

The Precision Oncology Program for Cancer of the Prostate (POPCaP) Network: A Veterans Affairs/Prostate Cancer Foundation Collaboration

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Background: The promise of precision oncology only can be realized when genetic alterations are identified that can be leveraged to improve response and minimize toxicity. Identifying those alterations as efficiently as possible and then giving patients access to targeted therapy and clinical study requires a comprehensive strategy across health care systems.

Observations: The US Department of Veterans Affairs (VA) and Prostate Cancer Foundation have established a network of VA centers to help develop best practices for precision oncology for the

treatment of veterans with advanced prostate cancer. This article describes the genesis and structure of this network and its potential for contributing to care and research in the VA and the health care system as a whole.

Conclusions: The Precision Oncology Program for Cancer of the Prostate network and its partnership with VA clinical and research efforts is anticipated to provide important insights into barriers and solutions to the implementation of precision oncology for prostate cancer across the VA.

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The US Department of Veterans Affairs (VA) is home to the Veterans Health Administration (VHA), which delivers care at 1,255 health care facilities, including 170 medical centers. The VA serves 6 million veterans each year and is the largest integrated provider of cancer care in the US. The system uses a single, enterprise-wide electronic health record. The detailed curation of clinical outcomes, laboratory results, and radiology is used in VA efforts to improve oncology outcomes for veterans. The VA also has a National Precision Oncology Program (NPOP), which offers system-wide DNA sequencing for veterans with cancer. Given its size, integration, and capabilities, the VA is an ideal setting for rapid learning cycles of testing and implementing best practices at scale.

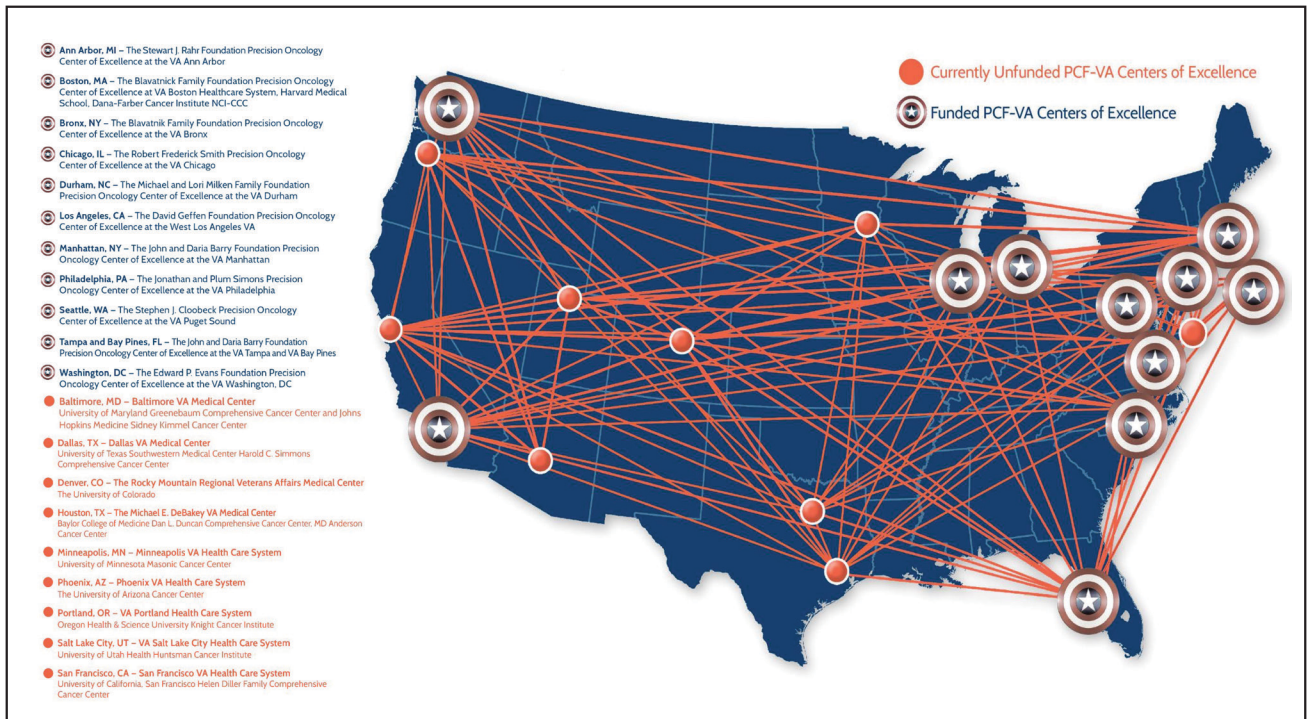
Prostate cancer is the most common malignancy affecting men in the US. It is the most commonly-diagnosed solid tumor in the VA, and in 2014, there were 11,376 prostate cancer diagnoses in the VA.¹ The clinical characteristics and treatment of veterans with prostate cancer largely parallel the broader population of men in the US.¹ Although the majority of men diagnosed with prostate cancer have disease localized to the prostate, an important minority develop metastatic disease, which represents a risk for substantial morbidity and is the lethal form of the disease. Research has yielded transformative advances in the care of

men with metastatic prostate cancer, including drugs targeting the testosterone/androgen signaling axis, taxane chemotherapy, the radionuclide radium-223, and a dendritic cell vaccine. Unfortunately, the magnitude and duration of response to these therapies varies widely, and determining the biology relevant to an individual patient that would better inform their treatment decisions is a critical next step. As the ability to interrogate the cancer genome has improved, relevant drivers of tumorigenesis and predictive biomarkers are being identified rapidly, and oncology care has evolved from a one-size-fits-all approach to a precision approach, which uses these biomarkers to assist in therapeutic decision making.

PRECISION ONCOLOGY FOR PROSTATE CANCER

A series of studies interrogating the genomics of metastatic prostate cancer have been critical to defining the relevance of precision oncology for prostate cancer. Most of what is known about the genomics of prostate cancer has been derived from analysis of samples from the prostate itself. These samples may not reflect the biology of metastasis and genetic evolution in response to treatment pressure, so the genomic alterations in metastatic disease remained incompletely characterized. Two large research teams supported by grants from the American Association for Cancer Research,

FIGURE The VA/PCF Precision Oncology Program for Cancer of the Prostate Network



Abbreviations: PCF, Prostate Cancer Foundation; VA, US Department of Veterans Affairs.

Stand Up 2 Cancer, and Prostate Cancer Foundation (PCF) focused their efforts on sampling and analyzing metastatic tissue to define the most relevant genomic alterations in advanced prostate cancer.

These efforts defined a broad range of relatively common alterations in the androgen receptor, as well as the tumor suppressors TP53 and PTEN.^{2,3} Important subsets of less common alterations in pathways that were potentially targetable were also found, including new alterations in PIK3CA/B, BRAF/RAF1, and β -catenin. Most surprisingly, alterations of DNA repair pathways, including mismatch repair and homologous recombination were found in 20% of tumors, and half of these tumors contained germline alterations. The same groups performed a follow up analysis of germline DNA from men with metastatic prostate cancer, which confirmed that 12% of these patients carry a pathogenic germline alteration in a DNA repair pathway gene.⁴ These efforts immediately invigorated precision oncology clinical trials for prostate cancer and spurred an effort to find the molecular alterations that could be leveraged to improve care for men with advanced prostate cancer.

Targetable Alterations

Currently a number of genomic alterations are immediately actionable. There are several agents approved by the US Food and Drug Administration (FDA) that exploit these Achilles heels of prostate cancer. Mismatch repair deficiency occurs when any of a group of genes responsible for proofreading the fidelity of DNA replication is compromised by mutation or deletion. Imperfect reading and correction subsequently lead to many DNA mutations in a tissue (hypermutation), which then increases the risk of developing malignancy. If a defective gene in the mismatch repair pathway is inherited, a patient has a genetic predisposition to specific malignancies that are part of the Lynch syndrome.⁵ Prostate cancer is a relatively rare manifestation of Lynch syndrome, although it is considered one of the malignancies in the Lynch syndrome spectrum.⁶

Alteration of one of the mismatch repair genes also can occur spontaneously in a tumor, resulting in the same high frequency of spontaneous DNA mutations. Overall, between 3% and 5% of metastatic prostate cancers contain mismatch repair deficiency. The majority of these cases are a result of

spontaneous loss or mutation of the relevant gene, but 1 in 5 of these tumors occurs as a component of Lynch syndrome.⁷ Identification of mismatch repair deficiency is critical because the resulting hypermutation makes these tumors particularly susceptible to intervention with immunotherapy. Up to half of patients with metastatic prostate cancer can have durable responses. This finding is consistent with the experience treating other malignancies with mismatch repair deficiency.⁸ Although screening for mismatch repair deficiency is standard of care for patients with malignancies such as colorectal cancer, few patients with prostate cancer may receive the mismatch repair deficiency screening (based on unpublished data). In contrast, screening is routine for patients with adenocarcinoma of the lung because their proportion of ROS1 and ALK alterations is similar to the frequency of mismatch repair deficiency when compared with patients with prostate cancer.⁹

Homologous recombination is another mechanism by which cells repair DNA damage and is responsible for repairing double strand breaks, the type of DNA damage most likely to lead to carcinogenesis. In advanced prostate cancer, *BRCA2*, *ATM*, *BRCA1* and other members of the Fanconi Anemia/*BRCA* gene family are altered 20% of the time. These genes also are the most common germline alterations implicated in the development of prostate cancer.^{2,10} Prostate cancer is considered a *BRCA*-related cancer much like breast, ovarian, and pancreatic cancers. Defects in homologous recombination repair make *BRCA*-altered prostate cancers susceptible to DNA damaging chemotherapy, such as platinum and to the use of poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitors because cancer cells then accumulate cytotoxic and apoptotic levels of DNA.¹¹

In May 2020, the FDA approved the use of PARP inhibitors for the treatment of prostate cancers that contain *BRCA* and other DNA repair alterations. Rucaparib received accelerated approval for the treatment of prostate cancers containing *BRCA* alterations and olaparib received full approval for treatment of prostate cancers containing an array of alterations in DNA repair genes.^{12,13} Both approvals were the direct result of the cited landmark studies that demonstrated the frequency of these alterations in advanced prostate cancer.^{2,3}

Beyond mismatch and homologous recom-

bination repair, there are a large number of potentially targetable alterations found in advanced prostate cancer. It is thus critical that we put systems into place both to find germline and somatic alterations that will inform a veteran's clinical care and to provide veterans access to precision oncology clinical trials.

THE POPCAP NETWORK

Because prostate cancer is such a significant issue in the VA and best practices for precision oncology can be implemented broadly once defined as successful, the PCF and the VA formed a collaboration to support a network of centers that would focus on implementing a comprehensive strategy for precision oncology in prostate cancer. There are currently 11 centers in the Precision Oncology Program for Cancer of the Prostate (POPCaP) network (Figure). These centers are tasked with comprehensively sequencing germline and somatic tissue from veterans with metastatic prostate cancer to find alterations, which could provide access to treatments that would otherwise not be available or appropriate.

The network is collaborating with NPOP, which provides clinical grade tumor gene panel sequencing for veterans with prostate cancer from > 90% of VA medical centers. POPCaP also partners with the University of Washington to use its OncoPlex gene panel and University of Michigan to use the OncoPrint panel to define the best platform for defining targetable alterations for veterans with prostate cancer. Investigators participate in a monthly molecular oncology tumor board continuing medical education-accredited program, which provides guidance and education across the VA about the evidence available to assist in decision making for veterans sequenced through NPOP and the academic platforms. These efforts leverage VA's partnership with IBM Watson for Genomics to annotate DNA sequencing results to provide clinicians with potential therapeutic options for veterans.

A clinical trials mechanism is embedded in POPCaP to broaden treatment options, improve care for men with prostate cancer, and leverage the sequencing efforts in the network. The Prostate Cancer Analysis for Therapy Choice (PATCH) clinical trials network employs an umbrella study approach whereby alterations are identified through sequencing

and veterans are given access to studies embedded at sites across the network. Graff and Huang provide a detailed description of the PATCH network and its potential as a multisite clinical trials mechanism.¹⁴ For studies within the network, funds can be provided to support travel to participate in clinical trials for veterans who would be eligible for study but do not live in a catchment for a network site. POPCaP also leverages both the resources of the National Cancer Institute (NCI)-designated cancer centers that are VA academic affiliates, as well as a VA/NCI partnership (NAVIGATE) to increase veteran access to NCI cutting-edge clinical trials.

The network has regular teleconference meetings of the investigators, coordinators, and stakeholders and face-to-face meetings, which are coordinated around other national meetings. These meetings enable investigators to work collaboratively to advance current knowledge in prostate cancer through the application of complementary and synergistic research approaches. Since research plays a critical role within the learning health care system, POPCaP investigators are working to optimize the transfer of knowledge from the clinic to the bench and back to the clinic. In this regard, investigators from network sites have organized themselves into working groups to focus on multiple critical aspects of research and care within the network, including sequencing, phenotyping, health services, health disparities, and a network biorepository.

VA Office of Research and Development

With support from the VA Office of Research and Development, there are research efforts focused on the development of data analytics to identify veterans with metastatic prostate cancer within the electronic health record to ensure access to appropriate testing, treatment, and clinical trials. This will optimize tracking and continuous quality improvement in precision oncology. The Office of Research and Development also supports the use of artificial intelligence to identify predictive markers for diagnosis, prognosis, therapeutic response and patient stratification. POPCaP investigators, along with other investigators from across the VA, conduct research that continually improves the care of veterans with prostate cancer. POPCaP has a special focus on prostate cancer among African Americans, who are dis-

proportionately affected by the disease and well represented in VA. The efforts of the working groups, the research studies and the network as a whole also serve to recruit both junior and senior investigators to the VA in order to support the VA research enterprise.

Active collaborations between the network and other elements of VA include efforts to optimize germline testing and genetic counseling in prostate cancer through the Genomic Medicine Service, which provides telehealth genetic counseling throughout the VA. POPCaP pilots innovative approaches to increase access to clinical genetics and genetic counseling services to support the volume of genetic testing of veterans with cancer. Current National Comprehensive Cancer Network (NCCN) guidelines recommend germline testing for all men with metastatic prostate cancer, which can efficiently identify the roughly 10% of veterans with metastatic disease who carry a germline alteration and provide them with access to studies, FDA-approved treatments, while also offering critical health care information to family members who may also carry a pathogenic germline alteration.

Million Veteran Program

The Million Veteran Program (MVP) has collected > 825,000 germline DNA samples from an anticipated enrollment of > 1 million veterans in one of the most ambitious genetic research efforts to correlate how germline DNA interacts with lifestyle, medications and military exposure to affect health and illness (www.research.va.gov/mvp). MVP is a racially and ethnically diverse veteran cohort that is roughly 20% African American and 7% Hispanic. More than 40,000 of the participants have had prostate cancer, one third of whom are African Americans, giving researchers unprecedented ability to discover factors that impact the development and treatment of the disease in this population. In particular, MVP will provide unique insights into the genetic mutations that drive the development of aggressive prostate cancer in all male veterans, including African Americans. These discoveries will undoubtedly lead to improved screening of and treatment for prostate cancer.

In order to demonstrate clinical utility as well as the infrastructure needs to scale up within the VHA, MVP has launched a pilot project that offers to return clinically actionable genetic results to MVP participants with

metastatic prostate cancer, opening the door to new therapies to improve the length and quality of these veterans' lives. Importantly, the pilot includes cascade testing in family members of enrolled veterans. Given that the original MVP consent did not allow for return of results, and MVP genetic testing is research grade, veterans who volunteer will provide a second consent and undergo clinical genetic testing to confirm the variants. Results from this pilot study also will inform expansion of VA precision oncology efforts for patients with other cancers such as breast cancer or ovarian cancer, where the specific genetic mutations are known to play a role, (eg, BRCA2). In addition, through an interagency agreement with the US Department of Energy (DOE), MVP is leveraging DOE expertise and high-performance computing capabilities to identify clinical and genetic risk factors for prostate cancer that will progress to metastatic disease.

This active research collaboration between POPCaP, MVP, and the Genomic Medicine Service will identify germline BRCA alterations from MVP participants with metastatic prostate cancer and give them access to therapies that may provide better outcomes and access to genetic testing for their family members.

FUTURE DIRECTIONS

The POPCaP network and its partnership with VA clinical and research efforts is anticipated to provide important insights into barriers and solutions to the implementation of precision oncology for prostate cancer across the VA. These lessons learned may also be relevant for precision oncology care in other settings. As an example, the role of germline testing and genetic counseling is growing more relevant in precision oncology, yet it is clear that the number of men and women dealing with malignancy who actually receive counseling and testing is suboptimal in most health care systems.¹⁴ Optimizing the quality and efficiency of oncogenetics within the VA system in a manner that gives access to these services for every veteran in urban or rural environments is an important goal.

The VA has done extensive work in teleoncology and the Genomic Medicine Service provides telehealth genetic counseling service to 90 VA medical facilities nationwide. Expanding on this model to create a distributed network system across the country is an opportunity

that will continue to raise VA profile as a leader in this area while providing increased access to genetic services.

Finally, the clinical trials network within POPCaP already has provided valuable insights into how research efforts that originate within the VA can leverage the VA's strengths. The use of the NPOP centralized sequencing platform to identify potentially targetable alterations across medical centers provides the potential to bring critical access to research to veterans where they live through virtual clinical trials. The VA has a centralized institutional review board that can service large multisite study participation efficiently across the VA. The promise of virtual clinical trials to interrogate relatively rare biomarkers would benefit from institution of a virtual clinical trials workflow. In theory patients with a potentially targetable biomarker could be identified through the centralized DNA sequencing platform and a clinical trial team of virtual investigators and research coordinators would work with health care providers at sites for study startup and performance. Efforts to design and implement this approach are actively being pursued.

The goal of the VA/PCF POPCaP network is to make certain that every veteran has access to appropriate genetic and genomic testing and that the results are utilized so that veterans with targetable alterations receive the best clinical care and have access to clinical trials that could benefit them individually while advancing knowledge that benefits all.

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Author Disclosures

The authors reports no actual or potential conflicts of interest with regard to this article.

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