology research.[3]

A qualitative study of veterans with advanced PCa explored decision-making regarding germline testing. Several veterans with service-connected disability benefits declined testing, fearing it might jeopardize their benefits.[4,5] Consequently, language in the veterans benefits manual was updated, clarifying that genetic results cannot disqualify service-connected benefits and emphasizing the importance of clear communication during counseling.[4]

Significant improvements in median OS for de novo metastatic hormone sensitive PCa were observed in patients diagnosed between 2000 and 2019 in SEER and VHA databases. The gains were notable in patients younger than 70 years, likely driven by the increased adoption of combination therapies.[6]

Prostate Cancer Burden[1-3,7-9]



Race and Genomic Alterations in Metastatic Prostate Cancer[3]

Black Veterans

- Younger age
- Higher prostate-specific antigen at PCa diagnosis
- Less likely to report Agent Orange exposure
- More likely to reside in neighborhoods with health and safety risks

After adjusting for sequenced tissue and clinicopathologic variables, Black veterans also had…

Genomic Alterations

- Higher rates in *SPOP* and immunotherapy targets
- Lower rates in *AKT/PI3K* pathway, AR axis, and tumor suppressor genes (*TP53* and *PTEN*)

The study also found…

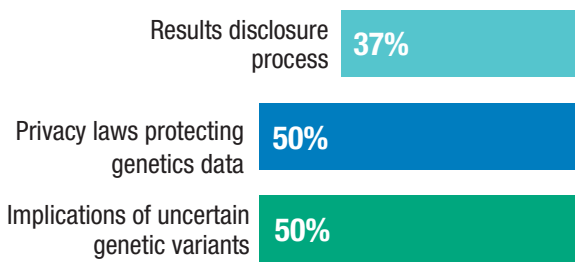
Risk Factors

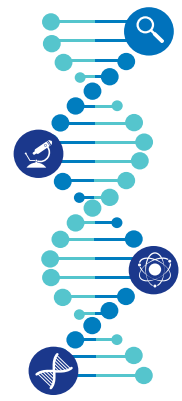
- Men with *TP53* alterations had a 50% higher risk for PCa-specific mortality (PCSM).
- Men with tumor suppressor pathways had a 30% higher risk for PCSM.
- However, race was not independently associated with PCSM.

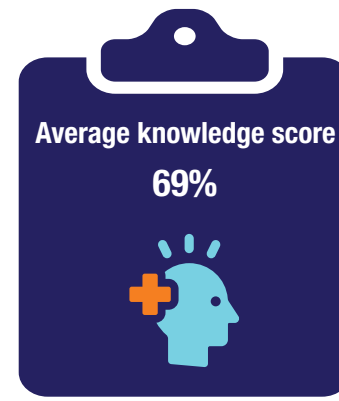
Associations among genomic alterations, race, and PCSM were studied in 5015 veterans with PCa (1784 Black and 3231 White veterans). Findings highlight the need for genetic testing to guide personalized treatments, using *SPOP* alterations to identify therapy targets and linking *TP53* to higher mortality risk.

Veterans' Knowledge of Germline Testing[4,5]

Patients were least knowledgeable about:
(% answering related questions correctly)







Top reasons for declining germline testing:

✘ Fear of losing service-connected disability benefits

Top reasons for desiring germline testing:

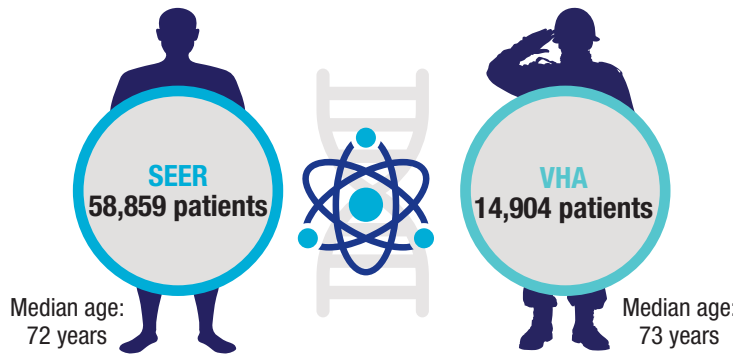
✔ Help family members

✔ Advance knowledge of the disease

Misconceptions regarding service-connected benefits pose a major barrier to germline testing for veterans with advanced PCa. In December 2023, the Veterans Benefits Administration clarified that **genetic test results do not affect previously granted service-connected benefits.** There is a crucial need for ongoing clear, patient-centered precision oncology communication, providing further education and reassurance to empower veterans to make informed decisions about germline testing.

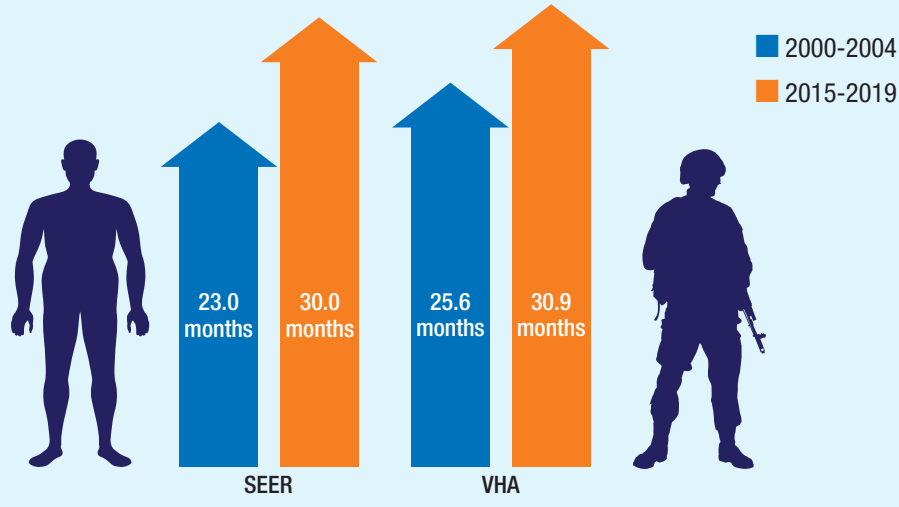
OS Improvement in Metastatic Hormone-Sensitive PCa[6]

Cohort Overview

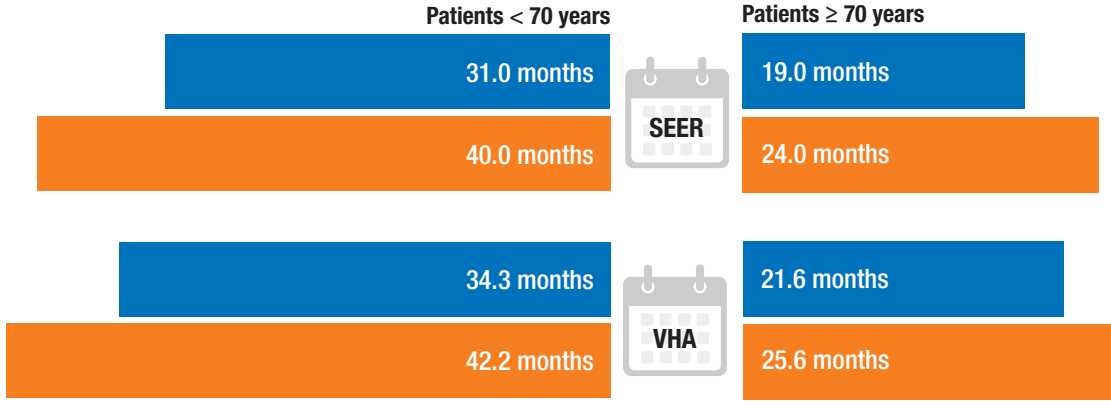


A large cross-sectional study found notable improvements in median OS for de novo metastatic hormone-sensitive prostate cancer in SEER and VHA patients diagnosed from 2000 to 2019. This was especially the case in patients younger than 70 years, likely because of increased use of combination therapies. However, outcomes remain poor for patients aged 80 years and older, underscoring the need for tailored treatments that take into account comorbidities and genetic factors.

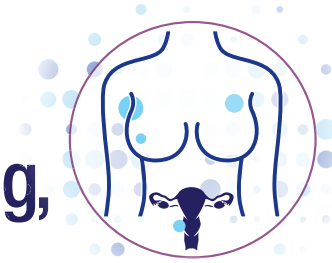
OS Improvement Over Time



OS by Age Group



Breast and Uterine Cancer: Screening Guidelines, Genetic Testing, and Mortality Trends

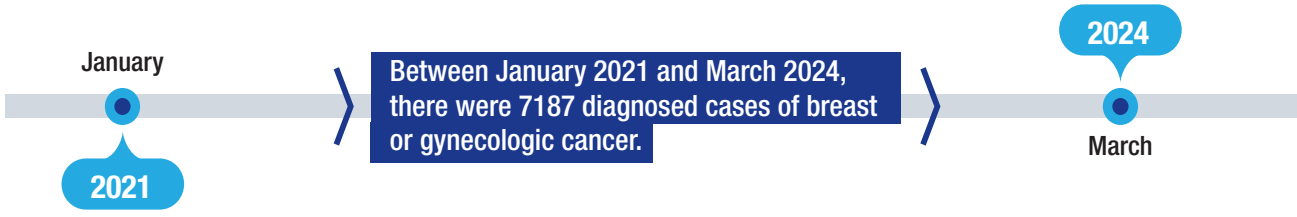


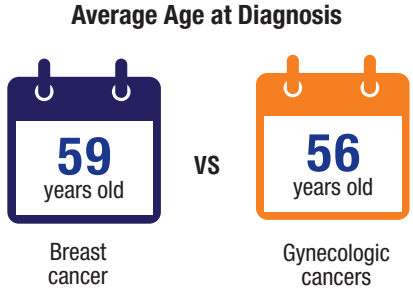
Haley A. Moss, MD, MBA

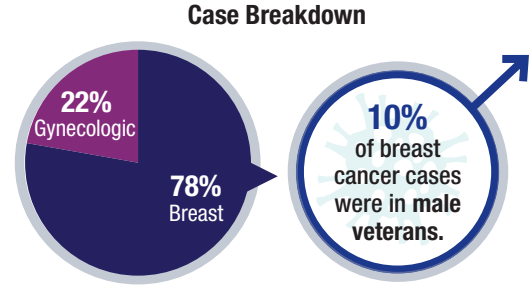
The VHA Breast and Gynecologic Oncology System of Excellence (BGSoE), established in 2021, provides comprehensive, high-quality cancer care tailored to veterans diagnosed with breast and gynecologic cancers and those considered high-risk based on genetic testing or family history.[1] Since its inception, the BGSoE has supported more than 7000 patients.[1] For breast cancer, new USPSTF guidelines now recommend initiating biennial mammography at age 40, reflecting efforts to address rising incidence in younger populations.[2] The VHA recommends genetic testing for all veterans diagnosed with invasive breast cancer in order to expand access to targeted therapies, facilitate risk reduction for seconday cancers, and enable cascade testing for at-risk family members.[3,4]

Uterine cancer is a growing concern for veterans, with rising incidence and mortality, particularly in aggressive nonendometrioid subtypes.[5,6] Black women in particular have higher uterine cancer mortality rates. This is of particular relevance within the VA, as Black women are overrepresented compared to the general population.[6,7] This disparity underscores the need to improve outcomes for all patients while prioritizing targeted interventions for Black women.

Women Veterans Treated Through the BGSoE[1]

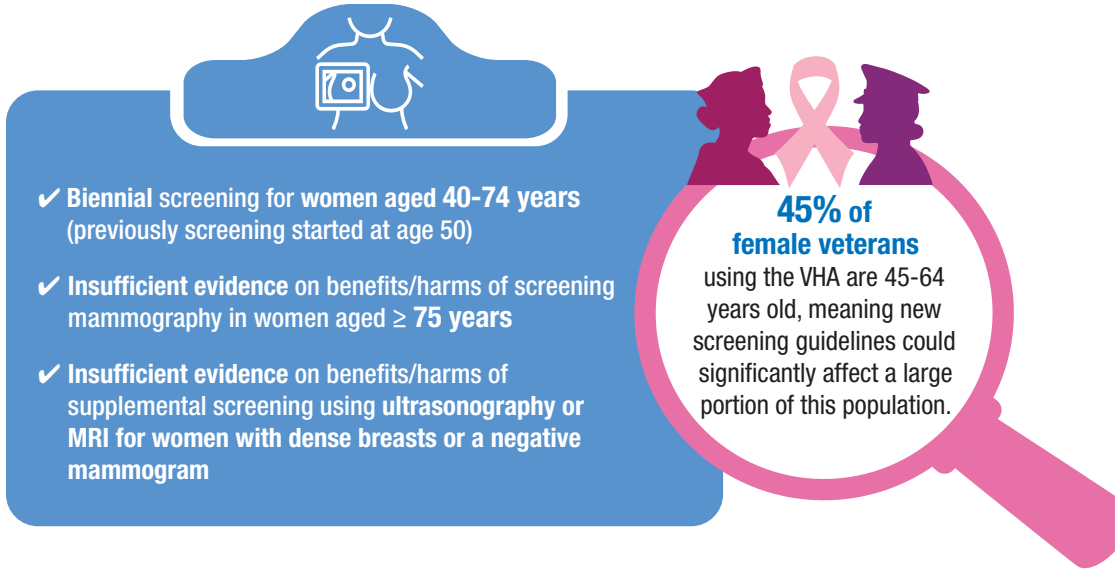






Within the veteran population, women are the fastest-growing group and face considerable risk factors for cancer. The VHA established the BGSoE to provide teleoncology and other cancer navigation services to women veterans. The VA is ensuring review of these programs through the Center for Oncology Outcomes Review and Gender (COURAGE).

Updated 2024 Breast Cancer Screening Guidelines[2,8]

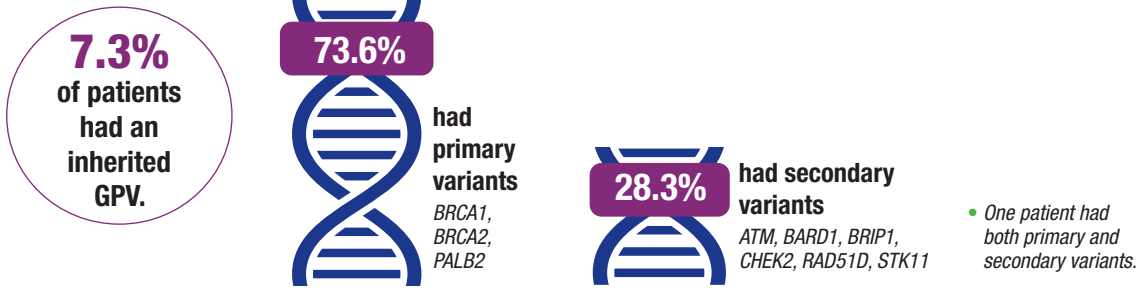


Breast cancer incidence is increasing among younger women, with a **2.0% average annual increase in incidence from 2015 to 2019 in women aged 40 to 49 years.** In response, the USPSTF updated its guidelines to start screening as early as age 40.[2] Other breast cancer screening guidelines, such as those for the National Comprehensive Cancer Network (NCCN) and the American Cancer Society (ACS), have also lowered the screening age for average risk to age 40.[9,10]

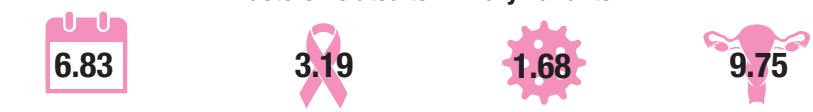
Universal Genetic Testing in Breast Cancer[4]

Traditional genetic testing criteria misses a portion of cases that could benefit from targeted therapies such as polyadenosine diphosphate polymerase (PARP) inhibitors, **with 5-10% of breast cancer cases associated with germline pathogenic variants (GPVs).** As genetic testing costs decrease and more treatments become available, there has been a push for universal genetic testing to help identify additional patients who may have otherwise been considered ineligible for targeted therapies. A recent study sought to evaluate the prevalence of GPVs in an ethnically diverse cohort of women with newly diagnosed invasive breast cancer.

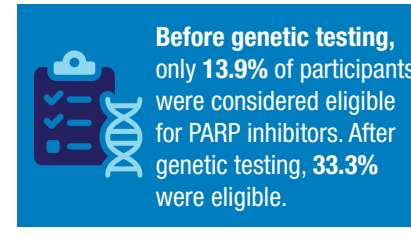
Of the patients who had GPVs,



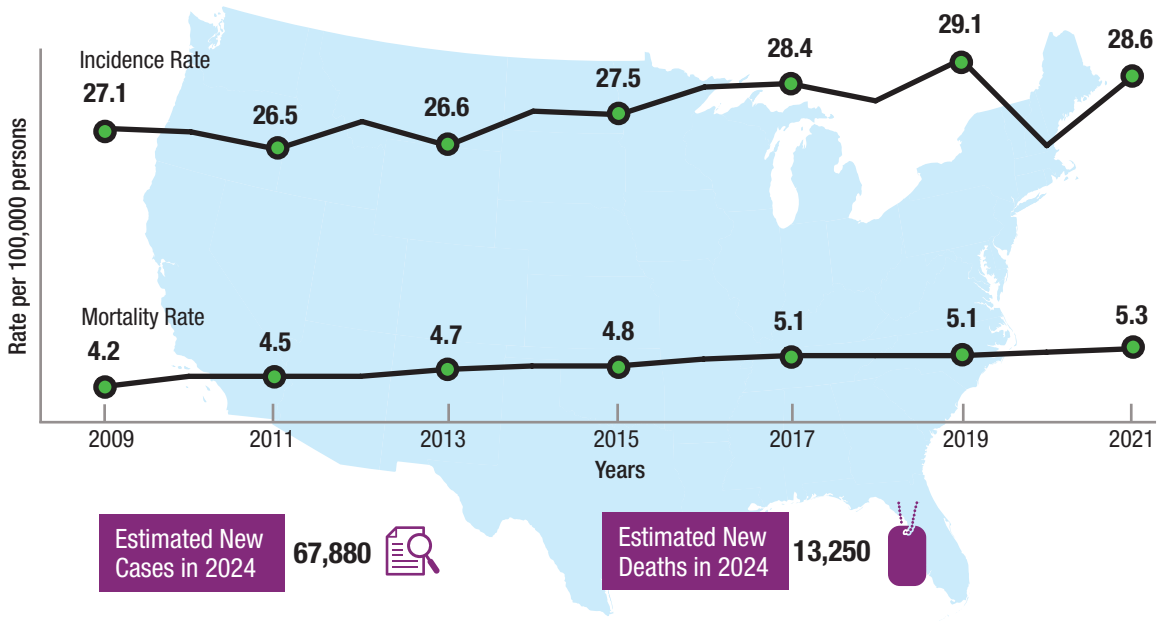
Factors Related to Primary Variants



Shown as odds ratios



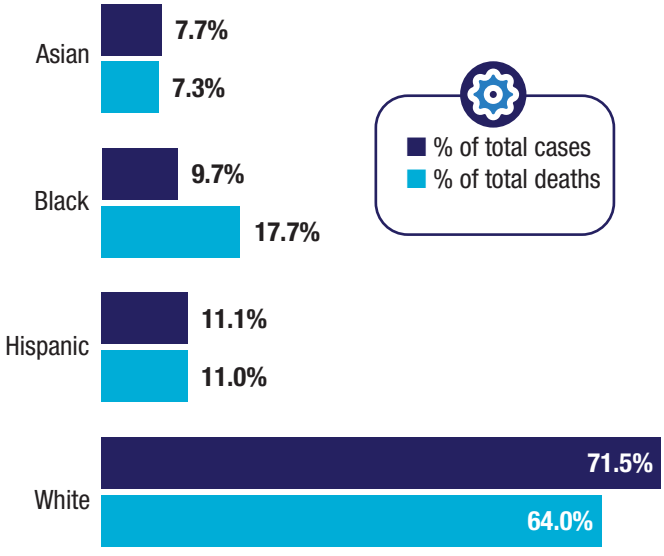
Uterine Cancer US Incidence and Mortality Rates[5]



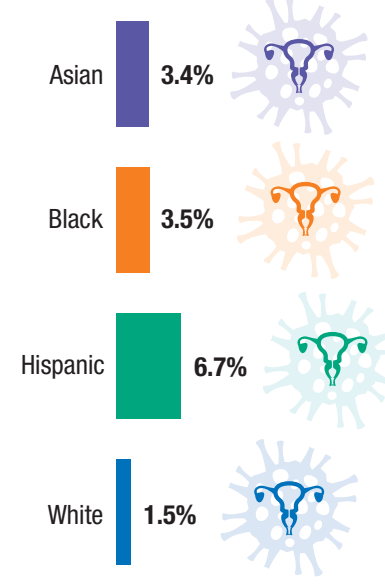
In most cancers, coinciding with increasing incidence, mortality tends to decrease, owing to the availability of new treatments. **Uterine cancer is one of the few cancers with both rising incidence and mortality and without a clear cause or specific factor to address.**[5] The average annual percent increase in uterine cancer mortality is highest in women aged 49 years and younger.[11]

US Racial/Ethnic Uterine Cancer Trends[6]

Uterine Cancer Diagnoses and Deaths by Race/Ethnicity



Annual Mortality Rate Increases in Nonendometrioid Cancers



Racial disparities in uterine cancer are evident across incidence, subtypes, and mortality. Incidence of aggressive nonendometrioid subtypes, which **disproportionately affect Black women,** is increasing. Uterine cancer mortality rates are also **higher among Black women, who account for < 10% of incident uterine cancer cases but nearly 18% of the total deaths** from the disease.[6] Within in the VA, Black women also comprise a higher percentage of uterine cancer cases.[7]

HCC Updates: Quality Care Framework and Risk Stratification Data

Janice Jou, MD; Cynthia Moylan, MD, MHS

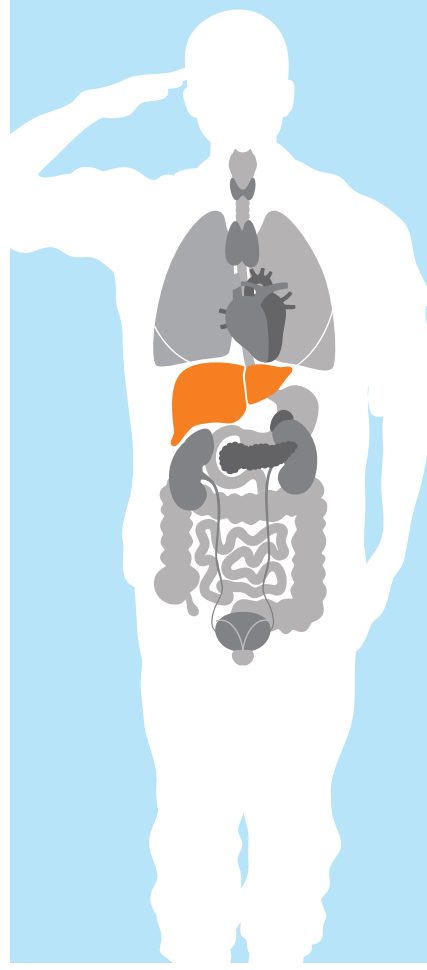
The VA National Gastroenterology and Hepatology Program, the largest provider of cirrhosis care in the United States, recently examined factors related to hepatocellular carcinoma (HCC) diagnosis stage, treatment options, and patient survival in veterans in a retrospective study.[1] The results emphasize the value of HCC screening and continuous patient engagement for improving diagnosis, treatment, and survival outcomes for veterans. They also demonstrate the practicality of creating a national quality improvement framework for HCC screening, diagnosis, and care.[1]

Veterans with cirrhosis due to chronic hepatitis C virus (HCV) remain at risk for HCC, even after achieving a sustained virological response (SVR). A 2024 retrospective cohort study of veterans with HCV-related cirrhosis concluded that liver stiffness measurement post-SVR could help stratify HCC risk.[2] These data highlight the importance of ongoing HCC screening and active patient engagement to improve survival and, ultimately, quality of life for veterans living with this condition.

Factors Influencing HCC Diagnosis, Treatment, and Survival[1]

More than 2300 veterans were diagnosed with HCC in 2021.

Of this group, **199 cases** were evaluated in a random subsample to assess factors associated with HCC diagnosis stage, treatment, and survival.



Key Demographics

71
Average Age

72%
Underlying Cirrhosis

Stage at Diagnosis

Early Stage (T1 or T2): **54%**

Factors Associated With Early-Stage Diagnosis:

- ✔ Receipt of VA primary care
- ✔ HCC diagnosis within the VA system
- ✔ Consistent screening for HCC prior to diagnosis
- ✔ Less advanced liver disease

Treatment Overview

73% Received liver-directed treatments

Median time to treatment: **37 days** (Range: 19-54 days)

35% Received potentially curative treatments

Factors greatly influencing receipt of treatment and better survival outcomes included:

HCC screening

Cirrhosis diagnosis
These patients are more likely to be screened regularly.

Early stage at diagnosis

Better performance status

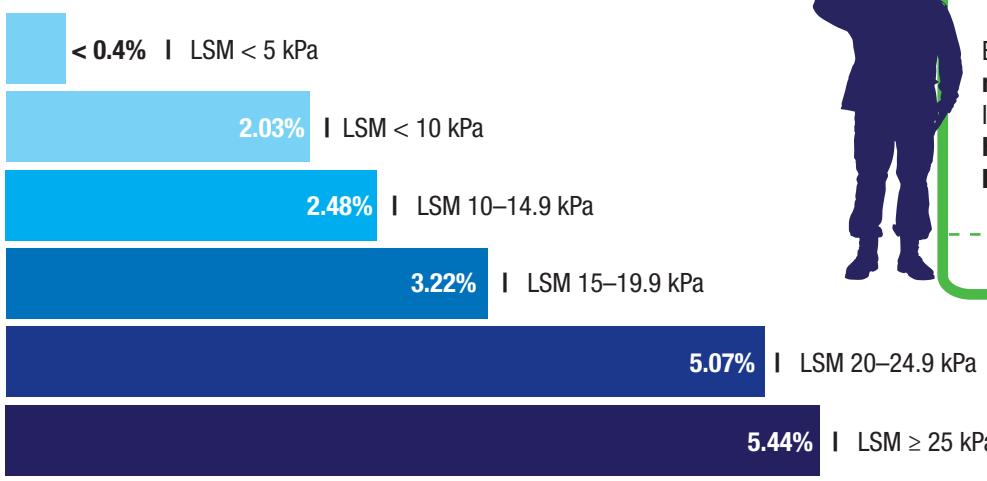
Receiving VA primary and liver care before diagnosis

Veterans without consistent primary care (VA or non-VA) were often diagnosed with HCC later because of gaps in screening and monitoring. Treatment delays were largely attributed to scheduling challenges (particularly outside the VA), advanced-stage disease at diagnosis, challenges with transportation, and patient preference.[1]

Liver Stiffness, Chronic HCV Cirrhosis, and HCC Risk[2]

To better understand the role of liver stiffness measurement (LSM) (using vibration-controlled transient elastography) as a predictive tool for HCC risk, a retrospective study examined 1850 veterans with chronic HCV cirrhosis and sustained virological response (SVR) for a follow-up of nearly 5100 person-years.

Adjusted Annual Risk for HCC by LSM Levels



HCC Risk:

Every 1-kPa increase in LSM **raises HCC risk by 3%**...
longer time since SVR **reduces HCC risk significantly, by 21%** risk reduction per year

LSM is a valuable predictor of HCC risk in patients with HCV cirrhosis after SVR and can identify portal hypertension-related complications and guide surveillance decisions. Patients with LSM < 5 kPa and no diabetes may discontinue surveillance because of low HCC risk.[2]

Rising Kidney Cancer Cases and Emerging Treatments for Veterans

Matthew Boyer, MD

Cases of kidney cancer, also known as renal cell carcinoma (RCC), are increasing, with more than 81,600 expected diagnoses in 2024, largely due to improved imaging and rising rates of risk factors, including obesity, hypertension, and diabetes.[1,2] Veterans, particularly those exposed to chemicals and perfluoroalkyl and polyfluoroalkyl substances (PFAS), face a higher risk for RCC. Under the PACT Act, RCC may be recognized as service-related for Gulf War and post-9/11 veterans.[3,4]

RCC accounts for more than 90% of kidney cancers and is often asymptomatic, making early detection reliant on an incidental finding on imaging.[4,5] Treatment for localized RCC typically involves surgery, with adjuvant immunotherapy for high-risk cases, though up to 50% of patients may still experience recurrence.[6] Emerging treatments like stereotactic body radiotherapy (SBRT) are gaining attention for managing inoperable or high-risk RCC as it has demonstrated high rates of effectiveness, local control, and strong survival outcomes; however, further comparison with surgical options is needed.[7] Advances in adjuvant therapies for kidney cancer emphasize the potential to extend survival for high-risk patients post-surgery, but balancing the benefits with risks of this treatment remains crucial.[8]

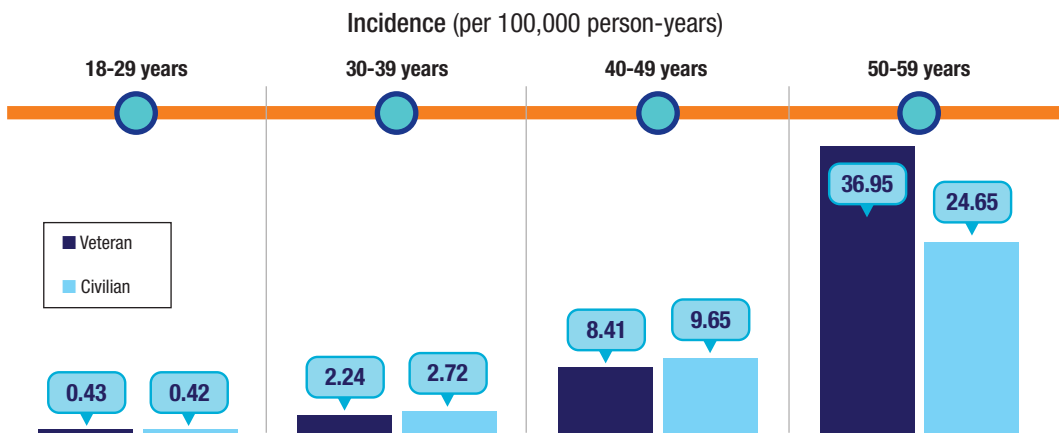
Kidney Cancer Incidence in Active Duty Servicemen[9]

From SEER

Study Population

Men aged 18-59 years,
diagnosed with
malignant kidney cancers between
1990 and 2013

From the DoD Automated
Central Tumor Registry (ACTUR)



Kidney cancer incidence was lower in younger and Black servicemen but higher for those aged 50 to 59 years compared with civilians. General health and health care access may influence these rates, though military exposures may affect older servicemembers. There were no differences observed by disease stage.

RCC Treatment[7,8]

Treatments and Recent Studies

Surgery

Standard of care for primary RCC

Focal Therapy

✔ **SBRT:** Inoperable or high-risk cases

✔ **Ablation:** Small tumors or cases ineligible for surgery

Systemic Therapy

When cancer has spread or is considered high-risk

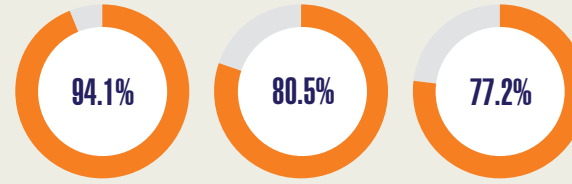
✔ **Immunotherapy:** PD-1 (pembrolizumab, nivolumab) and CTLA-4 (ipilimumab) inhibitors

✔ **Targeted therapy:** Tyrosine kinase inhibitors (sunitinib, cabozantinib) and vascular endothelial growth factor receptor inhibitors

✔ **Combinations:** Immune + Targeted Therapy

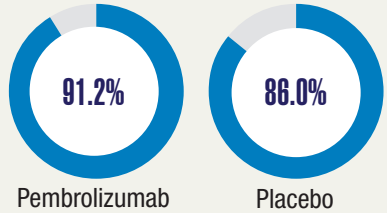
A systematic review of 36 studies assessed the use of **SBRT** as a **noninvasive option for primary RCC.**

SBRT was found to be both **safe and effective** in this setting.

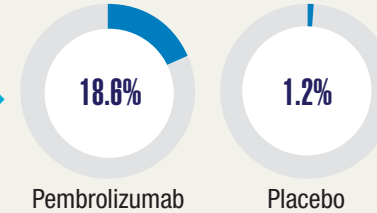


Pembrolizumab was approved in the adjuvant setting following surgery for RCC based on significant improvement in disease-free survival in the KEYNOTE-564 trial. In 2024, a separate analysis of this study examined its **impact on overall survival.**

Overall survival at 48 months

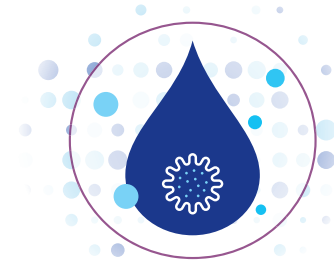


Incidence of treatment-related grade 3 and 4 adverse events



Pembrolizumab provided significant improvement in overall survival and disease-free survival after surgery for high-risk patients compared with placebo. It was also associated with higher incidence of serious adverse events.

Advances in Blood Cancer Care for Veterans



Thomas Rodgers, MD

Hematologic malignancies encompass a broad range of distinct cancers, generally categorized as lymphoid (eg, lymphoma), myeloid (eg, leukemia, myelodysplastic syndromes, myeloproliferative neoplasms [MPNs]), and plasma cell neoplasms (eg, multiple myeloma).[1] The veteran population is aging; this, in combination with other potential veteran-specific risk factors, is leading to an increased risk of hematologic malignancies.[2] Of note, the risk for MPN diagnosis has recently been studied in veterans who served during the Korean, Vietnam, and Persian Gulf War eras.[3] In addition, survival trends for different blood cancers, such as lymphoid malignancies, vary among veterans exposed to Agent Orange.[4] Conflicting results have been found that point to the importance of future research.[4]

Veterans in rural areas face barriers to treatment and clinical trial enrollment due to long travel distances and lack of trial availability, creating what are termed "clinical trial deserts."[5] Teleoncology has become crucial in bridging this gap by improving access to blood cancer treatments and clinical trials.[5,6] Novel decentralized trial designs involving telehealth can further expand participation in remote areas.[5]

Over the past year, there have been advances in the treatment of blood cancers as well as the use of large data sets to better understand cancers trends and new technologies to reduce disparities in access to care.[6,7] The availability of greater therapeutic options, new care modalities, and improved risk assessments herald an exciting time in the care of patients with hematologic malignancies, with the expectation that this care will continue to advance through 2025.

Risk and Survival Outcomes in Veterans With Blood Cancers[3,4]

Myeloproliferative Neoplasms (MPN)

Persian Gulf War–era veterans had the **highest risk for MPN** among the 3 service periods studied.

- **4.9 ×** higher risk vs Korean War era
- **2.5 ×** higher risk vs Vietnam War era

They also had the **lowest survival rates…**

- **5.6 ×** lower vs Korean War era
- **2.4 ×** lower vs Vietnam War era

…and were diagnosed at an earlier age.

- **67.5%** diagnosed at age < 50 years
- vs **13.6%** of all veterans with MPN

A study of veterans from 3 war eras sought to evaluate the connection between service period and MPN development.[3] Persian Gulf War–era veterans were found to have MPN more often than veterans from the Korean and Vietnam War eras.

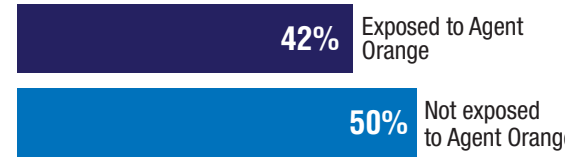
Persian Gulf veterans with MPN characteristics also had **higher risk for thrombosis and bleeding.**

Lymphoid Diseases

Median Overall Survival

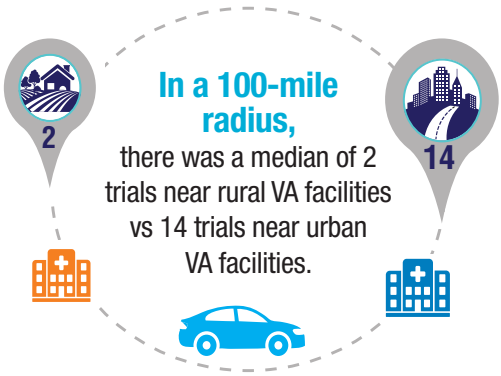
	Veterans **exposed** to Agent Orange		Veterans **not exposed** to Agent Orange
Diffuse large B-cell lymphoma (DLBCL)	8.0 years	vs	5.3 years
Hodgkin lymphoma	12.4 years	vs	8.7 years
Marginal zone lymphoma	15.3 years	vs	11.5 years

Deaths



Vietnam War–era veterans with lymphoid malignancy exposed to Agent Orange showed longer survival than non-exposed veterans, with no differences in number of comorbidities or amount of alcohol use. This could have potentially been due to increased health care utilization in those exposed to Agent Orange but this was only the case for patients with mantle cell lymphoma and not other subtypes.[4]

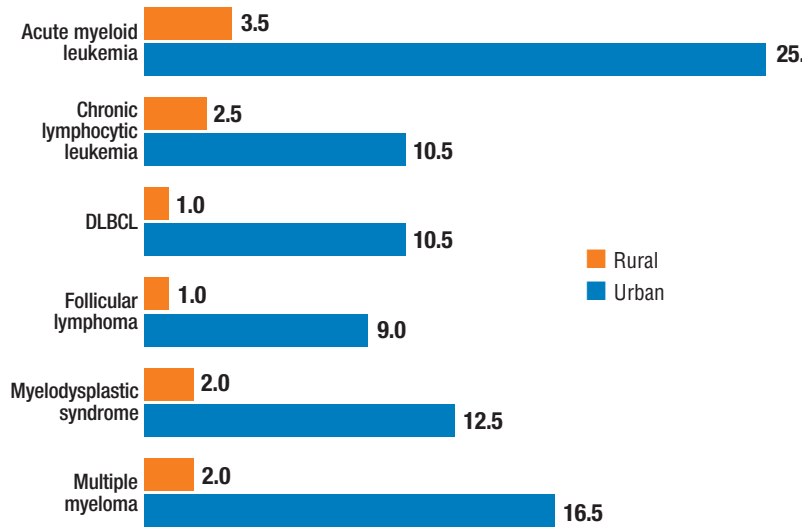
Expanding Blood Cancer Care for Rural Veterans[5,6]



A 2024 study evaluating trial availability in proximity to 13 VA medical centers identified rural areas as "clinical trial deserts." The study also explored provider referrals and patient interest in clinical trials. Over 16 months, **9% of veterans who expressed interest followed through with enrollment.**

Median Number of Clinical Trials by Blood Cancer Type

within a 100-mile radius of VA facilities



Teleoncology in the VA[6]

35 hematology/oncology physicians from across the country work through the National TeleOncology (NTO) Program virtual hub in Durham, North Carolina.

Lymphoproliferative diseases, such as chronic lymphocytic leukemia, are the 3rd most common diagnosis in NTO (following prostate and lung cancers).

Teleoncology care at the VA continues to increase and uses a range of different modalities, such as video consults and telephone visits. Video visits comprise 10%-12% of all VA outpatient care, **representing a 2300% increase from the pre-pandemic era.**

AI-Based Risk Stratification for Oropharyngeal Carcinomas: AIROC

Vlad Sandulache, MD, PhD

In recent years, human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPSCC) has been on the rise in the veteran population, where smoking rates (a contributor to OPSCC development) have historically been higher than in the general population.[1] Variable treatment response rates and survival in patients with OPSCC indicate that whereas some patients may benefit from treatment de-escalation and a concomitant reduction in treatment-related adverse effects, aggressive disease in a subset of patients mandates the use of rigorous chemoradiation treatments.[2,3] At present, effective stratification systems identifying these patient subsets are lacking.[4]

To address this clinical gap, a team of VA clinicians and researchers is developing AIROC (an artificial intelligence [AI]-based risk stratification algorithm for oropharyngeal carcinomas).[a] AIROC is an AI and machine learning (ML)-based algorithm that may successfully stratify veterans with HPV-associated OPSCC into risk categories that can enable safer de-escalation or escalation of cancer treatments.[5-7] By integrating AIROC into clinical practice, the VHA aims to personalize cancer treatment, improve patient outcomes, and establish a new standard of care for veterans with this deadly disease.

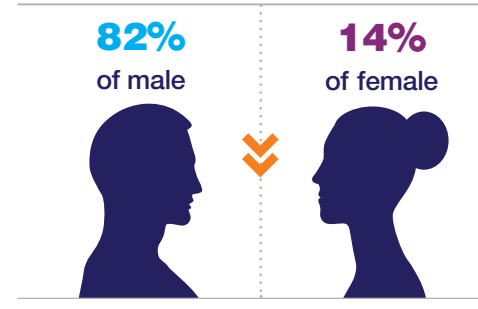
[a]This work is funded by the Veterans Affairs Clinical Science Research and Development (CSRD) Service (grant I01BX006380).

A Clinical Problem in the United States[1,8-10]

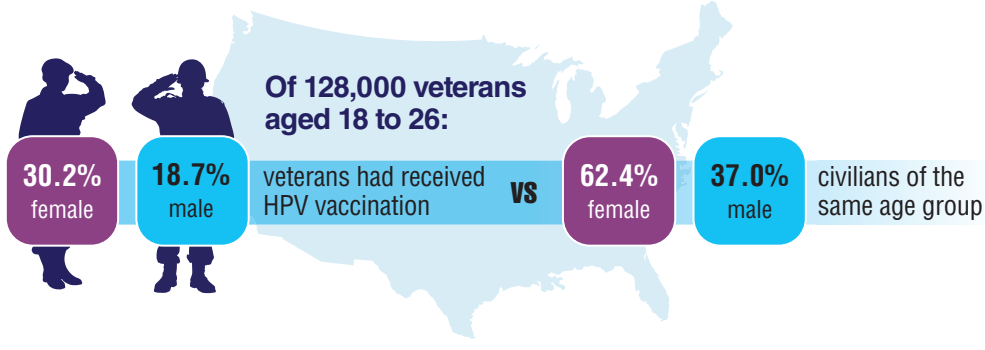
Estimated New OPSCC Cases in 2024: 58,450
Including both HPV- and non-HPV-related cases

Incidence of OPSCC is **rising 3x faster** in US veterans than civilians.

Each year, OPSCC accounts for…



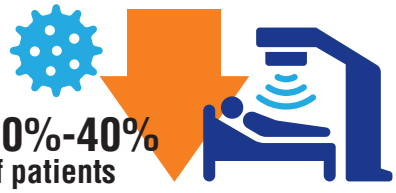
HPV-associated cancer cases



HPV-associated cancers cause substantial clinical and economic burden to the VHA. There are no vaccination requirements or campaigns targeting the young veteran and active-duty populations. These low HPV vaccination rates will contribute to thousands of avoidable HPV-associated cancers and cancer-related deaths over the coming decades.

Modifying Treatment Intensity

HPV-associated OPSCC demonstrates highly variable response rates to conventional chemoradiation. It is estimated that:



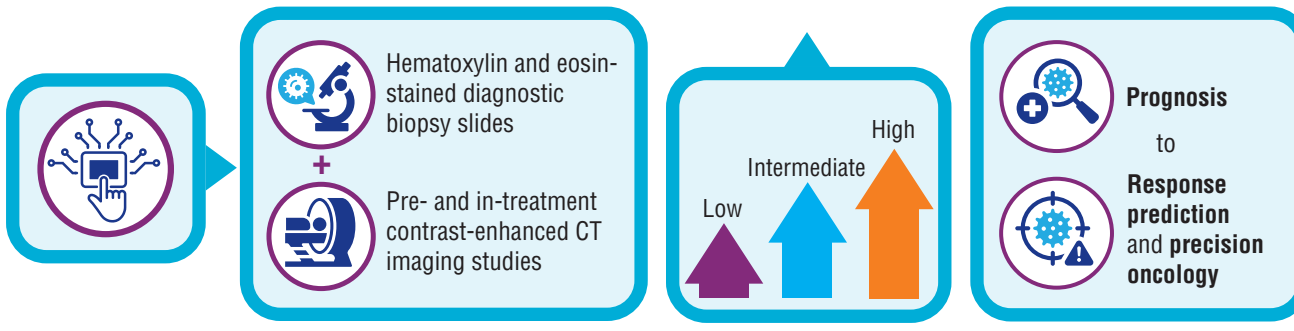
30%-40%
of patients
could have treatment intensity reduced, while sustaining efficacy and reducing treatment-associated morbidity and mortality.

40%
of patients
whose aggressive disease is linked to high recurrence and distant metastasis **could benefit from treatment escalation.**

Current unselective approaches to de-escalation and escalation have not demonstrated success, generating a significant unmet clinical need.

AIROC: Objectives and Innovation[4,11-13]

AI and ML-based analysis of image patterns from:



Veterans with OPSCC are then classified by calculated disease risk:

This helps better stratify patients for future clinical trials, shifting the focus from:

American Joint Committee on Cancer Staging System (AJCC, 8th Edition) vs AIROC

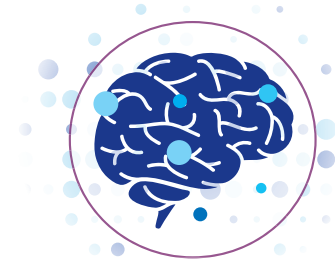
Currently the most refined risk stratification system for HPV-associated OPSCC

- Dominated by tumor and nodal stage, accounting for HPV status
- Does not consider non-HPV risk factors (eg, tobacco exposure)
- Fails to sufficiently stratify patients for treatment escalation or de-escalation as appropriate

A novel approach that builds on the AJCC staging system while capturing previously unavailable features of disease biology from clinically available radiomic and pathomic datasets

- Incorporates data from the tumor itself with data from the tumor microenvironment (TME) and the tumor immune microenvironment (TIME)
- Uses features from the tumor (multinucleation), TME, and TIME (lymphocyte infiltration and distribution), which have all been linked to treatment response and survival
- May accurately identify patients with OPSCC who could safely undergo treatment de-escalation and those with aggressive disease

Brain Cancer: Epidemiology, TBI, and New Treatments



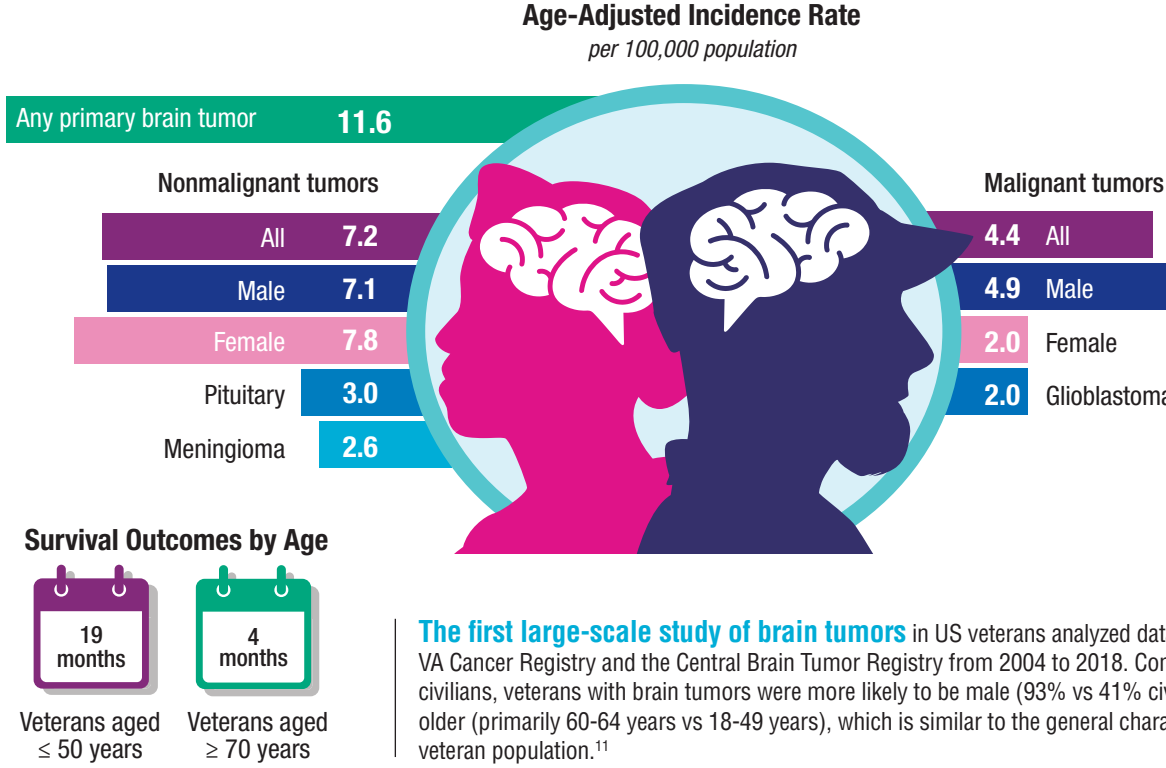
Margaret O. Johnson, MD, MPH

Brain cancer represents a notable health challenge for veterans. The first large-scale study on brain tumors in US veterans showed that the most frequently diagnosed tumors were nonmalignant pituitary tumors, nonmalignant meningiomas, and glioblastomas.[1] Exposure to combat-related traumatic brain injuries (TBIs) may contribute to the risk for brain tumors, and further research is ongoing.[2,3] A 2024 study demonstrated that veterans with moderate/severe and penetrating TBIs had an increased risk of brain cancer, but previous research in civilians has not echoed these findings.[2,4]

As our understanding of the connection between TBI and brain cancer evolves, health care initiatives and new research are aiming to serve the veteran population most at risk. Telehealth is being used throughout the VA to help veterans, especially those in rural locations, receive neuro-oncology care.[5,6] In terms of research, the DoD and Uniformed Services University have established a Brain Tissue Repository. This program may be better able to explore the TBI/brain cancer connection through veteran brain tissue donation.[3]

New assays are also being developed to help identify brain cancer faster. Liquid biopsy techniques focused on *IDH1* have shown promise.[7] In terms of treatment, the IDH1/IDH2 inhibitor vorasidenib prolonged progression free survival in grade 2 *IDH*-mutant gliomas in clinical trials and was approved by the FDA in 2024.[8,9] Although not pertaining directly to the veteran population, a new treatment for pediatric brain tumors also was approved by the FDA in 2024.[10] These milestones reflect an encouraging trend in precision medicine, opening doors for more targeted brain tumor therapies and tools across various patient groups.

Brain Tumors in Veterans[1]

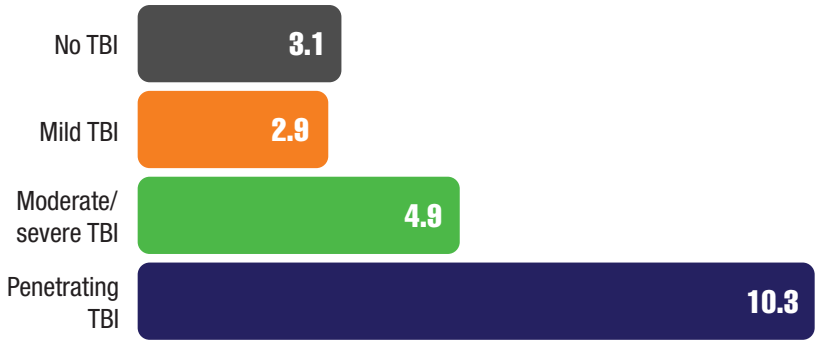


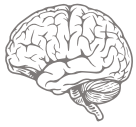
The first large-scale study of brain tumors in US veterans analyzed data from the VA Cancer Registry and the Central Brain Tumor Registry from 2004 to 2018. Compared with civilians, veterans with brain tumors were more likely to be male (93% vs 41% civilians) and older (primarily 60-64 years vs 18-49 years), which is similar to the general characteristics of the veteran population.[11]

TBI and Brain Tumor Risk in Veterans[2]

Brain Tumor Incidence by TBI Severity

per 100,000 person-years

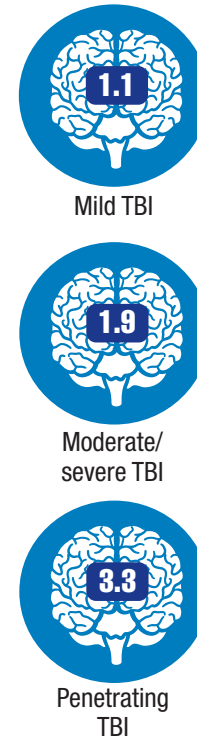




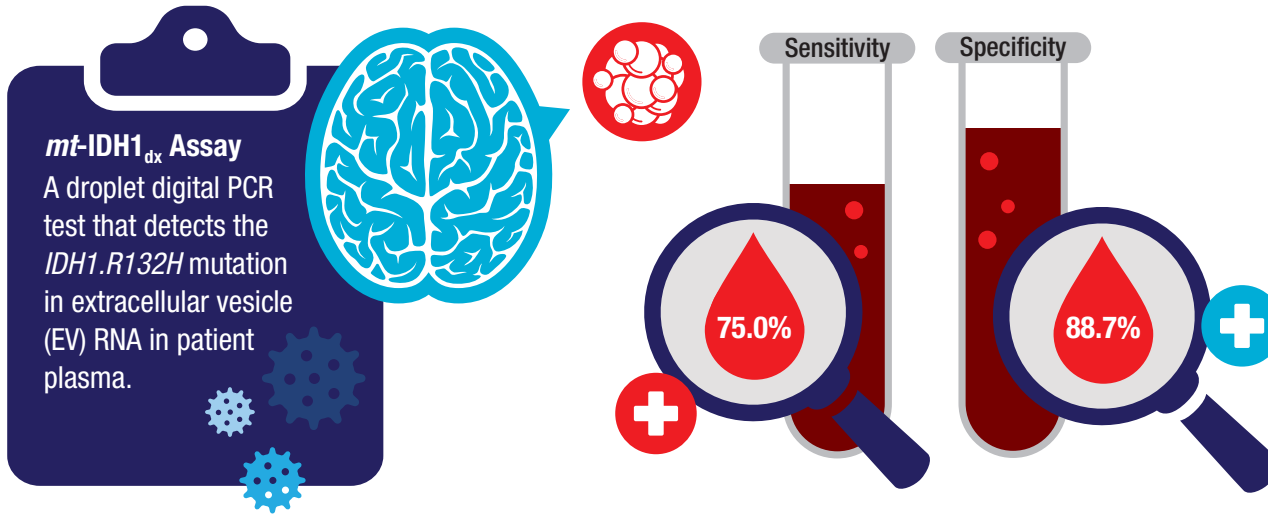
In a study of US veterans from the post-9/11 Iraq and Afghanistan wars, researchers identified an association between TBI and brain cancer. Although mild TBI showed no significant link, the findings suggested that **more severe TBI may be associated with risk for brain cancer,** highlighting the potential for long-term health consequences of combat-related head injuries.

Brain Cancer, by TBI Severity

Based on adjusted hazard ratios



Investigational Blood-Based Assay for *IDH*-Mutant Gliomas[7]



Neuroimaging followed by tissue confirmation via biopsy or resection is the current standard for diagnosis of *IDH*-mutant gliomas. Liquid biopsy techniques, which may be faster and less invasive than tissue biopsies, are being explored for glioma, **with the mt-IDH1$_{dx}$ assay showing promise in early-stage testing.** Beyond diagnosis, these tools could also be used in **monitoring disease progression and providing prognostic information.** In addition, cerebrospinal fluid-based tests are also being investigated.[12]

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