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Commentary

Precision Oncology at VA: Clinical Applications for a Learning Healthcare System

Michael Kelley, MD, Executive Director, VA National Oncology Program

VA takes care of approximately 450,000 patients every year who are on the cancer care continuum – from screening to survivorship. There are about 43,000 new cancer diagnoses every year in VA, and approximately 25 percent are rare cancers. VA is leading the fight against cancer through precision oncology approaches that are informed and reinforced by new discoveries from cancer research. This fusion of clinical treatment and research is the cornerstone of the care VA provides Veterans undergoing cancer treatment.

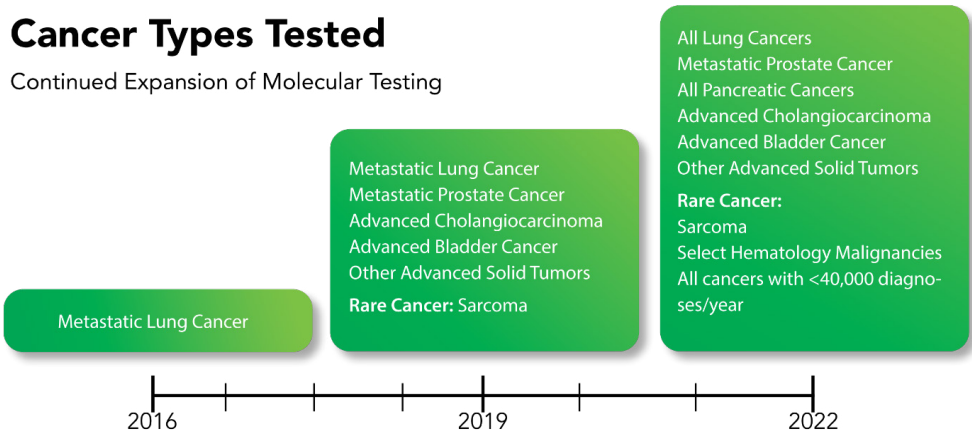
VA actively leverages treatment discovery and clinical development by collecting population-wide data on cancer recurrences and metastatic cancer development – accomplished by the cancer registry data that underpins programmatic decisions within cancer care. By linking these data points to individual characteristics of patients and their tumors, treatments, and clinical outcomes, VA is building systemic, comprehensive data tools that support both clinical needs and research priorities. Cancer is a genomic disease, and it has been firmly established that inherited and acquired genetic variations have a profound impact on the effectiveness of different anti-cancer drugs. As such, the use of precision oncology approaches in the treatment of our Veterans is essential.

The National Precision Oncology Program (NPOP) was created in response to the 2016 Cancer Moonshot call to action. Since the program launched, more than 34,000 Veterans, most with advanced cancer, have had their care guided by molecular testing, and more than 50,000 molecular tests have been ordered. Having expanded from just one cancer type – metastatic lung cancer – to lung cancers, pancreatic cancers, and advanced cholangiocarcinoma, bladder, other advanced solid tumors and all rare cancers, NPOP has evolved into a program that equips providers with the right treatment for the right Veteran, at the right time.

NPOP then uses its molecular testing database in novel clinical decision support tools that aid in Veteran treatment decisions, help families understand potential risks for developing certain cancers, determine program operational needs, and that inform research.

NPOP is one of the few programs in the nation that routinely screens cancer patients for genomic and proteomic abnormalities to align targeted therapies to tumor type. Further, when new clinical guidelines or therapies enter the scientific body of knowledge, NPOP re-analyzes the current database of Veterans to identify if new therapies or approaches have become available. From there, clinicians can evaluate if treatment approaches need to be adjusted.

Veterans are uniquely able to access genomic testing without the financial burden that may be experienced by their civilian peers. Precision oncology generates vast amounts of complex



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DIRECTOR'S LETTER

Precision Medicine

The old saying "what's sauce for the goose is sauce for the gander" doesn't apply in medicine. Every clinician knows that treatments that work for one patient may not work for another.[1] Treating chronic diseases such as hypertension or depression often involves multiple rounds of trial and error to find a drug that provides the greatest benefit and fewest side effects. The growth of predictive analytics has improved our ability to estimate benefits or harms based on demographic or clinical data while pharmacogenomic research has uncovered physiologic mechanisms underlying differences in drug metabolism, drug effectiveness, and side effects. Nowhere has the progress been more visible than in the development of drugs targeted to underlying genetic abnormalities in specific cancers. A future where doctors can prescribe the right treatment to the right patient at the right time is no longer a distant reality.

That said, claims about precision medicine can get ahead of solid evidence of clinical value, abetted by commercial interest in selling genomic tests or electronic health record-based decision tools. The solution to this is better research. As more of these tests and tools come to market several critical questions arise that neither manufacturers nor regulatory agencies are positioned to address. First, where are precision medicine approaches, and specifically searches for genomic determinants, most useful for guiding therapy? Many factors contribute to variable responses to therapy, and not all of them are biologic/physiologic factors. Especially for patients with chronic diseases, individual factors such as health priorities, health literacy, and trust in the health system may have an important effect on a patient's ability to adhere to specific treatments, and none of these factors are addressed by a genomic test. Second, when is evidence sufficient to scale any of these approaches across a health system? For genomic tests, we need more studies like that of Oslin et al. (which is described in this issue) that measure the extent to which precision medicine tests alter treatment decisions, and whether those decisions lead to better outcomes. Finally, for interventions ready for wider adoption, how do we best equip clinicians to use them in practice? This last question suggests an area ripe for implementation science. Advances in precision medicine are exciting, but we will need health services researchers to implement these advances into practice so they can benefit patients.[2]

David Atkins, MD, MPH, Director, HSR&D

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genomic and molecular data that clinicians must interpret and apply to patient care. This requires a high level of expertise in molecular biology and genomics, as well as specialized bioinformatics tools to help analyze the data. VA clinicians must also communicate the significance of this data to patients in a way that is easily understandable, keeping in mind that Veterans often have dynamic social environments with family members and caregivers intimately engaged in the cancer journey.

Improved accuracy of genomic profiling helps clinicians identify the most appropriate treatment options for individual patients. That is why clinical treatment of cancer is increasingly driven by precision oncology approaches – and has moved from treatments based on type and histology alone to treatment decisions based on patient-specific molecular characteristics including protein expression and comprehensive genomic profiling.

Precision oncology can also help identify environmental exposures that may have contributed to a Veteran's cancer diagnosis. For example, some patterns of genetic mutations may be linked to exposure to carcinogens such as Agent Orange or radiation. Identifying these environmental exposures can help clinicians develop more targeted treatment plans and prevent future exposures.

One such effort is the Molecular Analysis Researching Carcinogenic Exposures research project (MARCE), which is focused on a cohort of tumor samples from Veterans who were stationed at Marine Corps Base Camp Lejeune between 1950 and 1985. Researchers are looking to understand and identify the impact that contaminated drinking water may have had on the pattern of DNA mutations that occur in tumors linked to exposure to the drinking water contaminants, including cancers of the kidney, multiple myeloma, bladder, liver, leukemia (bone marrow), and others. This specific research effort is geared towards further understanding the effects of military environmental exposures, and their clinical implications.

As seen with MARCE, precision oncology generates new questions and challenges for cancer researchers. As precision oncology approaches become more widespread, and researchers continue to explore new targets for therapy, our community of clinician-scientists must work to expand and refine biomarkers that predict response to treatment and develop strategies to overcome resistance to treatment. We must also develop new technologies and tools for analyzing the complex molecular and genetic data that is generated by precision oncology.

Overall, precision oncology and cancer research are mutually reinforcing fields that depend on each other for progress. Precision oncology relies on the findings of cancer research to develop new therapies, while cancer research depends on precision oncology to validate new discoveries and successfully translate them into clinical practice. This symbiotic approach embodies the learning healthcare model that VA strives towards, all while centering on the needs of the Veteran.

The Potential for Precision Oncology to Enhance Cancer Detection, Diagnosis, and Treatment for Veterans

Kenute Myrie, PhD, and Grant Huang, PhD, VA Office of Research and Development

The VA Precision Oncology Initiative integrates clinical and research domains with the aim of transforming VA into a System of Excellence for oncology care; the Initiative both provides individualized cancer treatment to Veterans based on the characteristics of their tumors *and* creates a learning healthcare system for oncology care. The National Precision Oncology Program (NPOP) has provided Veterans with centralized molecular testing for their cancers and genetic counseling is available from the Clinical Cancer Genetics Service. NPOP provides molecular testing (somatic and germline) of advanced cancers at over 90 percent of VA medical centers and provides expert consultation service to assist oncologists with interpretation and therapeutic decision making. These capabilities along with a robust data, informatics, and analytic infrastructure offer signature components for a system where the generation of data and use of evidence are critical to providing Veterans with high quality oncology care.

To further the creation of this system, the Office of Research and Development (ORD) and the National Oncology Program Office (NOPO), both parts of the Veterans Health Administration within VA, have partnered to establish multiple synergistic care and research networks. For example, the Prostate Cancer Analysis for Therapy Choice (PATCH) network works with the Precision Oncology Program for Cancer of the Prostate (POPCaP) and genitourinary (GU) sites to increase the number of VA facilities involved in clinical trials. In turn, the number and diversity of Veteran participants in clinical trials of precision therapies for prostate cancer can be increased. Appropriate studies developed from within the PATCH network by VA investigators allow Veterans with prostate cancer to participate in biomarker stratified basket trials in which they are assigned to one of the treatments based on the genetic changes identified in their tumors, thereby providing Veterans with the most advanced clinical trials. PATCH provides a coordinated effort to perform a range of multi-site studies focused on targetable molecular alterations for Veterans with prostate cancer. Simultaneously, similar efforts are being developed for lung cancer through the Lung Precision Oncology Program (LPOP) to carry out a robust set of biomarker studies in which "on-" and "off-label" Food and Drug Administration-approved therapies are paired with specific mutations identified in advanced cancer.

It is important to note that POPCaP, GU, and LPOP are part of a larger set of networks, coordinated and managed by the VA Cooperative Studies Program (CSP), that include the Network of Dedicated Enrollment Sites (non-cancer specific studies) and the National Cancer Institute (NCI) VA Interagency Group to Accelerate Trials Enrollment (specific to NCI-supported trials). Under this umbrella, these groups have undertaken a pilot program aimed at engaging rural VA medical centers interested in enrolling Veterans in clinical trials called Advancing Capacity for Clinical Research through Engagement and Strategic Sites. By developing capabilities to run clinical trials across multiple therapeutic areas, these groups can share and disseminate best practices to build expertise and to focus efforts on novel ways of reaching out to Veterans and building rapport with them across the VA enterprise.

Despite the success of molecular targeted therapy, the benefit for patients has been modest since only some patient populations show significant improvement in their response to targeted treatment and survival. It remains to be seen if additional genomic signatures apart from driver mutations can be utilized to further expand targeted therapeutic efforts. More specifically, it is uncertain if these signatures can predict response to treatment. Identifying such biomarkers will require deep whole genome sequencing of tumors, matched controls, and bioinformatic analyses to identify potential mutational signatures involved in cancer development. ORD is supporting investigations in this area of research with initial pan-cancer studies. This effort also has the potential to shed light on the effects of environmental exposure, epigenetic changes, and other mutational processes in the genome.

Similarly, immunotherapy has shown durable benefit in some cancers and more so in lung cancer where it is effective in approximately 20 percent of patients. However, in most cancers, there is resistance and/or no benefit from immunotherapy due to immune checkpoint blockade. Efforts are under way through ORD funded research to examine the combination of immunotherapy with other treatment modalities (chemotherapy, radiation, etc.) to potentiate anti-tumor immune response, thereby increasing the efficacy of immunotherapy (i.e., enhance the efficacy of checkpoint inhibitors). Since resistance to treatment and recurrence continue to be major problems for cancer patients, ORD is investing in the development of novel molecular and immune biomarkers and molecular diagnostic assays to monitor treatment response and recurrence in real time. These assays utilize protein profiles, ctDNA, microRNAs, circulating tumor cells, and other tumor fragments circulating in plasma. If successful, these assays would be less invasive and could be impactful in clinical management of patients.

A comprehensive understanding of cancer in which genomic, molecular, and clinical data are integrated is critically important to enable discovery and opportunities to translate those discoveries into the clinic. Data that are curated, cleaned, validated, and optimized for system-wide access by clinicians and researchers are crucial to realizing the power of VA data to drive innovation and advance therapies more quickly to benefit Veterans and the public. Data integration, combined with a data governance framework that applies across the enterprise, is necessary for sharing data and knowledge, and for fostering collaborations, partnerships, and cross-disciplinary approaches to operationalize findings into care.

ORD and NOPO are actively working to harmonize data systems that organize and integrate various pieces of genomic, phenotypic, imaging, and clinical data combined with bioinformatics and

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Access to the Promise of Precision Medicine: Lessons Learned from the Organization and Delivery of Genetic Services in the Veterans Health Administration

Maren T. Scheuner, MD, MPH, San Francisco VA Health Care System, San Francisco, California

Genetic information can transform healthcare and improve health outcomes through better diagnosis, prognosis, risk assessment, and targeted treatment, screening, and prevention. The demand for genetic services is growing. Yet currently, there are insufficient numbers of genetics professionals to meet the demand. Adding to the access challenge in the Department of Veterans Affairs (VA), most genetics professionals work in academic, metropolitan settings; in contrast, more than one-third of Veterans live in rural areas and referral to non-VA genetic services is not a viable option in many communities. For more than a decade, our health services research team has been investigating the organization and delivery of genomic medicine for VA patients.

Genetic services became widely available within VA in 2010 with the launch of the VA Genomic Medicine Service (GMS), a model program serving about 80 VA facilities nationwide using only telehealth modalities (i.e., video-to-clinic, video-to-home, telephone). Telehealth is a sensible approach for genetic services in VA because telehealth enables the reach of clinical genetics expertise across long distances, and telehealth modalities are medically appropriate for most genetic consultation referral reasons for adults. Still, some patients prefer in-person encounters, possibly due to the novel and complex nature of genetic information. In addition to GMS, at least six traditional genetics programs exist in VA today serving patients at one or multiple VA facilities within a region via in-person or telehealth delivery modalities.

We conducted a cross-sectional study of VA patients referred for genetic consultation from 2010 to 2017 with two years of follow-up to assess care coordination of genetic care delivered by GMS, VA traditional programs, and non-VA care.[1] There were 24,778 patients with genetics referrals, including 12,671 (51 percent) women, 13,193 (53 percent) aged 50 years or older, 15,639 (63 percent) White patients, and 15,438 (62 percent) patients with cancer-related referrals. GMS received 14,580 (59 percent) consultations. Like other studies comparing VA and non-VA care, we found VA genetic care had better care coordination than non-VA care. Timeliness and ability to schedule and complete genetic consultations were significantly better within VA.[1]

Comparing GMS with VA traditional programs, we found improved access with GMS.[1] However, compared with the traditional programs, the uptake of both cancer screening and risk-reducing procedures within two years following the genetics referral was hindered under GMS. Patients were significantly more likely to have these procedures if they completed their consultations, but only if completed under the traditional programs.[1] With most GMS encounters conducted solely by genetic counselors, this likely constrained the recommendations made and the ability to directly order them given their scope of practice. To better understand the differences observed in cancer screening and prevention uptake, we reviewed medical records and conducted interviews with referring clinicians. We learned personalized recommendations (e.g., begin colonoscopy at age 30, then every 1-2 years) were more typical of records from traditional programs compared with GMS. Moreover, more personalized, specific recommendations better met the expectations of referring providers.

We also found that while GMS increased access to genetic services, the telehealth model exacerbated healthcare disparities based on race or ethnicity compared with the traditional programs.[1] The disparities are likely multidimensional and may be explained by the centralized structure and uniform approach of the GMS telehealth model. Centralized services may improve efficiencies of operational and administrative processes, but also can challenge care coordination by constraining the ability to tailor services to local needs, stifling initiative and innovation, and complicating communication processes between the staff, patients, and referring clinicians. Further, vulnerable subpopulations are less able to benefit from a centralized approach because of inconsistencies between the social and cultural assumptions of those implementing the approach and the targeted groups.

In VA, telehealth use is known to be lower in Asian, Black, and Hispanic patients compared with White patients. We observed this happening at the consultation referral stage for patients of Asian, American Indian/Alaskan Native, and Native Hawaiian/Pacific Islander ancestry who were significantly less likely than White patients to be referred to GMS compared with the VA traditional model programs, and at the consultation

Key Points

- Genetic services became widely available within VA in 2010 with the launch of the VA Genomic Medicine Service (GMS), which serves approximately 80 VA facilities nationwide using telehealth modalities.
- A cross-sectional study of VA patients referred for genetic consultation from 2010 to 2017 with two years of follow-up, found that VA genetic care had better care coordination than non-VA care. However, the uptake of both cancer screening and risk-reducing procedures within two years following a genetics referral was hindered under GMS.
- The study also found that while GMS increased access to genetic services, the GMS' telehealth model exacerbated healthcare disparities based on race or ethnicity compared with the traditional programs.

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completion stage for Black patients who were significantly less likely than White patients to complete consultations, but only if referred to GMS.[1] The digital divide cannot explain the disparities we observed in completing genetic consultations, since video-to-clinic encounters were used rather than video-to-home during the study period. Thus, improving access to telehealth equipment and the Internet will not suffice to ensure health care equity.

Mainstreaming genetic services within the practice of frontline clinicians is an alternative approach to improving access to genetic testing. To understand the readiness of frontline VA clinicians to use genetic tests, we administered a web-based survey from August-September 2020 to clinicians (physicians, nurse practitioners, physician assistants, and pharmacists) with VA email who were working at 20 VA facilities with precision oncology programs (10 Prostate Cancer Foundation Centers of Excellence, 10 conducting precision oncology clinical trials) to guarantee experience with genetics among some clinicians.[2] The survey response rate was 11 percent and 909 were eligible.

We found 21 percent felt prepared to use genetic tests and only 13 percent had ordered genetic tests in the past year, and most had ordered only one or two tests. Other surveys of non-VA clinicians show 30-50 percent ordered a genetic test in the past year. We would expect most VA clinicians to have large numbers of patients in their practice with indications for genetic testing, such as pharmacogenetic testing, tumor testing, or testing for hereditary cancer syndromes. Common reasons for not ordering genetic tests among VA survey respondents included not believing genetics is relevant to their practice or uncertainty about the relevance, not knowing how to order the testing, or preferring to refer patients to genetics or other specialists, revealing their lack of awareness and preparedness to use genetic tests.[2]

Most VA survey respondents indicated that they would prefer to refer all or some of their patients to genetics or have a genetics provider embedded in their clinic to facilitate genetic testing.[2] Clinicians felt prepared to use genetic tests themselves if they had genetics education in the past year, experience with ordering genetic tests, or were knowledgeable about genetic testing guidelines.[2] Even among the more prepared clinicians – the cancer specialists – most did not order any genetic tests, and those who did lacked full confidence in their abilities to carry out pre- and post-test activities.

Somewhat paradoxically, as frontline clinicians ordered genetic tests, they were more likely to have referred patients for genetic consultation in the past year.[2] This might be due to more post-test genetic consult requests to help interpret and communicate positive, unexpected, or uncertain genetic test results. Additionally, as frontline clinicians take on genetic test ordering, they may be learning what they don't know about genetic testing. With increasing recognition of their limitations, they may be learning to value the expertise and input of genetics professionals. When asked who should be responsible for updating VA clinicians about genetics, the clinical genetics team or service received the highest rating (57 percent of survey respondents) compared with other options, such as educational programs provided by local VA facilities or VA National Program Offices, academic affiliates, or professional societies.[2] Thus, genetics professionals are key to the integration of genetics into the practice of frontline clinicians; they are needed to receive genetics referrals and to educate their colleagues.

In VA, as in other healthcare settings, access to genomic medicine has become increasingly relevant to nearly all aspects of clinical care. Adoption and implementation of genetic testing will require a multilevel effort that includes education of clinicians and administrators, opportunities for observing the benefits of genetic medicine, strategies for reducing the complexity of genomic medicine, expanded strategies for accessing genetics expertise, and streamlined usage and resources dedicated to assessing the value of genetic information.[3] With increasing use of genetic tests by frontline clinicians, our findings suggest the demand for genetics professionals will remain high rather than decrease. Thus, planning to expand the genetics professional workforce is necessary. Given the limited number of genetics professionals in the United States and their concentration in academic, metropolitan settings, organizing the genetics workforce is challenging, particularly for healthcare systems like VA that cover large geographic areas. In VA, perhaps centralizing administrative and business functions and de-centralizing clinical genetic services through a consortium structure might be best, with regional traditional genetics hubs having both remote and on-site genetics professionals providing virtual care and face-to-face care when needed or desired. This model could improve access to genetic services while ensuring delivery of more patient-centered, effective, and equitable care.

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Implementation Challenges to the Impact of Pharmacogenomic Testing in Mental Healthcare

David W. Oslin, MD, VISN 4 Mental Illness Research, Education, and Clinical Center (MIRECC), Philadelphia, Pennsylvania, Laura O. Wray, PhD, VA Center for Integrated Healthcare, Buffalo, New York, and Andrea Ford, MS, VISN 4 MIRECC

Major depressive disorder (MDD) is one of the most common conditions among Veterans receiving VA healthcare, and antidepressants, a first-line treatment for MDD, are among the most prescribed classes of medications. However, only about a third of patients treated with antidepressants achieve remission on their first treatment attempt, and the odds of success decline with each attempt. Thus, improved use of MDD treatment could have a substantial impact on Veteran health outcomes.

Pharmacogenomic testing is a tool providers can use to identify medications and dosing that may best match patients' individual genome, potentially improving medication response and avoiding adverse reactions. However, while pharmacogenomic testing has demonstrated effectiveness and has seen wide clinical adoption in fields such as oncology, evidence for its utility in psychiatry has emerged only recently. VA has been a leader in supporting efforts to study and implement precision mental healthcare.

Pharmacogenomic Testing in Mental Health: The PRIME Care Study

The VA-funded **Pr**ecision Medicine **i**n **Me**ntal Health Care (PRIME Care) study,[1] a randomized controlled trial, enrolled 1,944 Veterans and 676 frontline providers in mental health and primary care settings across 22 VA sites. After the Veteran and provider determined that a new episode of MDD treatment was needed, Veterans received a pharmacogenomic test and were randomized to either receive results immediately (pharmacogenomic-guided care) or after a six-month delay (usual care). All treatment decisions, including medication choice, dose, and any subsequent changes, were determined only by the patient and provider. Research outcomes were assessed by study staff after 4, 8, 12, 18, and 24 weeks.

The study found that for patients with MDD who received pharmacogenomic-guided care, the estimated risk for treatment with an antidepressant with a substantial drug-gene interaction was 11 percent. This rate was significantly reduced compared to the delayed results group, where 20 percent of patients received antidepressants with potential drug-gene interactions.

Remission rates were significantly better for the pharmacogenomic-guided group, with differences peaking between the two groups at 8 and 12 weeks (see Figure 1). While the overall effect was small, a key insight was that only about 1 in 5 patients with depression was prescribed an antidepressant with substantial gene-drug interaction potential.[2] Therefore, while the population-level benefit may be limited, pharmacogenomic testing could be critically important for 20 percent of patients.

Challenges to Implementation and the Path Forward

As evidence builds, VA must continue to address how to scale up pharmacogenomic testing. Among the central barriers to implementation in mental healthcare are the knowledge and comfort gaps among frontline providers about whether and how to use test results.

A survey[3] conducted in PRIME Care found that at the outset of the study, only about 22 percent of enrolled primary and mental healthcare providers had ordered a pharmacogenomic test in the past year (see Figure 2). Slightly more than half of mental health providers and only a quarter of primary care providers said they felt comfortable ordering a pharmacogenomic test. We also learned that only about a quarter of surveyed providers were aware that the Food and Drug Administration has revised medication labeling to include pharmacogenomic information.

Key Points

- Veterans whose treatment for major depressive disorder was guided by pharmacogenomic testing had higher rates of remission and were less likely to be prescribed an antidepressant with a drug-gene interaction.
- At present, many VA providers in both specialty mental health and primary care have limited knowledge, comfort, and experience with pharmacogenomic testing.
- Scaling up pharmacogenomic testing in mental healthcare will require increased provider and patient education, local subject matter experts like pharmacists, and IT and informatics investments for clinical decision support, and will benefit from approaches developed based on implementation science.

Surveyed providers enrolled in PRIME Care who did not refer any patients to the study unanimously indicated that they "did not trust the results of the testing" and that they "worry that test results are influenced by specific pharmaceutical companies." Some providers worried about the ethics and safeguarding of patient privacy when handling genetics reports.

These findings highlight the need for educational initiatives focused on the application of pharmacogenomics in standard practice. Providers and patients also need to understand that there are safeguards in place to guard privacy and protect against genetic discrimination. PRIME Care provided considerable educational resources for participants, including videos, talks, written materials, and one-on-one consultations. Availability of similar resources could help expand implementation across the workforce.

Another potential barrier to implementation is that providers need support at the point of care, not only to ensure that they are using the information correctly, but also to help

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them integrate testing into their workflows. In interviews conducted for PRIME Care, providers expressed concerns about potential delays in treatment, and they worried that they would have insufficient time to properly provide education and discuss testing with patients. Influential clinical leaders and role models can help busy providers overcome reluctance and develop new workflows.

A clinical decision support (CDS) platform that accommodates pharmacogenomic testing will save valuable time and maximize the value of results. However, developing the platform will require thoughtful consideration and IT and informatics investment, as pharmacogenomic information has some unique qualities. For example, unlike other laboratory results, pharmacogenomic test results are valuable throughout a patient's lifetime, so the platform will need to provide convenient access to the information in a way that is not time dependent. In addition, most pharmacogenomic test reports are returned in formats not searchable in the electronic health record, so retrieving them can be labor-intensive. Also, approaches to genotyping and its interpretation can vary, so it is important to standardize information so that consistent recommendations are given at the point of care.

With the current expectation being that routine use of pharmacogenomic testing will continue to expand, overall, the PRIME Care study has helped create a clearer picture of both the potential benefits of, and some challenges to, implementing this practice in VA mental healthcare.

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Figure 1. Percent Remission from Major Depressive Disorder

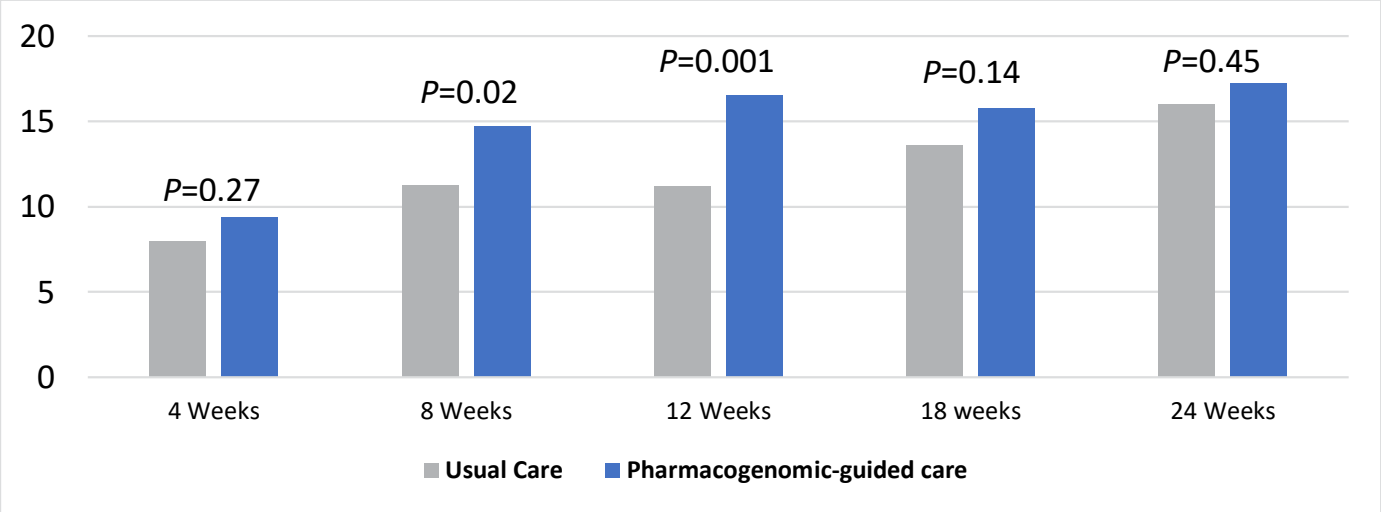
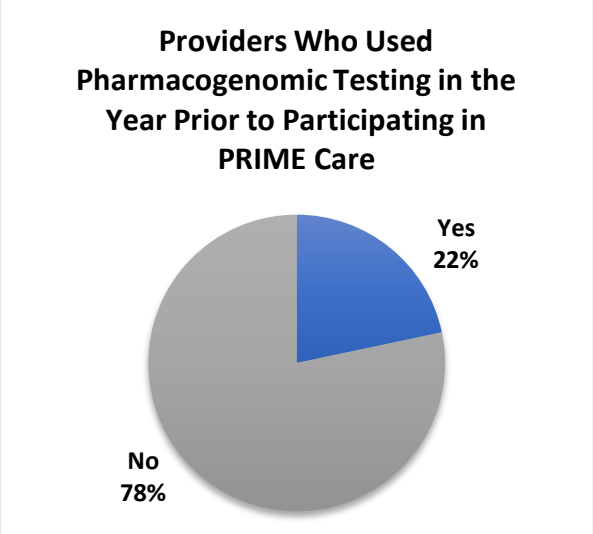
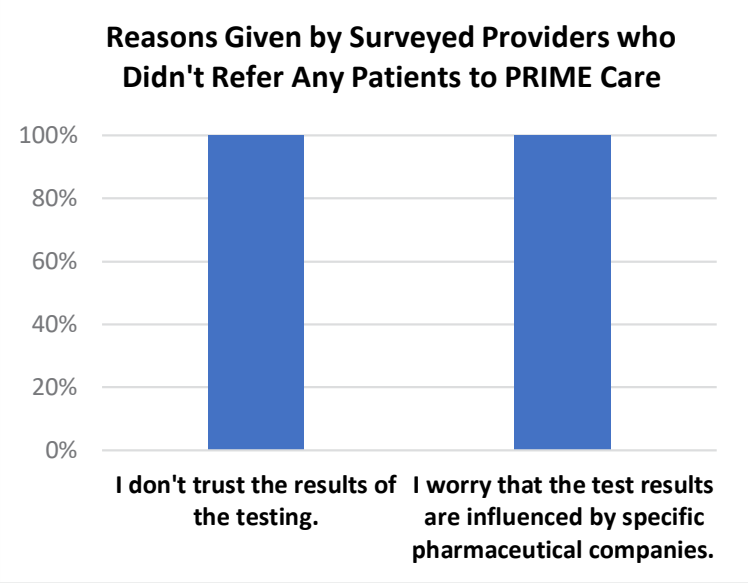


Figure 2. Clinician Provider Experience and Attitudes toward Pharmacogenomic Testing





Incorporating Precision Medicine in VA Healthcare: A Qualitative Analysis of Veterans' Considerations and Interests in Genome Sequencing

Sara J. Knight, PhD, HSR&D Informatics, Decision Enhancement, and Analytical Sciences Center of Innovation (COIN), VA Salt Lake City Health Care System, Salt Lake City, Utah

The VA Genomic Medicine Services (GMS) and the VA Million Veterans Program (MVP) were launched in 2010 and 2011, respectively. The goals of these programs were 1) to establish national clinical genetic counseling services for Veterans,[1] and 2) to create a national VA-based mega biobank and cohort study to accumulate generalizable, representative, and longitudinal data on Veterans' health and health risks. The MVP was richly informed by the Electronic Health Record, Veteran-reported health experiences and outcomes, and biomedical information, including genetics and genomics.[2]

In the following decade, VA introduced new genomic technologies for informing health recommendations and medical care. VA conducted several studies of VA health professionals' beliefs and experiences with the adoption of precision medicine and two early surveys sought Veterans' opinions to inform the launch of MVP.[1-3] Yet, little evidence has been available on Veterans' perspectives on these emerging genomic technologies.

We sought to understand Veterans' interests in precision medicine and to align new policies and practices with Veterans' needs, goals, and preferences for genome sequencing. In this study, we conducted 14 focus groups of 65 Veterans in Boston, Massachusetts, Durham, North Carolina, and Salt Lake City, Utah. The sample included 18 percent women Veterans, 34 percent African American Veterans, 6 percent more than one race, 5 percent Hispanic ethnicity, and 52 percent White Veterans. We moderated the focus groups using a discussion guide. We analyzed de-identified transcript data using deductive content coding and subsequent inductive qualitative analysis of the coded data.

We asked Veterans about their understanding of genetic testing, genome sequencing, and precision medicine, their interest in results from genome sequencing, their concerns about the impact of this information on privacy, insurance and healthcare costs, and their considerations about sharing genetic information with their children and other family members. Four themes that emerged from the qualitative analyses of the transcript data are presented below and are accompanied by quotes in italics, each from a unique individual, that illustrate a range of perspectives among the focus group participants.

Enthusiasm for personal genomic information. Veterans' enthusiasm for improving their understanding of personal health information based on genetics emerged as the first theme from the focus group discussions. Veterans described the information as "exciting," "empowering," "beneficial," and "valuable." Most described genetic and genomic information as allowing them to be proactive in treatment, medication, and prevention decisions. The excitement about genomic medicine extended to MVP and most described the program as highly valuable; Veterans stated that they hoped to learn more about the discoveries and other findings coming from MVP studies.

All groups discussed the greater number and complexity of results available through genome sequencing. Only a few Veterans saw the complexity of genomic results as difficult or distressing. Most expressed interest in genome sequencing even if the information did not inform a diagnosis, course of care, or prevention – or yielded results that indicated a genetic variant of unknown significance. Most commented on the advantages of obtaining more information from genome sequencing than genetic testing would provide.

Key Points

- Recent focus groups with Veterans explored their understanding of genetic testing, genome sequencing, and precision medicine.
- Veterans expressed enthusiasm about the potential to understand personal health information based on genome sequencing, and to use that information to be proactive in treatment, medication, and prevention decisions.
- Veterans reviewed their concerns about the potential impact of genetic information on privacy, insurance and healthcare costs, and their desire to share this information with family members to aid in healthcare decision making.

I definitely want to know. I think that all the information about my personal healthcare should be delivered to me as it's known…. So I think for me, giving me the power, giving me the knowledge, giving me the control over every possibility, things that could come up even if they're not treatable now is the best power, that knowledge of what can and can't be. But I think it's the whole point of this type of genome study, that's what we need to do is to educate, empower, and inform our Veterans about their personal healthcare.

I would really like to see the VA do more research, release the results. And if there's things that can benefit Veterans' lives through lifestyle choices and having more information, I feel like that's better for everyone. And especially because the VA has done the Million Veteran Program and they have a large sample to use for testing, for research, and to help improve people's lives through education and just more information. I think that would be very beneficial.

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Envisioning genomic medicine. Veterans' aspirations for genome sequencing emerged as a second theme of the focus group discussions. Veterans discussed their hopes for genomic medicine and the promise of precision medicine even though they acknowledged limits to their understanding of genetics and its uses. Veterans saw the potential that genomic information could inform diagnosis, treatment, or prevention of a condition. Some reflected on genomic information used to inform reproductive decision making and to guide family decisions about care for children with hereditary conditions.

Veterans in all the groups expressed the hope that genomic medicine would provide an explanation for how toxic exposures during their military service may contribute to health conditions. While a few thought that they would not want to know about a condition that could not be treated, a large proportion of participants described their interest in knowing whether they have an untreatable health condition, noting the importance of the diagnosis in planning for their lives and their families. Many indicated an interest in working with the VA Genomic Medicine Service and VA doctors to help them understand the genomic information and its potential use in their healthcare.

Even if it's something that's terminal, if it's something that's going to go with me through my lifetime, I would still like to know regardless. And you don't want to be blindsided. It would be nice to basically just know and then that way you can continue with your quality of life or make whatever decisions you need to make.

…maybe you're exposed to something and we think that it might cause this condition or illness but by looking at the entire genome or by looking at more of the information that's available, maybe it would also cause other things.…so say you're exposed to something like Agent Orange before you have children and it causes a change in your genome so then that change may produce undesired results in your children.

Family matters. The implications of genomic information for Veterans' family members, especially their children, emerged as a third theme of the focus group discussions. Most Veterans acknowledged feelings of responsibility for sharing their genetic information with family members to facilitate decision making about additional genomic sequencing for diagnosis, reproductive decisions, and managing health risk information. Some Veterans noted the challenges of these family discussions, especially the potential to increase family discomfort and distress. Yet most embraced the opportunity to help their children with significant health and life decisions based on genetic information.

I want to know and I think I should know so that my children can know. And I don't know how you explain that to a 16 and 18 and 20-year-old when they're deciding, do you have kids or not?...I would at least want to share that and know it.

Value of information weighs heavily in decisions where privacy is a concern. A fourth theme of the focus group discussions reflected two critical factors that influence choices about genetic testing and genome sequencing: 1) privacy and information security concerns, and 2) the significance of genomic information in decisions about health and healthcare. Many of the Veterans in this sample noted that their desire to obtain genetic information surpassed their concerns about privacy and data security in doing so. Some noted that they had experienced a privacy breach in the past and now accepted the potential for loss of privacy; these Veterans wanted the health information provided through genome sequencing more than they were concerned about loss of privacy.

Personally, I'd rate the benefit that genetics could have to improving health above the privacy concerns and those kinds of things. But I don't think the privacy concerns can be completely ignored because of those benefits. So it's kind of like you got to go a little bit in both directions.

Our findings highlight the significance of the VA clinical and scientific advances in genomics and precision medicine for Veterans and their families, and identify key challenges. Across the groups, Veterans consistently expressed strong enthusiasm for genomic information to guide healthcare and prevention broadly. Some choices appear preference sensitive, such as receiving information about incurable health conditions. Veterans expressed interest in education and learning from VA research on genomics to inform their choices related to environmental exposures and hereditary conditions. A challenge for VA precision medicine services is how to serve Veterans' families and children who are impacted by information from VA genome sequencing. Our findings suggest that opportunities for education from VA programs, such as GMS and MVP, could address some of the challenges in meeting Veterans' needs and goals.

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An Effort to Understand Factors Associated with Variable Veteran Uptake of Pre-emptive Clinical Pharmacogenomics

Corinne Voils, PhD, William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

The VA National Pharmacogenomics Program (NPP) is among the largest pre-emptive clinical pharmacogenomics (PGx) programs in the United States. Pre-emptive testing refers to testing without a specific indication or medication needed to justify testing. The NPP currently offers tests of 11 genes that affect over 40 medications and, to date, has tested over 30,000 Veterans by over 3,000 providers across 60 VA health systems. Initial program data showed variable uptake. Therefore, the NPP evaluation team, funded by a Quality Enhancement Research Initiative (QUERI) partnered evaluation, is exploring factors associated with variability in uptake. The team used program data to identify five facilities with higher and five with lower numbers of PGx orders. From these ten facilities, team members conducted qualitative interviews with 1) chiefs of staff, pharmacy, laboratory, and site champions; 2) high-, medium-, and low-ordering prescribers; and 3) Veterans who accepted and declined PGx testing. Preliminary findings with Veterans suggest that accepters and decliners alike are aware of the logistics, risks, and benefits of testing. These two groups differed in how they weighed the risks versus benefits of testing. Whereas accepters focused on the potential for PGx testing to identify efficacious medications and to reduce side effects and polypharmacy, decliners focused on the potential of data breaches and negative impact of genetic information on insurance coverage. Data from the Corporate Data Warehouse (CDW) are being used to examine factors associated with patient receipt of PGx testing. Among those are demographic characteristics, type of prescriber (MD, pharmacist, or mid-level provider), and prior negative reactions to PGx-targeted medications. Analyses of CDW data and interviews with VA employees are ongoing. Findings will be used to improve patient understanding of the risks and benefits as well as other aspects of program implementation, uptake, and utilization of PGx testing in VA.

Evaluation team: Corrine Voils, PhD, Abigail Silva, PhD, R. Ryanne Wu, MD, MHS, Nina Sperber, PhD, Esra Alagoz, PhD, Diana Gutierrez-Meza, MPH, Karina Melendez, BS, Kara Gavin, PhD, MPH, Allison Hung, MPH, Brian Bartle, MS, Zhiping (Jenny) Huo, MS, Megan Roberts, PhD

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other technologies such as artificial intelligence and machine learning to enhance cancer detection, diagnosis, and treatment and to improve patient outcomes by optimizing clinical trials for appropriate patient populations and research. Together this effort can support new investigations (whether or not funded by VA), development of novel biomarkers, and targeted and immunotherapy approaches; increase the use of technologies to improve the analysis of data that informs precision oncology; and make it possible to translate discoveries into clinical care.

With respect to data, VA is also partnering with the NCI in the Big Data Scientist Training Enhancement Program and providing access to data as part of training the next generation of experts for using large, complex datasets that VA expects to continue to generate. ORD is also working with the University of Chicago Center for Translation and Data Science and the Precision Oncology Data Repository to provide access to and share de-identified data with the research community to enable rapid advances for Veterans. In addition, ORD supports the development of the Computer Vision and Machine Learning in Precision Oncology (CoMPL) hub within LPOP to accelerate the development of computer vision and machine learning (CVML) tools to address cancer diagnosis, prognosis, risk stratification, prediction of treatment response, and improving outcomes in the VA population. These tools are regulated as software as a medical device and are the future for cost-effective, precision treatment. CoMPL serves as a resource for building and expanding the community for CVML precision oncology research within the VA through collaborative efforts. Critical to this effort will be the development of a repository of curated, de-identified, and annotated high quality data with clinical information from all cancer types to be available to researchers to develop, test, and validate algorithms that can be used in healthcare. CoMPL leverages expertise from the Million Veteran Program and CSP, which were instrumental in developing GenHub and Genesis data analytics platforms. ORD has been building these platforms as enterprise resources to enable investigators to perform high computational analyses in a secure environment. Since its phased implementation in 2022, CoMPL is bringing VA investigators together and fostering collaborative multidisciplinary studies in prostate, lung, head and neck, and other cancers.

To exemplify the power of partnerships that leverage these resources, bioinformatics, and data science capabilities, VA has made a centerpiece of its participation in the Cancer Moonshot relaunch. Specifically, data from Applied Proteogenomics Organizational Learning and Outcomes (APOLLO), a tri-agency partnership among VA, Department of Defense, and NCI, will be made available through the Genomic Data Commons, Proteomic Data Portal and Cancer Imaging Archive of the NCI. APOLLO is focused on advanced genomic and protein analyses of high-quality tumor samples from service members and Veterans to identify potentially actionable therapeutic molecular targets and determine whether and how protein expression predicts patient response to treatment. The goal is to enable a continual learning process involving data obtained from trials and clinical care to inform Veteran care that builds upon experiences from each case.

Together, these efforts within the precision oncology initiative have positioned VA to leverage its resources, expertise, human capital, and diverse patient population to become a leader in developing and advancing clinical evidence for care. More importantly, they enable VA to improve cancer outcomes for Veterans and their loved ones.