Oncology
Learning Network

Prostate Cancer Care in the Veterans Administration (VA) Health System

Adapting and Integrating Evolving Innovation in the Treatment of De Novo mHSPC

Supported by an educational grant from AstraZeneca

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Faculty Disclosures

- **Dr. Graff** has disclosed no relevant financial relationship with any ineligible company (commercial interest)
- **Dr. Savage:** Advisory Board—Janssen; consultant—Prodeon; Speakers' Bureau—Tempus

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Learning Objectives

- Evaluate factors, including the impact of chemical exposures during military service, that influence the risk of developing PC in VA patients
- Evaluate VA patient-centered care strategies to improve de novo mHSPC diagnosis, treatment, and outcomes, including early immunohistochemistry and PTEN testing and advanced diagnostic imaging tools for measuring risk stratification and prognosis
- Apply strategies to reduce disparities, enhance clinical trial access and enrollment, and improve shared decision-making in veteran patient populations with de novo mHSPC in the comprehensive care model of the VA health system

mHSPC = metastatic hormone-sensitive prostate cancer; PC = prostate cancer; PTEN = phosphatase and tensin homolog.

Prostate Cancer Care in the Veterans Administration (VA) Health System: Adopting and Integrating Evolving Innovation in the Treatment of De Novo mHSPC

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Matanya [commons.wikimedia.org. Last updated November 12, 2012. Accessed September 10, 2024. https://commons.wikimedia.org/wiki/File:Flickr_-_The_U.S._Army_-_Vietnam_smoke_bomb.jpg.

Agent Orange Exposure and Cancer Associations

Sufficient evidence of an association	• Soft-tissue sarcoma • Non-Hodgkin lymphoma • Hodgkin disease • Chronic lymphocytic leukemia (CLL)
Limited/suggestive evidence of an association	• Respiratory cancers (lung, trachea/bronchus, larynx) • **Prostate cancer** • Multiple myeloma
Inadequate/insufficient evidence to determine whether an association exists	• Hepatobiliary cancers • Nasal/nasopharyngeal cancer • Bone cancer • Breast cancer • Female reproductive cancers • Urinary bladder cancer • Renal cancer • Testicular cancer • Leukemia (other than CLL) • Skin cancers • Acute myelogenous leukemia in the children of veterans
Limited/suggestive evidence of NO association	• Gastrointestinal cancers • Brain tumors

Frumkin H. *CA Cancer J Clin*. 2003;53(4):245-255.

Agent Orange (AO)

1962-1971

Operation Ranch Hand

19 million gallons of herbicide on 3.6 million acres to remove forest cover, destroy crops, and clear vegetation in Vietnam

Phenoxy herbicides

2,4-dichlorophenoxyacid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T)

1970-1971

1970

2,4,5-T found to cause birth defects in animals; use of it was suspended in Vietnam

1971

Use of all military herbicide in Vietnam stopped

1970s

Veterans

Veterans found to have rashes, cancer, psychological symptoms, congenital abnormalities, and handicaps in their children

1984

Settlement Reached

Lawsuit against Dow, Monsanto, Diamond Shamrock, Hercules, Uniroyal, etc.;

1988-1996

Funds Distributed

Agent Orange Settlement Fund distributed $200 million to veterans

Hohum [commons.wikimedia.org]. Last updated April 1, 2013. Accessed September 10, 2024. https://en.m.wikipedia.org/wiki/File:Agent_Orange_at_Johnston_Atoll_1976.jpg.

Other Predisposing Factors

- DNA damage
- Endocrine dysfunction
- Epigenetic disruption
- Protein aggregation

DNA = deoxyribonucleic acid.

Occupational Exposure and Genotoxicity Biomarkers Linked to Cancer

Genetic damage	Pesticides	Reference
DNA strand breaks	Acephate, chlorpyrifos, dimethoate, monocrotophos, phorate, cypermethrin, fenvalerate, carbendazim	Grover et al. (2003)
	Dimethoate, ethephon, omethoate, oxydemeton-methyl, thiometon, befenthrin, B-cyfluthrin, deltamethrin, mancozeb, carbendazim, endosulfan, chlorothalanil, iprodione, diflufenicanil, L-cyhalothrin, pyrimethanil, fluroxypyr, cyproconazole, epoxyconazole, flutriafol, tebucanazole, atrazine	Lebailly et al. (1998)
DNA adducts	Glyphosate, methamidophos, monocrotophos, parathion methyl, methomyl, metam-sodium, dazomet, zineb, benomyl, carbendazim, paraquat, captan, folpet, endosulfan	Peluso et al. (1996)
Chromosomal aberration	Acephate, chlorpyrifos, dimethoate, fenitrothion, fenthion, fosetyl, isofenphos, methamidophos, naled, pyrazophos, cypermethrin, deltamethrin, fenpropathrin, fenvalerate, methiocarb, methomyl, oxamyl, mancozeb, propineb, zineb, benomyl, diquat, paraquat, captan, folpet, procymidone, endosulfan, abamectin, kasugamycin, iprodione, oxadixyl, buripimate, metribuzin, linuron, methabenzthiazuron, triforine, vinclozolin, bitertanol, fenbutatin oxide, amitraz, propargite, dithiocarbamate	Carbonell et al. (1993)
	Diazinon, dichlorvos, dimethoate, malathion, ethylazinophos, monocrotophos, parathion, parathion methyl, phorate, prothoate, terbufos, trichlorofon, cypermethrin, fenpropathrin, permethrin, maneb, thiram, dazomet, mancozeb, zineb, ziram, thiabendazole, paraquat, captan, folpet, endosulfan, dodemorph, chlorothalonil, iprodione, acetic metaldehyde, barium polysulfide, copper oxychloride, copper sulfate, sulfur, white oil, dinocap, DNOC, alachlor, simazine, MCPA, linuron, vinclozolin, phenmedifam, methalaxyl, ethofumesate, 2,4-D, dicofol	De Ferrari et al. (1991)
	Dimethoate, mevinphos, monocrotofos, parathion, parathion methyl, aldicarb, maneb, dazomet, propineb, zineb, captan, endosulfan, aldrin, aramite, chlordimeform, heptachlor, tetradifon	Dulout et al. (1985)
	2,4-D	Garry et al. (2001)
	Chlorpyriphos, cypermethrin, deltamethrin, fenpropathrin, methomyl, thiram, pirimicarb, benomyl, carbendazim, endosulfan, chlorothalonil, iprodione, buprofezin, atrazine, triforine, vinclozolin, cyhexatin, fetin acetate, carboxin, 2,4-D, chloridazon, defenamide, oxadiazon, propargyl	Lander et al. (2000)
Micronucleus formation	Metham sodium, dodemorph, zineb, antracol, captan, dazomet, dichloropropane, dichloropropene	Bolognesi et al. (1993)
	Diazinon, dichlorvos, fosetyl-aluminum, malathion, ethamidophos, parathion methyl, cypermethin, carbaryl, methomyl, mancozeb, pirimicarb, benomyl, captan, endosulfan, lindane, diuron, 2,4-D, aldrin, ametrina, BHC, DDT, dacomil, dieldrin, di-syxtox, endrin, furadan, gusathion, javelin, metalaxyl, nuvacron, oxidemeton methyl, talstar, tordon	Gomez-Arroyo et al. (2000)
	Deltamethrin, carbaryl, mancozeb, propineb, benomyl	Pasquini et al. (1996)
Sister chromatid exchange	Azynphos methyl, dimethoate, malathion, methyl parathion, 2,4,5-T, 2,4-D	Laurent et al. (1996)
	Mancozeb-contained fungicide	Jablonicka et al. (1989)
	A complex mixture of pesticides (atrazine, alachlor, cyanazine, 2,4-dichlorophenoxyacetic acid, and malathion)	Zeljezic and Garaj-Vrhovac (2002)
	DDT, BHC, endosulfan, malathion, methyl parathion, phosphamidon, dimethoate, monocrotophos, quinalphos fenvelrate, and cypermethrin	Rupa et al. (1991)
	DDT, BHC malathion, parathion, dimethoate, fenitrothion, urea and gromor	Rupa et al. (1988)

DNOC = 4,6-dinitro-*ortho*-cresol; MCPA = 2-methyl-4-chlorophenoxyacetic acid; BHC = benzene hexachloride; DDT = dichloro-diphenyl-trichloroethane.

Mostafalou S, Abdollahi M. *Toxicol Appl Pharmacol*. 2013;268(2):157-177.

Actual Data

Most studies of veterans did not find an increased risk of cancer

- Vietnam Experience Study (VES) by the CDC*
- CDC Selected Cancers Study (focus on 8)*
- VA studies (large-scale cohort studies, case control studies)*
- Air Force Health Study (1200 Ranch Hand veterans)
- State-level studies (New York, Massachusetts, Wisconsin, Michigan)
- Australian Vietnam veterans

Additional Non-US veteran studies

- Vietnamese soldiers and civilians
- Workers exposed to herbicides: herbicide manufacturers, herbicide applicators, farmers, lumberjacks, forest and soil conservatists
- People accidentally exposed to dioxins after industrial accidents

***Not specific to Agent Orange exposure.**
CDC = Centers for Disease Control and Prevention.

Cancer Risk: Exposure and Evidence

Cancer Type	Evidence
Soft tissue sarcoma	Case-control study in Sweden exposed to phenoxy herbicide exposure; chemical manufacturing workers in USA; some other occupational and environmental exposures
Non-Hodgkin lymphoma	Selected Cancers Study showed 50% increased risk in Vietnam, but not linked to AO. Farmers might be at higher risk.
Hodgkin disease	Case-control study in Sweden. Farmers and agricultural workers at increased risk.
Respiratory cancers (lung, trachea/bronchus, larynx)	Ranch Hand study suggested an increased risk of lung cancer. Chronic workplace exposures to dioxin are associated with an increased risk of respiratory cancer.
Prostate cancer	Australian veterans study showed an increased risk. Florida pesticide applicators had an increased incidence of prostate cancer.
Multiple myeloma	Studies in farmers and agricultural workers show a small increase in multiple myeloma.

Frumkin H. *CA Cancer J Clin*. 2003;53(4):245-255.

Prostate Cancer Risk: Exposure and Evidence

Study of veterans in Northern California VA system

Matched veterans with AO exposure (n=6214) with those who did not have exposure (n=6930)

TABLE 3
Disease Parameters of the Cohort Diagnosed With Prostate Cancer

Variable	No. of Patients (%)		
	Agent Orange Exposure, N = 239	No Exposure, N = 124	*P*
Gleason score			
≤6	103 (43.3)	64 (54.8)	.15
7	74 (31.1)	47 (37.9)	.20
8-10	52 (21.8)	13 (10.5)	.009
Metastasis on presentation	32 (13.4)	5 (4)	.005

TABLE 4
Multivariate Analysis for Developing Prostate Cancer

Variable	OR	95% CI	*P*
Agent Orange exposure	4.83	3.42–6.81	<.001
Preoperative PSA	1.93	1.82–2.06	<.001
Age at diagnosis	1.06	1.03–1.09	<.001
BMI	1.02	0.99–1.05	.21
Race (AA vs other)	1.55	1.06–2.26	.02
Finasteride	0.43	0.20–0.89	.02
Smoking history (0-5)*	0.78	0.72–0.85	<.001

OR indicates odds ratio; CI, confidence interval; PSA, prostate-specific antigen; BMI, body mass index; AA, African American.
*Smoking history was graded on a scale from 0 to 5 as follows: 0, lifetime nonsmoker; 1, quit >14 years ago; 2, quit >7 years ago; 3, quit >4 years ago; 4, quit in the last year; and 5, current smoker.

PSA = prostate-specific antigen; BMI = body mass index; AA = African American.
Chamie K, et al. *Cancer*. 2008;113(9):2464-2470.

Prostate Cancer Risk: Exposure and Evidence

AGENT ORANGE AS A RISK FACTOR FOR HIGH-GRADE PROSTATE CANCER

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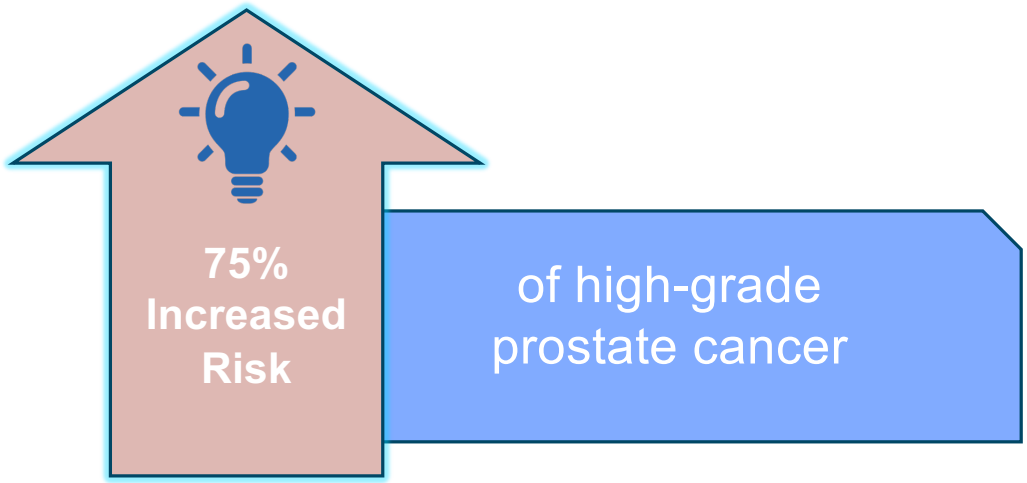
[4]Oregon Health & Science University Knight Cancer Institute, Portland, OR

[5]Oregon Health & Science University Departments of Urology and Radiation Medicine, Portland, OR

Ansbaugh N, et al. *Cancer*. 2013;119(13):2399-2404.

Does Exposure to AO Increase Prostate Cancer Incidence and Lethality?

- Used 2720 historical controls from VAPORHCS (93.6% white; 7.5% exposed to Agent Orange)



VAPORHCS = VA Portland Healthcare System.

Ansbaugh N, et al. *Cancer*. 2013;119(13):2399-2404.

Does Prior Agent Orange Exposure Affect Response to Treatment?

Variable	Odds Ratio	95% Confidence Limits		P-value
Agent Orange	0.972	0.309	3.063	0.9618
Prior docetaxel	0.445	0.117	1.686	0.2335
Metformin	0.912	0.261	3.187	0.8853
Statin	0.683	0.263	1.774	0.4333

Graff J, Lamble N. Prospective analysis of 101 veterans receiving either abiraterone or enzalutamide at the VAPORHCS.

Honoring Our PACT Act

The new PACT Act

- Expands toxic-exposed veterans' access to VA care
- Extends healthcare eligibility for Vietnam, Gulf War, and post-9/11-era combat veterans
- Adds new presumptive conditions for radiation, Agent Orange, Gulf War toxins, and burn pit exposures

PACT Act = Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act of 2022.

Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act of 2022, Public Law 117-168, 117th Congress. 2022. https://www.govinfo.gov/content/pkg/PLAW-117publ168/pdf/PLAW-117publ168.pdf.

Patient Scenarios

I was never boots on the ground in Vietnam, but I worked on the ships that transported Agent Orange.”

I spent time in Vietnam, but the army lost my paperwork, and now I cannot prove it.”

I drank the polluted waters at Camp Lejeune every day for 11 months, but I cannot get a service connection for my prostate cancer.”

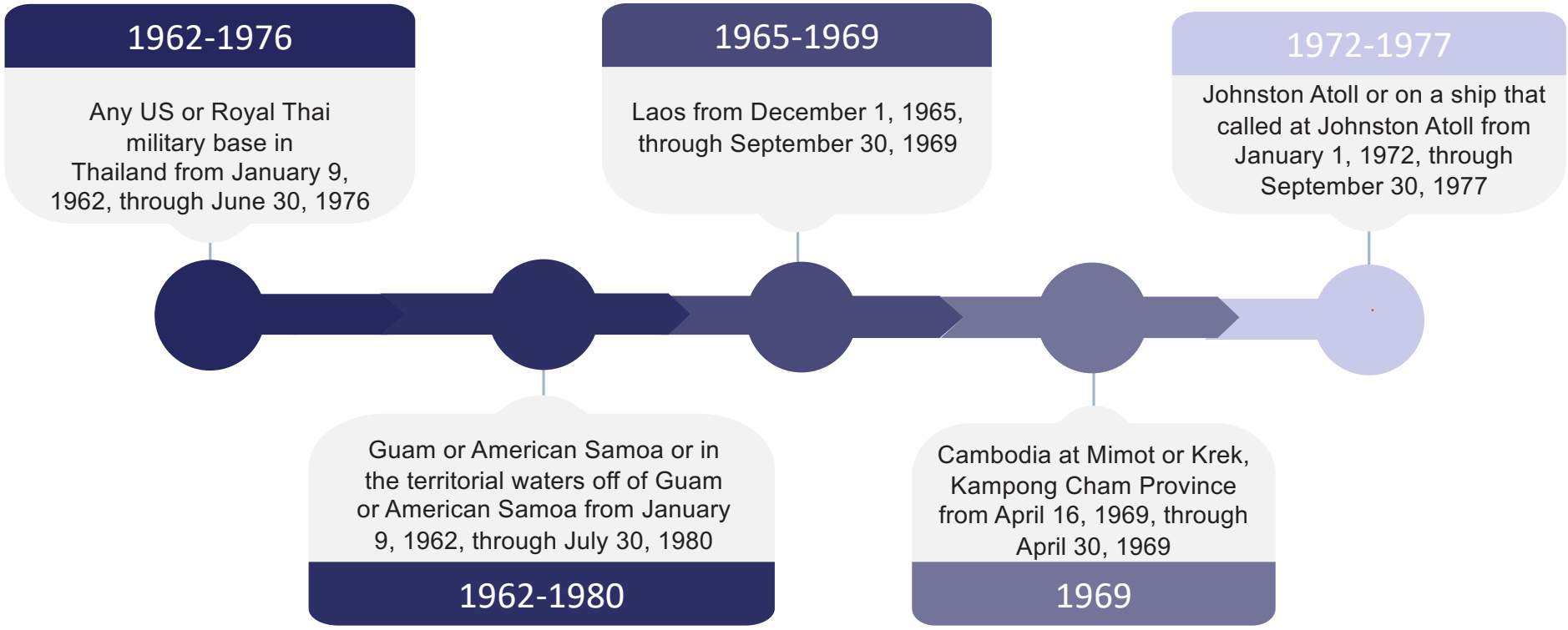
I served in Desert Storm. The burning oil pits made the air so thick with smoke that we covered our faces with wet cloth when we went outside. Surely that was not good for me.”

What Does the PACT ACT Provide?

Gulf War veterans and post-9/11 veterans	
These cancers are now presumptive conditions	
• Brain cancer • Gastrointestinal cancer of any type • Glioblastoma • Head cancer of any type • Kidney cancer • Lymphatic cancer of any type	• Lymphoma of any type • Melanoma • Neck cancer • Pancreatic cancer • Reproductive cancer of any type • Respiratory (breathing-related) cancer of any type

Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act of 2022, Public Law 117-168, 117th Congress. 2022. https://www.govinfo.gov/content/pkg/PLAW-117publ168/pdf/PLAW-117publ168.pdf.

5 New Locations Have Been Added to the List of Presumptive Locations for Agent Orange Exposure



Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act of 2022, Public Law 117-168, 117th Congress. 2022. https://www.govinfo.gov/content/pkg/PLAW-117publ168/pdf/PLAW-117publ168.pdf.

There Are 3 New Response Efforts Added to the List of Presumptive Locations for Radiation Exposure

- Cleanup of **Enewetak Atoll** from January 1, 1977, through December 31, 1980
- Cleanup of the Air Force B-52 bomber carrying nuclear weapons off the coast of **Palomares, Spain**, from January 17, 1966, through March 31, 1967
- Response to the fire onboard an Air Force B-52 bomber carrying nuclear weapons near **Thule Air Force Base in Greenland** from January 21, 1968, to September 25, 1968

Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act of 2022, Public Law 117-168, 117th Congress. 2022. https://www.govinfo.gov/content/pkg/PLAW-117publ168/pdf/PLAW-117publ168.pdf.

Get Your Toxic Exposure Screening

Who: All Veterans enrolled in VA health care

What: A brief screening averaging 5–10 minutes to identify and document any potential exposures to toxins during military service

When: At least once every 5 years

Where: At VA medical centers/clinics, including virtual encounters

Why: To provide exposure-informed care, support long-term health plans, and connect with follow-up resources, as requested

How: Ask about the toxic exposure screening at your next VA appointment

If you do not have an upcoming appointment or want to be screened sooner, contact your local VA facility and ask to be screened by the Toxic Exposure Screening Navigator.

Exposure Assessment

- What were you exposed to? Chemical (pollution, solvents, etc.), biological (infectious disease), or physical (radiation, heat, vibration)
- What precautions were taken? Avoidance, PPE, treatment, etc.
- How were you exposed? Inhaled, on skin, swallowed, etc.
- How concerned are you about the exposure?
- Where were you when you were exposed?
- When were you exposed?
- Who else may have been affected?

The PACT Act Toxic Exposure Screening is recommended to be performed at least once every 5 years for all veterans enrolled in VA healthcare.

PPE = personal protective equipment.

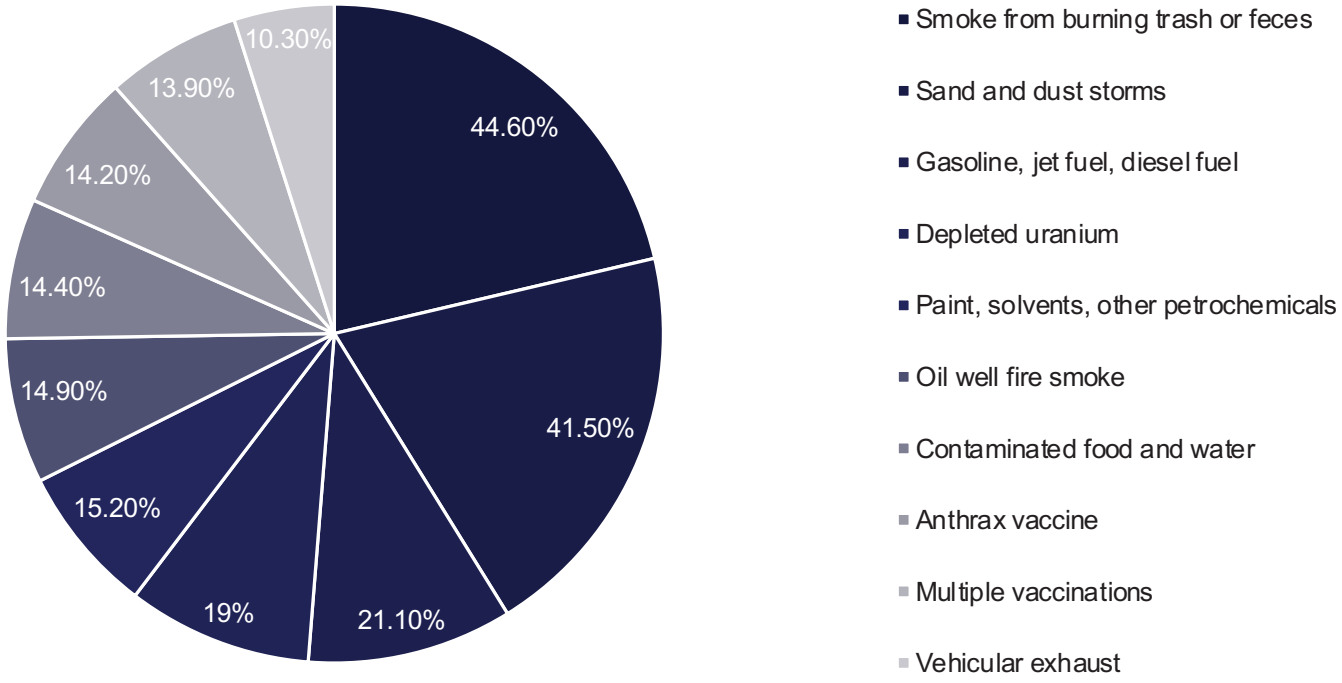
US Department of Veterans Affairs [www.va.gov]. Last updated April 16, 2024. Accessed September 11, 2024. https://www.va.gov/milwaukee-health-care/programs/pact-act-toxic-exposure-screening-and-your-va-benefits.

Become Informed as a Provider

- Email education
- Related health concerns: Agent Orange-related diseases, Gulf War veterans' illnesses, radiation-related disease, vaccinations and medications
- Wars and operations: Operation Enduring Freedom (Afghanistan), Iraq War (OIF/OND), Gulf War, Vietnam War
- Exposure categories: chemicals (AO, contaminated water), radiation (nuclear weapons, X-rays), air pollutants (burn pit smoke, dust), occupational hazards (asbestos, lead), warfare agents (chemical and biological)

OIF/OND = Operation Iraqi Freedom/Operation New Dawn.

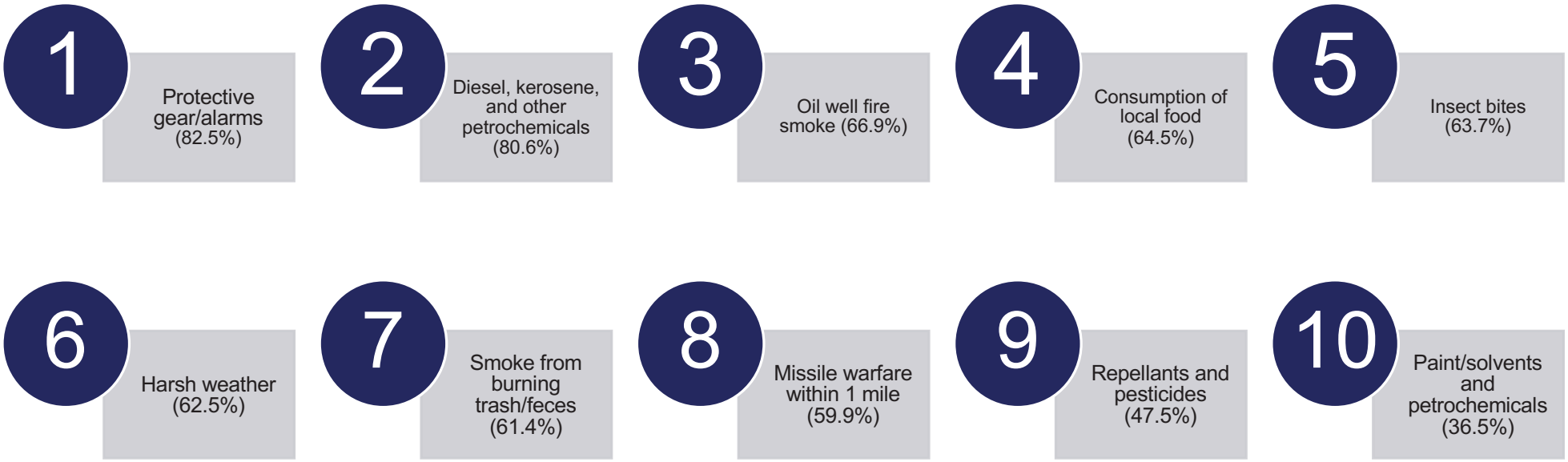
Top Ten Environmental Exposures of Concern: OEF/OIF



OEF = Operation Enduring Freedom.

Santos SL [publichealth.va.gov]. Last updated August 2013. Accessed September 10, 2024. https://www.publichealth.va.gov/docs/exposures/risk-communication.pdf.

Top Ten Environmental Exposures: Gulf War

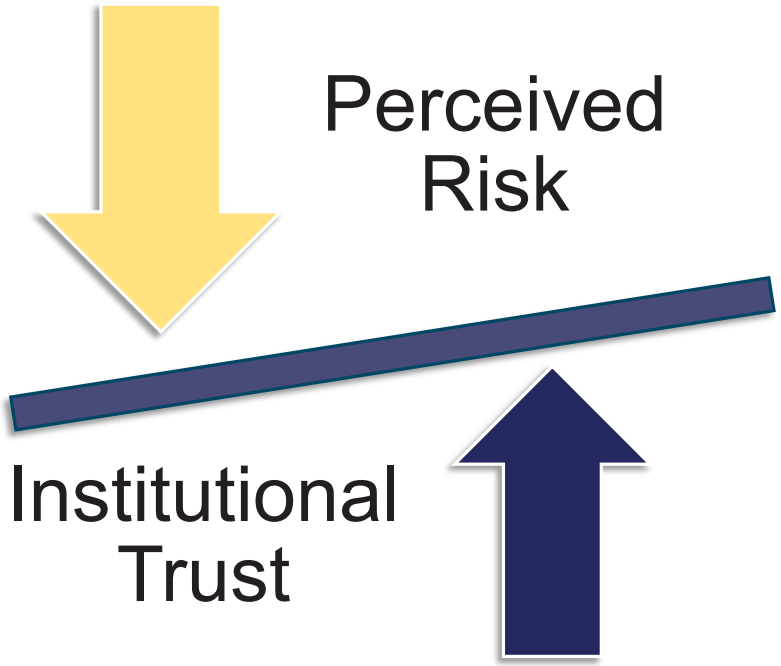


N=651.

Schneiderman AJ, et al. Presented at: 133rd Annual Meeting of the American Public Health Association (APHA); December 14, 2005; Philadelphia, Pennsylvania; in Santos SL [publichealth.va.gov]. Last updated August 2013. Accessed September 10, 2024. https://www.publichealth.va.gov/docs/exposures/risk-communication.pdf.

Institutional Trust and Perceived Risk

- Numerous studies indicate that as institutional trust increases, perceived risk decreases
- Magnitude of effect depends on population and hazard



Flynn J, et al. *Risk Anal*. 1992;12(3):417-429. Siegrist M, Cvetkovich G. *Risk Anal*. 2000;20(5):713-720. Allum N. *Risk Anal*. 2007;27(4):935-946. Santos SL [publichealth.va.gov]. Last updated August 2013. Accessed September 10, 2024. https://www.publichealth.va.gov/docs/exposures/risk-communication.pdf.

Steps Involved

1. Claim received
2. Initial review
3. Evidence gathering (longest part)
4. Evidence review
5. Rating
6. Preparing decision letter
7. Final review
8. Claim decided

Google Search for Prostate Cancer Ratings

- First, AI generates a summary based on two case findings
- Second, dozens of websites for lawyers promise to get you a good rating successfully
- Bottom line: If diagnosed with prostate cancer, presumed relationship to Agent Orange, you are 100% disabled until 6 months after treatment; if in remission or cured, your rating decreases, and the percentage is based on urinary side effects
- Importantly, if the condition results in unemployment, the rating remains 100%

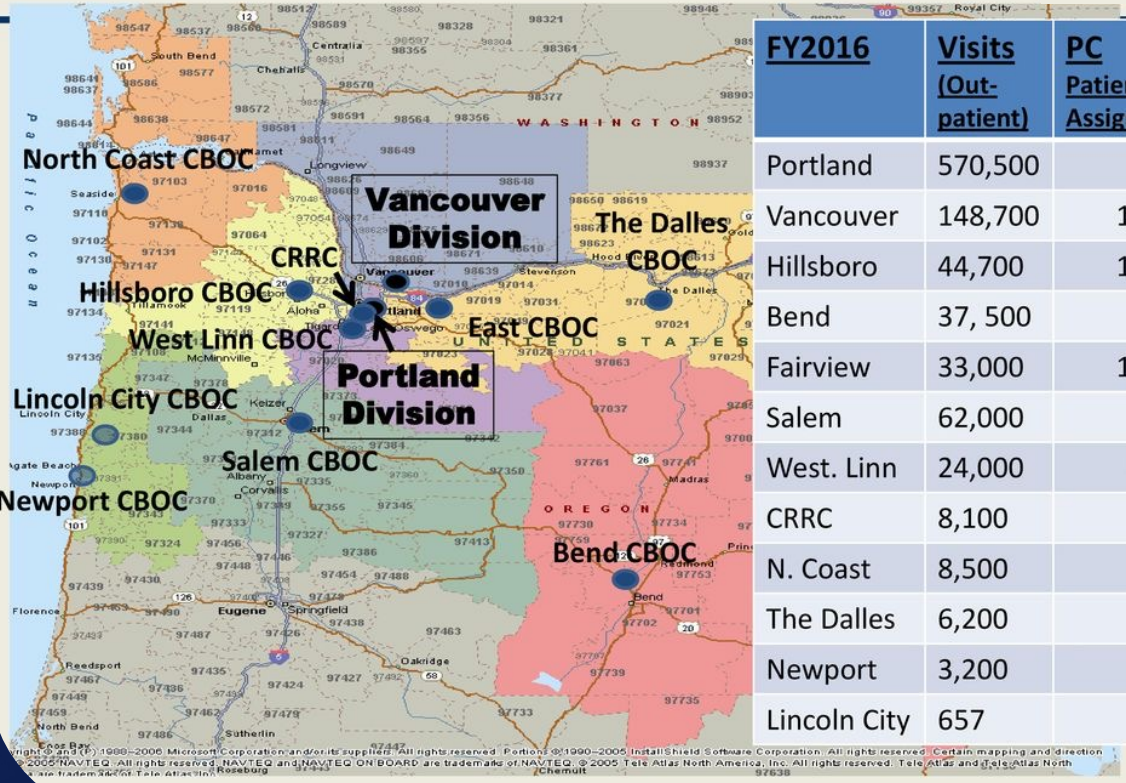
AI = artificial intelligence.

Key Learning Points

- According to an historical cohort analysis of veterans, men exposed to Agent Orange have a 75% higher risk of high-grade prostate cancer
- VA has significantly expanded benefits to veterans exposed to potential carcinogens during their service
- The PACT Act Toxic Exposure Screening is recommended to be performed at least once every 5 years for all veterans enrolled in VA healthcare
- Presumptive diagnoses
- Ratings

VA Facility-Based Care vs Contracted Community Cancer Care

VA Portland Health Care System



FY2016	Visits (Out-patient)	PC Patients Assigned
Portland	570,500	3,013
Vancouver	148,700	12,300
Hillsboro	44,700	11,748
Bend	37, 500	6,480
Fairview	33,000	11,748
Salem	62,000	7,842
West. Linn	24,000	8,833
CRRC	8,100	800
N. Coast	8,500	2,100
The Dalles	6,200	2,340
Newport	3,200	1,277
Lincoln City	657	143

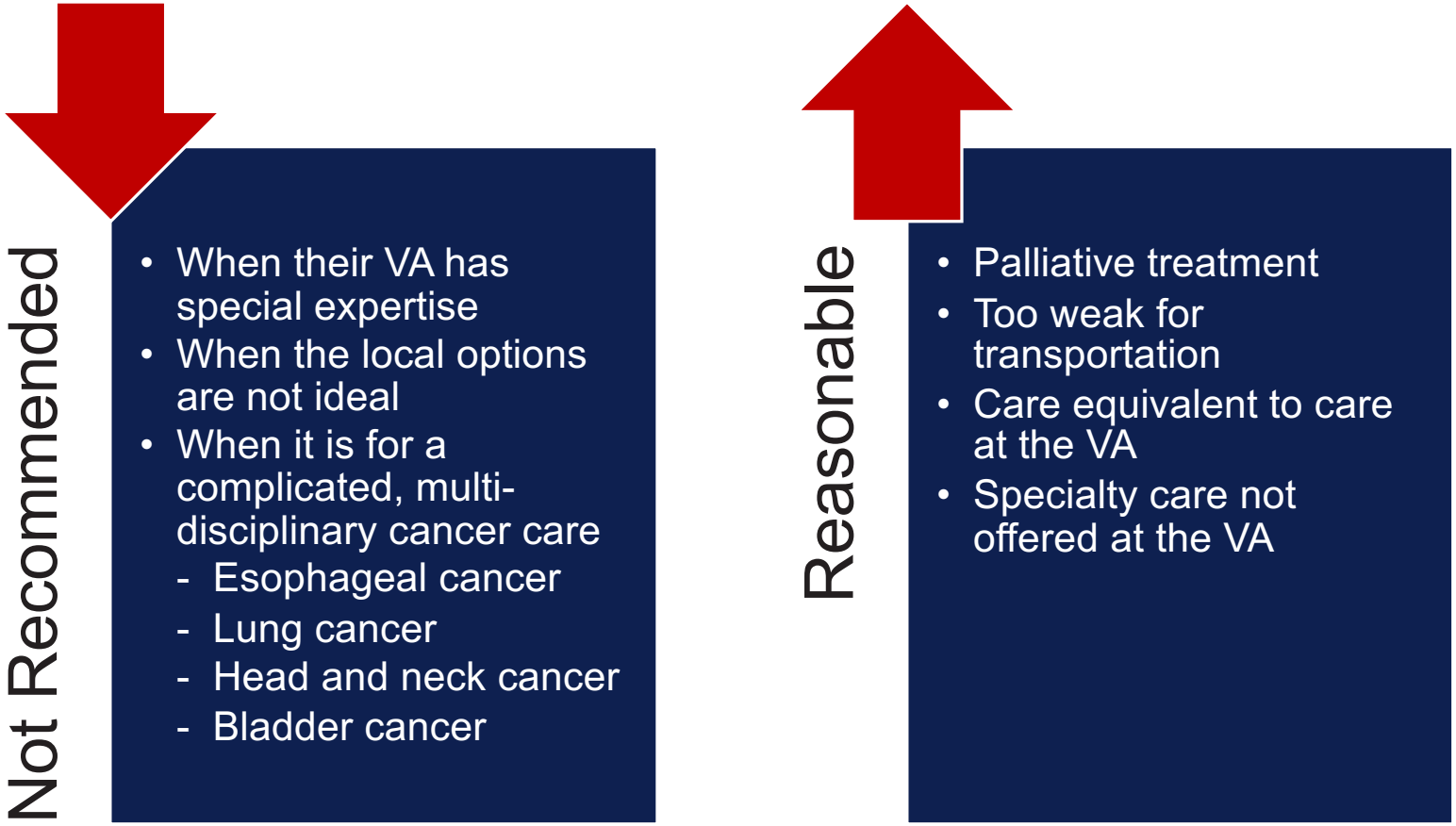
FY = fiscal year; CBOC = community-based outpatient clinic.

Herrigstad D. Presented at April 2017 Military Officers Association of America (MOAA) Columbia River Chapter Lunch; April 20, 2017. Accessed September 11, 2024. https://moaacolumbiariver.org/wp-content/uploads/2017/04/VA-briefing-to-MOAA-lunch-April-20-2017.pptx.

Simple Rule

- If a veteran lives 60 minutes away from a specialist or 30 minutes away from primary care, he can “opt out” of VA services
- For cancer care, when does that make sense?

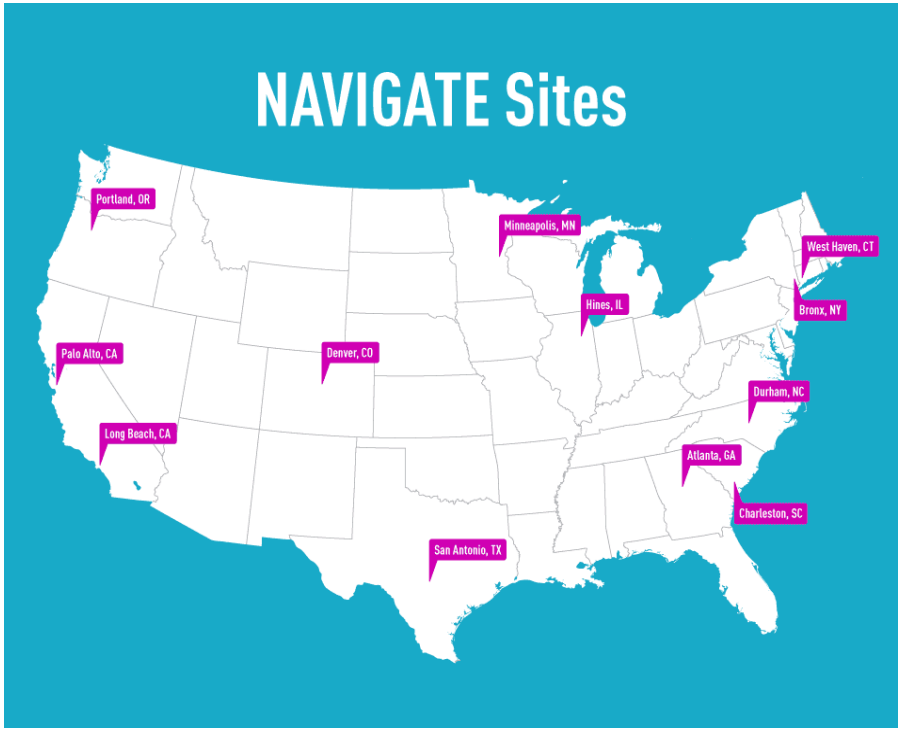
Opting Out of VA Care

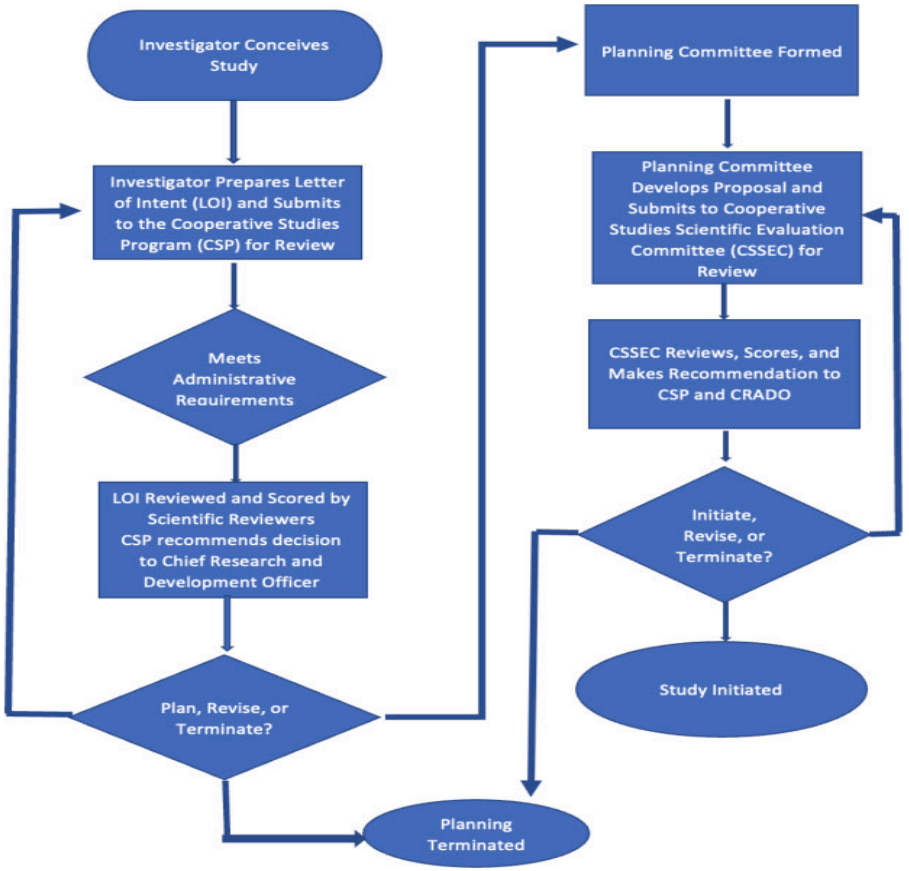


How Does It All Work?

BotMultichillT [commons.wikimedia.org]. Last updated August 12, 2010. Accessed September 12, 2024. https://commons.wikimedia.org/wiki/File:Zan_Zig_performing_with_rabbit_and_roses,_magician_poster,_1899.jpg

Some Clinical Research in the VA





- PATCH @ VA
- Cooperative Studies Program

National Institute of Health (NIH) National Cancer Institute (NCI) [www.cancer.gov]. Last updated July 10, 2018. https://www.cancer.gov/news-events/press-releases/2018/navigate-va-clinical-trials. Burnaska DR, et al. *Contemp Clin Trials Commun*. 2021:23:100811.

PCF-VA Partnership Network of Centers of Excellence (COE) (2016-2023) $63 Million of Philanthropic Support to Centers, Teams, Investigators

Ann Arbor, MI—The Stewart J. Rahr Foundation Precision Oncology Center of Excellence at the VA Ann Arbor

Boston, MA—The Blavatnik Family Foundation Precision Oncology Center of Excellence at VA Boston Healthcare System, Harvard Medical School, Dana-Farber Cancer Institute NCI-CCC

Bronx, NY—The Blavatnik Family Foundation Precision Oncology Center of Excellence at the VA Bronx

Chicago, IL—The Robert Frederick Smith Precision Oncology Center of Excellence at the VA Chicago

Durham, NC—The Drew Foundation Precision Oncology Center of Excellence at the VA Durham

Los Angeles, CA—The David Geffen Foundation Precision Oncology Center of Excellence at the West Los Angeles VA

Manhattan, NY—The John and Daria Barry Foundation Precision Oncology Center of Excellence at the VA Manhattan

Philadelphia, PA—The Jonathan and Plum Simons Precision Oncology Center of Excellence at the VA Philadelphia

Portland, OR—The Michael and Lori Milken Family Foundation | Robert and Cindy Citrone Precision Oncology Center of Excellence at the VA Portland Health Care System Oregon Health & Science University and Knight Cancer Institute

San Francisco, CA—The Drew Foundation Precision Oncology Center of Excellence at San Francisco VA Health Care System, UCSF

Seattle, WA—The Stephen J. Cloobeck Precision Oncology Center of Excellence at the VA Puget Sound

Tampa and Bay Pines, FL—The John and Daria Barry Foundation Precision Oncology Center of Excellence at the VA Tampa and VA Bay Pines

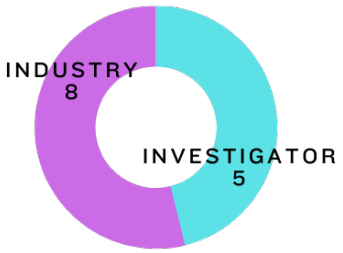
Washington, DC—The Edward P. Evans Precision Oncology Center of Excellence at the VA Washington, DC

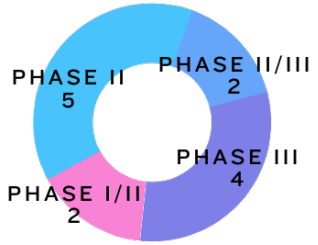
PCF = Prostate Cancer Foundation; CCC = Comprehensive Cancer Center; UCSF = University of California—San Francisco.

TRIAL Enrollment and Demographics

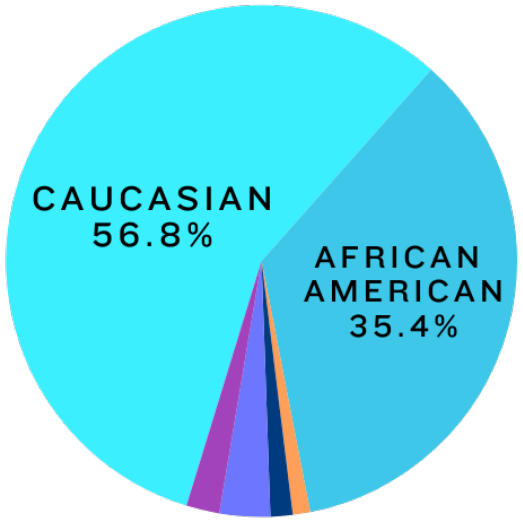
TOTAL VETERANS SCREENED **483 VETERANS**

TOTAL VETERANS ENROLLED **280 VETERANS**

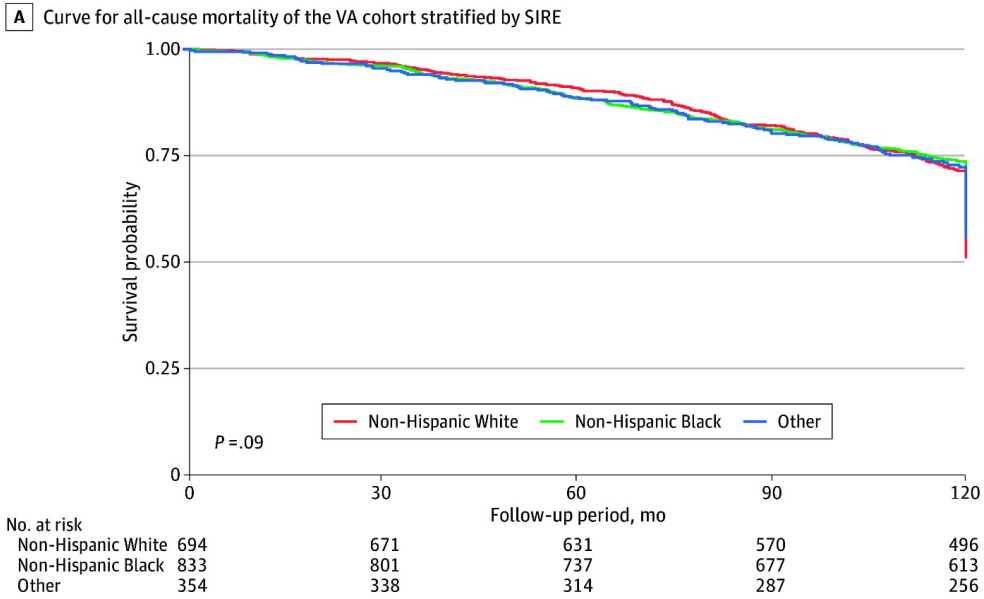


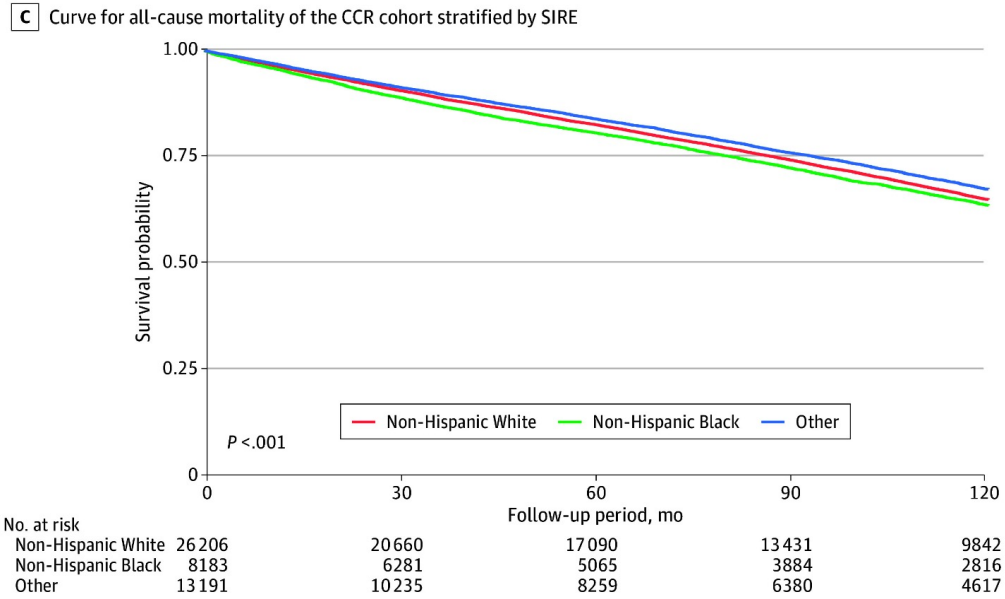


ALL NETWORK TOTAL	Screened	Enrolled	%
Caucasian	238	159	56.8%
African American	160	99	35.4%
Native American/Alaska Native	4	3	1.1%
Asian/Pacific Islander	9	4	1.4%
Hispanic/Latino	16	9	3.2%
Unknown	56	6	2.1%
TOTAL	483	280	100.0%



Is Care in VA More Equitable?





SIRE = self-identified race and ethnicity; CCR = California Cancer Registry.
Wadhwa A, et al. *JAMA Netw Open*. 2024;7(3):e242852.

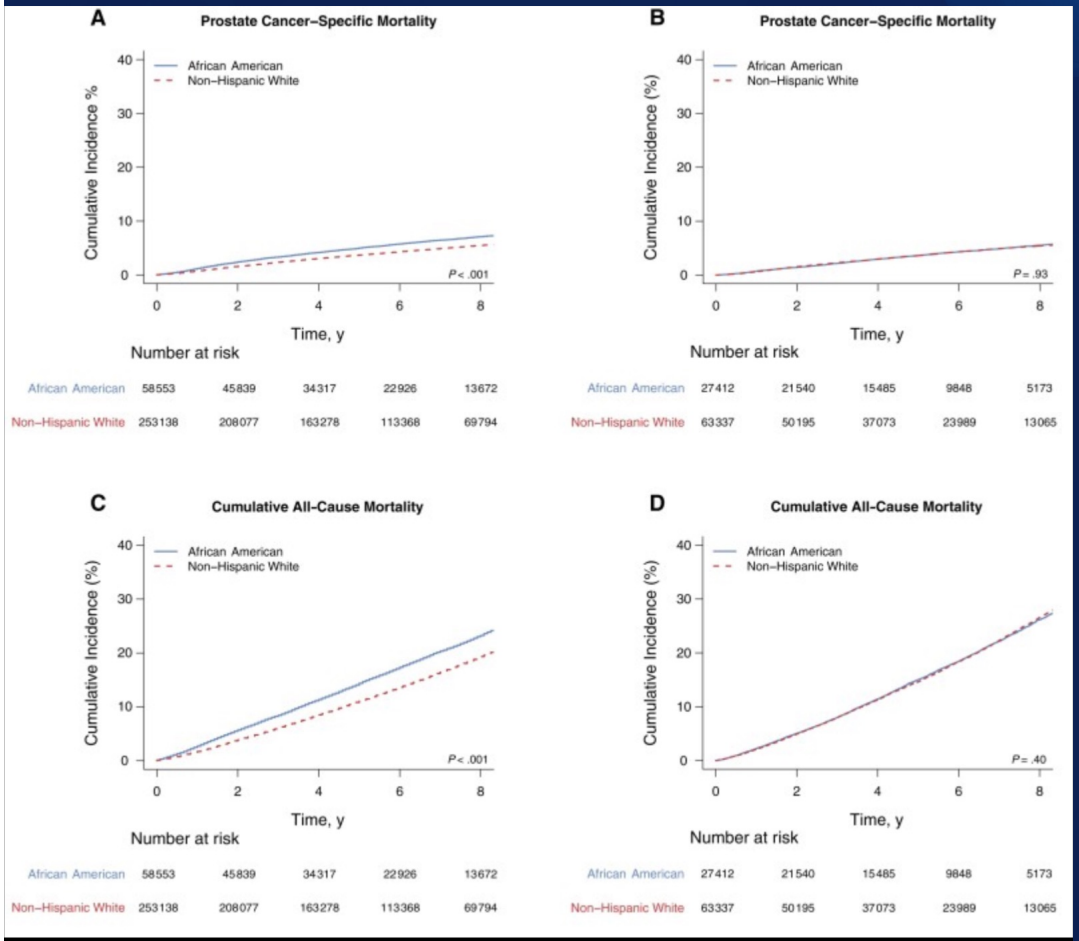


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Figure 1. Cumulative incidence of prostate cancer-specific mortality **(A, B)** and all-cause mortality **(C, D)** among African American and non-Hispanic White men in the Surveillance, Epidemiology, and End Results **(A, C)** and Veterans Health Administration **(B, D)** cohorts. Two-sided *P* values calculated using Gray test.

Black prostate cancer patients do as well as non-Hispanic white prostate cancer patients in the VA system.

Daniella K, et al. *J Natl Cancer Inst*. 2021;113(10):1343-1351.

Key Learning Points

- Access to providers outside of the VA has increased significantly, but it often makes sense to keep care within the VA
- Clinical trial opportunities for prostate cancer and other cancers have also expanded dramatically
- Care within VA appears to close the gap between outcomes for non-Hispanic white and black patients

DeNovo Metastatic Hormone-Sensitive Prostate Cancer (mHSPC)

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Medical University of South Carolina
Chief, Section Urology, Ralph H. Johnson Veterans Affairs Health Care System (VAHCS)
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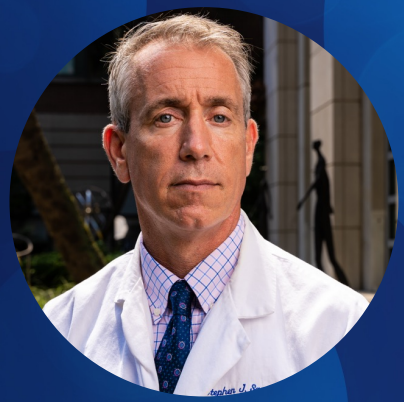


Case Study

- 55-year-old male Gulf War veteran s/p radiation and 4-month androgen deprivation 4 years earlier for GG4 prostate cancer
- Imaging at diagnosis included MRI and bone scan
- No other testing done
- PSA 5.2 with doubling time of 15 months
- Serum testosterone of 582
- Referred for consideration of further therapy for failure to respond to treatment

s/p = status post; GG = grade group; MRI = magnetic resonance imaging.

Prostate Cancer Diagnosis

- **Localized cancer**
  - Screened with prostate-specific antigen (PSA) or digital rectal exam (DRE)
  - Incidental—surgical or imaging (MRI)
  - Recurrent (after previous local therapy)
- **Metastatic cancer**
  - Hormone-sensitive (responds to androgen deprivation)
    - ***De novo—first presentation***
    - Recurrent—progresses to metastatic
  - Hormone-resistant (no response to standard ADT)
    - Subsequent to androgen deprivation

ADT = androgen deprivation therapy.

Initial Diagnostic Testing

- **PSA risk stratification**
  - Low risk—0-10
  - Intermediate risk—0-20
  - High risk— > 20
- **Physical examination**
  - Nonpalpable—T1c
  - Prostate-confined—T2
  - Extracapsular or seminal vesicle—T3
  - Local invasion (rectum/bladder)—T4

Pathologic Testing

- **Gleason grade group (1-5)**
  - Comprised of patterns (3-5), Gleason 4+3 = GG3
  - Risk: Low—1; intermediate—2,3; high—4,5
- **Number of cores positive**
  - Typically out of 12
- **Percentage of cores positive**
  - 10 mm core
- **Lymphovascular invasion**
- **Perineural invasion**
- **Additions**
  - Ki-67, PTEN, genomic

Ki = Kiel.

Risk Stratification

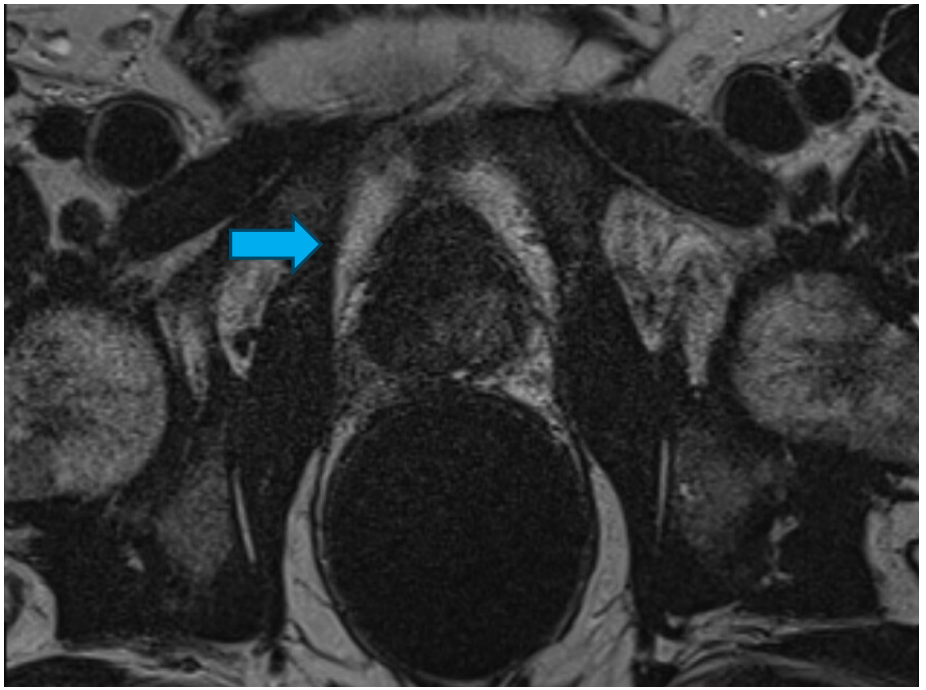
- **Predictive nomograms**
  - MSKCC, Partin
- **Genomic testing**
  - Prolaris®, Decipher®, Oncotype®
- **PTEN testing**
  - 20% localized, 40% mCRPC
  - Increased risk of recurrence in PTEN loss
- **P53 testing**

Is there value in “adjuvant” therapy with increased risk of recurrence?

MSKCC = Memorial Sloan Kettering Cancer Center; mCRPC = metastatic castration-resistant prostate cancer; P = protein.

Clinical Staging (Imaging)

- **Local imaging**
  - Ultrasound-real time imaging
  - CT scan
    - Fast acquisition, readily available
    - Reproducible
  - MRI
    - Peri-prostatic state of the art
    - Lymph node diagnostics
    - Focal therapy potential



CT = computed tomography.

Clinical Staging (Imaging—Advanced)

- **Distant imaging**
- **Standard**
  - CT or MRI—soft tissue
  - Bone scan/plain films—bones
- **Prostate-specific**
  - PSMA PET scan—fused images
  - Emerging radionuclide tracers
  - 27% improved detection
  - 32% for nodal mets
  - 22% for distant mets

PSMA PET = prostate-specific membrane antigen positron emission tomography.

Multidisciplinary Treatment Input

“If you are a hammer, everything is a nail”

- **Varied consideration of risks and benefits**
  - Advances in testing and approach
  - Disease spaces crossover (early risk assessment)
  - Multiple vs sequential treatment
- **Patients identify with differing approaches and perspective**
  - Improves engagement
- **Challenging to align schedules and access**
- **Care pathways** (NCCN, AUA, VA)
- **Improvement of longitudinal care** (seamless coverage)

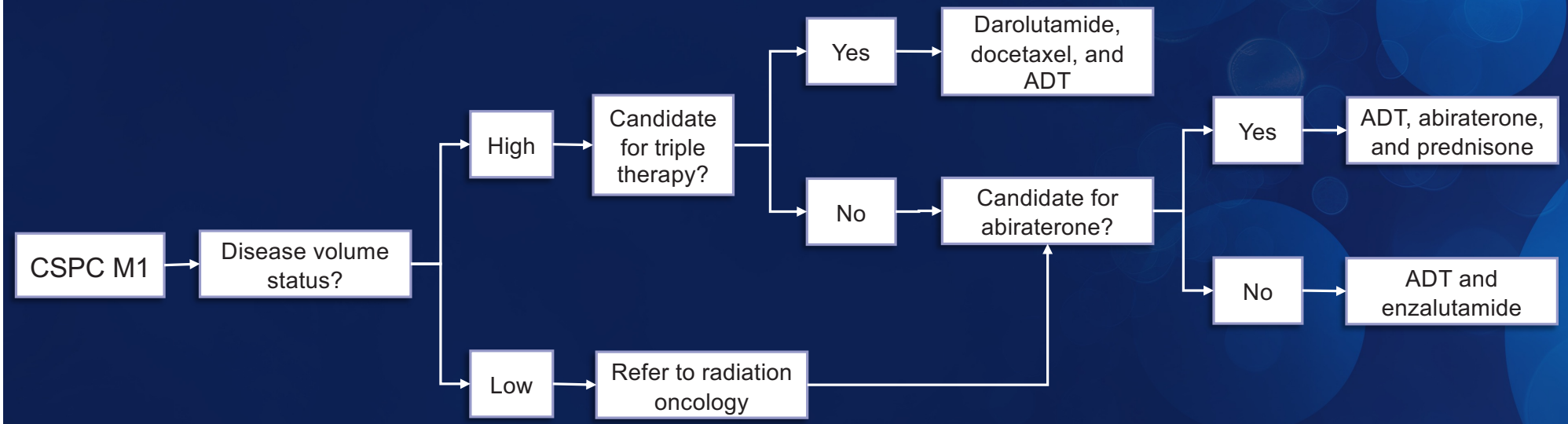
NCCN = National Comprehensive Cancer Network; AUA = American Urological Association.

VA Prostate Cancer Risk Stratification

Risk Group	Defined by Clinical/ Pathologic Features			Imaging for Nodal or Metastatic Disease	Germline Testing	Initial Therapy
Very low	All the following: • T1c • Grade group 1 • PSA < 10 ng/ml • < 3 prostate biopsy fragments/ cores positive; ≤ 50% cancer in each fragment/core • PSA density < 0.15 ng/ml/g			Not indicated	Recommended for any of the following: • Ashkenazi Jewish ancestry • Family history of high-risk germline mutations • Strong family history of cancer	Follow **Very Low Risk** pathway
Low	All the following: • T1-T2a • Grade Group 1 • PSA < 10 ng/ml					Follow **Low Risk** pathway
Intermediate	All the following: • No high-risk group features • No very high-risk group features • One or more intermediate risk factors (IRF) ○ T2b-T2c ○ Grade Group 2 or 3 ○ PSA 10-20 ng/ml	***Favorable Intermediate***	All the following: • One IRF • Grade Group 1 or 2 • < 50% positive biopsy cores	• Bone imaging not recommended for staging • Pelvic ± abdominal imaging recommended if nomogram predicts >10% probability of pelvic LN involvement		Follow **Favorable Intermediate Risk** pathway
		Unfavorable Intermediate	At least one of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% positive biopsy cores	• Bone and Soft Tissue Imaging: use PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging (with either Tc99m-MDP/HDP SPECT/CT, F18-NAF PET/CT) + soft tissue imaging (with CT, MRI, F18-fluciclovine PET) + PSMA PET/CT for equivocal findings		Follow **Unfavorable Intermediate Risk** pathway
High	At least one high-risk feature: • T3a • Grade Group 4 or 5 • PSA > 20 ng/ml			• Bone and Soft Tissue Imaging: use PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging (with either Tc99m-MDP/HDP SPECT/CT, F18-NAF PET/CT) + soft tissue imaging (with CT, MRI, F18-fluciclovine PET) + PSMA PET/CT for equivocal findings	Recommended	Follow **High or Very High-Risk** pathway
Very High	At least one of the following: • T3b-T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • > 4 cores with Grade Group 4 or 5			• Bone and Soft Tissue Imaging: use PSMA PET/CT, (or PET/MRI) if available, or a combination of bone imaging (with either Tc99m-MDP/HDP SPECT/CT, F18-NAF PET/CT) + soft tissue imaging (with CT, MRI, F18-fluciclovine PET) + PSMA PET/CT for equivocal findings	Recommended	
Regional	Any T, N1, M0: Consider testing tumor for HRRm and MSI or dMMR				Recommended	Follow **Regional Risk** pathway
Metastatic	Any T, Any N, M1: Recommend testing tumor for HRRm and MSI or dMMR				Recommended	Follow **CSPC M1** pathway

US Department of Veterans Affairs [www.cancer.va.gov]. Last updated March 2024. Accessed September 12, 2024. https://www.cancer.va.gov/assets/pdf/clinical-pathways/13/PrCCP.pdf.

CSPC M1 Treatment Pathway*



*Clinical trial(s) always considered on pathway.
CSPC = castration-sensitive prostate cancer.
US Department of Veterans Affairs [www.cancer.va.gov]. Last updated March 2024. Accessed September 12, 2024.
https://www.cancer.va.gov/assets/pdf/clinical-pathways/13/PrCCP.pdf.

Decisions in De Novo mHSPC Care

- **Further testing**—imaging, bone density, genomic, genetic
  - Cascade testing
- **Treatment of primary**
  - Radiation, hormone, surgical, tumor ablation
- **Androgen deprivation modality**
- **Secondary hormonal treatment**
- **Systemic chemotherapy**
- **Oligometastatic treatment**
- **Clinical trials**

Opportunities in mHSPC

- Identify "**at risk**" and earlier disease state
  - Path/genomic (general), PTEN (targeted)
- Explore more limited treatment course
- Target multiple molecular pathways
  - Androgen receptor and PI3K/AKT (PTEN loss) work reciprocally
- Examine synergy between modalities
- Treat prior to resistance

Early testing of the PI3K/AKT pathway in de novo mHSPC patients for PTEN-deficient tumors may improve prognosis, outcomes, and access to clinical trials.

PI3K = phosphoinositide 3-kinase; AKT = protein kinase B.

Fizazi K, et al. *J Clin Oncol*. 2021;39(6 suppl):TPS178.

Shared Decision Making

- Collaborative decision making between patients and care team when one or more options is clinically acceptable
- AUA white paper in 2015 with USPSTF with PSA screening
  - Change from recommendation against screening
- Equipoise and active engagement
- Decision aid vs decision coach
  - Individual tools for patient
  - Trained nurse or nurse navigator

SDM Implementation

- **S**eek your patient's participation
- **H**elp your patient explore and compare treatment options
- **A**ssess your patient's values and preferences
- **R**each a decision with your patient
- **E**valuate your patient's decision

SDM = shared decision making.

Veteran Population

- Underrepresented minorities
  - Health care mistrust
  - Clinical trial skepticism
  - Relatively unexplored variations in disease
- Known and unknown exposure risk
- Health care literacy
  - Increasingly complex disease space
- Risk of fragmented care
- Shared decision-making efforts
  - vs following orders

Key Learning Points

- **Shared decision making**
  - What is possible vs what does patient desire?
- **Multidisciplinary input**
  - Understand ramifications of each test and treatment
- **Early risk stratification**
  - Nomogram/genomic testing/PTEN testing
- **Innovative treatment combinations**
  - Early testing of the PI3K/AKT pathway in de novo mHSPC patients for PTEN-deficient tumors may improve prognosis, outcomes, and access to clinical trials
- **Address unmet needs**