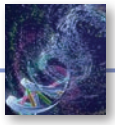

Implementation of a Precision Oncology Program as an Exemplar of a Learning Health Care System in the VA

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The program determines and disseminates precision oncology best practices; enhances patient and provider engagement; and fosters collaboration among the VA, National Cancer Institute, academia, other health care systems, and industry to provide cancer patients with access to clinical trial participation.

Traditional research methods, well suited for scientific discovery and drug development, fall short of providing health care systems with pragmatic information in 2 important ways: Current funding and institutions cannot support comparative effectiveness studies in sufficient numbers to answer the plethora of important clinical questions that confront health care providers (HCPs). The resultant knowledge gap manifests in treatment variability based on clinician impression rather than on direct evidence. A second equally important deficiency is the inability to make full use of the knowledge acquired in treating past patients to determine the best treatment option for the current patient.

Digitization of medical records, creation of health care system corporate data warehouses, and state-of-the-art analytical tools already allow for this revolutionary approach to patient care. Obstructing progress, however, is a lack of understanding by health care system managers and HCPs of the capability of the approach, and unfamiliarity with the requisite informatics by traditional medical researchers. Furthermore the regulatory approach is tilted against the reuse of medical record data for learning and toward strict adherence to patient confidentiality.

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THE CASE FOR VA LEADERSHIP

A solution to these 2 central dilemmas will result in continued health care improvement and, arguably, meaningful cost reduction through elimination of inferior treatments and optimization of individual patient care strategies. Since the current research culture does not reward such accomplishments, the responsibility for moving forward is left squarely on the health care systems. Said differently, a health care research budget that is a small fraction (5%) of health care expenditures is undersized and too culturally foreign for the task.[1]

A critical attribute that enables the VA to promote progress to the benefit of both veterans and taxpayers is an accountable care organization incentive to use a long horizon and invest in opportunities that reduce overall cost and improve outcomes for its beneficiaries

over their entire lifespan. Although this feature is common to a handful of other large health care providers (Kaiser Permanente, Intermountain Healthcare, Mayo Clinic), those systems lack the assets fundamental to solution design that are broadly represented across VA medical centers: a staff, culture, and apparatus in support of research at most medical centers; an integrated electronic health record (EHR) for data access; and a patient population receptive to participating in activities that will aid fellow veterans.

Table 1. Key Points on a VA Learning Health Care System

1.	Health care systems suffer from a lack of comparative effectiveness information and the inability to effectively re-use patient electronic health record data to inform treatment for subsequent patients. Health care systems, not the research community, must address their deficiencies. This is one of the greatest challenges and perhaps the greatest opportunity confronting health care systems today. Through the Point-of-Care Research, Precision Oncology, and Million Veteran programs, the VA is optimally positioned to lead in the establishment of a learning health care system and thereby continue to provide 'the best care anywhere' for veterans.
2.	Requirements for moving forward include funding support from VA, a change in cultural and regulatory perspective and reintegration and support from VA Office of Information & Technology for learning and research activities.

ONGOING PROGRAMS

The VA is in an excellent position to create an efficient and scalable apparatus to perform comparative effectiveness studies. The Point-of-Care clinical trials program, proposed and championed by the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) and supported by the VA Cooperative Studies Program, embeds low-risk clinical trials directly into the clinical ecosystem with a resultant decreased cost and increased relevance owing to study designs driven by current patient care processes.

This methodology and program is applauded by the Institute of Medicine and the Society for Clinical Trials, and each has invited MAVERIC to present at national meetings and roundtable discussions.[2] Designation as a research "transformative initiative" by the VA Office of Research and Development (ORD) provided sufficient support to culminate in the imminent launch of the first national VA Point-of-Care Clinical Trial—the Diuretic Comparison Study. The VA is proceeding with this trial at 50 VA sites for a significantly lower cost. (VA Cooperative Studies Program study #597, methods manuscript in preparation). Results will inform the optimal initial treatment for hypertension and impact the care of millions of veterans and nonveterans.

Precision Oncology Program

The VA Precision Oncology Program (POP), initiated in VISN 1 and funded through a clinical care budget, goes a step further toward creating learning opportunities. The POP sequences the DNA of tumor tissue from veterans newly diagnosed with cancer to determine the DNA mutations responsible for the tumor development and behavior. Armed with this information, HCPs can optimize therapy based on mutation status by the delivery of drugs that are targeted against particular gene products.

Systematic implementation of the POP across all VAMCs will reduce disparities in cancer care induced by variation in medical center familiarity with treatment options. Features supported by the POP include enhanced enrollment of patients into clinical trials of novel targeted therapeutics and sharing of patient outcomes data to assist in decision support for future patients. In addition, this approach could facilitate the creation of a national VA database of cancer patient characteristics, tumor mutations, and cancer-related treatments and outcomes to accelerate the pace of discovery in VA cancer care.

Million Veteran Program

The Million Veteran Program (MVP) is a VA ORD initiative that asks veterans to share their medical data, lifestyle, and genetic data with researchers to allow for the discovery of correlations between their genetic profile and their health, disease and response to

treatments. Currently more than 430,000 veterans have agreed to participate and have donated data and blood samples, and researchers are performing the first projects to use this resource.

Although the knowledge gained from these studies will be indirectly relevant to veterans in general, the MVP presents an opportunity to present specific findings to individual participants that will directly affect their care. While reuse of the MVP resource for precision medicine is under consideration, there are important cultural and technical barriers that must be addressed. Like POP, integration of the MVP research program with clinical care should be carried out with consideration of a community of stakeholders and not driven exclusively by a research agenda.

CHALLENGES IN MOVING FORWARD

Central to the implementation of a learning mechanism in health care systems is the recognition by administrators of the importance of the activity and appreciation of the business argument favoring the investment. This runs counter to the current notion of separate silos for health care and medical research whereby health care systems are liberated from the cost of investigation but then suffer from a dearth of knowledge relevant to their operation.

Additionally, research enterprises are not structured for such activities. Academic investigators are incentivized to create knowledge and generate publications, and they understand best the currency of grant funding. Their world is not geared to reinvent or engineer solutions for health care systems. In light of these considerations, a decentralized approach that creates institutions for local learning needs to be developed and "owned" by individual and groups of medical centers with engagement of administration, patient, scientific, and community stakeholders. The Patient-Centered Outcome Research Institute (PCORI) and the consortia it has funded, PCOR-Net, have adopted this approach.[3]

Importantly, a new set of ethical and regulatory standards that distinguish it from traditional research must accompany progress in the creation of a learning health care system (LHS). Sharing of patient data to benefit fellow patients must come to be expected and without the formalized sharing agreements that are required in traditional research activities. Although the digitization of medical records makes most of what this article discusses possible, execution requires access to information technology resources and a talented staff.

More than a decade ago, the decision was made to dis-integrate the Office of Information Technology from VHA. This was executed with no provision to support the small army of VA clinician-informaticists who had done much in support of patient care, including the creation of the initial iteration of the VA EHR. Although the VA includes small pockets of this clinical informatics culture throughout its organization, the community has been largely silenced and taken refuge at academic affiliates. Access to VA information systems and funding opportunities for development and implementation of tools essential for learning will draw this intellectual capital back to the VA and allow for the VA to lead in this critical arena.

THE VA PRECISION ONCOLOGY PROGRAM

Precision medicine is a medical model that incorporates the results of genetic diagnostic testing to customize or tailor medical decision making and treatment for the individual patient. Characteristics of the VA health care system that create a favored environment for introducing precision medicine include the single-payer model, where implementation decision and authority are centralized, a standardized EHR that enables informatics requirements, and a clinician and patient culture that supports innovation. To date, the benefits of precision medicine are most robust in cancer care. Under the leadership of Michael Mayo-Smith, MD, the VA New England Healthcare System has completed a regional pilot project in precision oncology that demonstrated feasibility of incorporating a precision medicine program in the clinical care environment.

For the majority of patients with lung cancer, DNA sequencing of tumor tissue identifies driver mutations—alterations believed responsible for tumor growth and behavior. The abundance of both driver and passenger mutations (those alterations whose significance is unknown) identified within an individual cancer specimen and the diversity of alterations found across the spectrum of all patients with cancer virtually assures the unique genetic profile (hence behavior) of any given patient's tumor. The new generation of antineoplastic agents are targeted therapies that disrupt the downstream effects of these alterations and result in improved anticancer effects and reduced toxicity compared with conventional chemotherapy. The POP approach to cancer treatment determines the

mutation profile of malignancies and identifies targeted therapies with the highest likelihood of treatment success. Although many driver mutation-targeted therapy combinations have been FDA approved, many more are in development and are available only as investigational agents.

Table 2. The VA Precision Oncology Program Aims

1.	Determine and disseminate best practices for precision oncology in VA through learning health care system methodologies
2.	Create a cooperative national program to enhance patient and provider engagement and opportunities
3.	Create collaborations between VA, National Cancer Institute, academia, other health care systems and industry to provide cancer patients with state-of-the-art treatments through enhanced clinical care and clinical trial participation
4.	Monitor implementation of the Precision Oncology Program to determine its cost-benefit profile

Work Accomplished

Developed over the past 2 years in VISN 1, POP is a demonstration project that standardizes the processes necessary to deliver precision oncology care for veterans with lung cancer. With approval of the cancer care specialist, targeted sequencing of cancer genes (multiple biomarker panels) is performed on formalin-fixed, paraffin-embedded tissue from newly diagnosed lung cancers as part of routine POP cancer care. Samples are shipped within 48 hours of diagnosis to Personal Genome Diagnostics (CancerSelect-88 targeted genome panel: PGD, Baltimore, MD) or Personalis (ACE Extended Cancer Panel: Menlo Park, CA). Following the sequencing of the targeted gene regions for mutations, a formal report of identified genomic aberrations is collated, annotated, and transmitted for inclusion in patient medical records. Both PGD and Personalis use N-of-One (Lexington, MA) to curate the medical literature and provide mutation annotations. The VA Computerized Patient Record System shares mutation results with the treating clinician, and a consultation service, offered through Specialty Care Access Network-Extension for Community technology, is available to help clinicians incorporate the test results into a treatment plan for the patient.

The POP is highly interdisciplinary: design and implementation required buy-in and coordinated efforts from the clinical medicine, laboratory medicine, pathology, pharmacy, radiology, and research services as well as from contracting, human resources, information technology, and procurement. With more than 150 specimens processed, procedures for tissue selection, processing, shipment, and tracking have been refined, and the informatics challenges met.

A Learning Health Care System Approach

Although the standard of care in oncology is evolving to include sequencing for all solid tumors and hematologic malignancies, the lack of correlated mutation status, patient outcomes data available for analysis, and difficulties in identifying subjects eligible for clinical trials of novel therapeutics combine to slow progress. The former problem arises from the effort required to aggregate EHR data from disparate systems as well as technical and cultural barriers to data sharing. The latter problem stems from the relative rarity of patients (and the difficulty identifying them) with a given mutation that determines eligibility for a clinical trial of a particular targeted therapy.

The POP attempts to overcome these limitations by embracing the principles of a LHS with clinical trials embedded to the extent possible in the clinical care ecosystem. The creation of a precision oncology data repository derived largely from the VA Corporate Data Warehouse makes correlated data available. This repository contains patient demographics and comorbidities, tumor features and mutation status, treatments, and outcomes. Data in the repository are used to both inform individual patient care (ie, what can we learn from past patients that would inform the care of the present patient?) and to allow for generalizable discovery and validation (ie, traditional data-mining research). Given a sufficiently large POP population, clinical trial-matching algorithms will identify patients available for any number of studies open for enrollment, thus reducing the existing bottleneck in clinical trial participation.

Rationale for a National Program

Numerous organizations, including the National Comprehensive Cancer Network, the American Society of Clinical Oncology Institute for Quality, and the

Society for Gynecologic Oncology, already propose tumor sequencing as the standard of care for a variety of malignancies, and there is much to suggest that additional recommendations will be forthcoming.[4-6] Expanding the VISN 1 POP across the nation provides a mechanism to minimize disparities in the delivery of precision oncology across the VA. The POP will afford opportunities to create VA-centric expertise derived from the POP data repository and filtered through a national tumor board. The POP will also expand opportunities for patients to participate in clinical trials and receive state-of-the-art treatments beyond what can be offered regionally.

Both knowledge generation and the creation of a large-scale clinical trial operation require the numbers of patients that only a national POP can achieve. The economies of scale introduced by wide participation will also reduce the cost of tumor sequencing, therapeutics, and infrastructure development and will eliminate otherwise duplicate efforts that would be required to create a number of smaller regional activities. Importantly, a national POP with sufficient voice would be far more effective at moving forward the LHS agenda.

Research Activities

For the majority of POP participants, the best hope for improved quality and quantity of life lies with targeted therapeutics that are under development and available only through research protocols. The VISN 1 Clinical Trial Network (directed by Mary Brophy, MD) has developed an Oncology Consortium that includes facilities both within and outside of VISN 1. The consortium has partnered with the National Cancer Institute through a storefront mechanism with the Southwest Oncology Group to become the first national VA cancer consortium to participate in intergroup protocols. Novel therapeutics will be available to POP participants through this and other partnerships with a variety of industry sponsors.

Novel, efficient, and nationally scalable mechanisms have been proposed to facilitate clinician participation and patient enrollment in clinical trials. Additionally, MAVERIC is working with the VA Central Institutional Review Board to advance a distributed enrollment innovation, which brings the clinical trial to the patient rather than have patients travel to facilities where studies are open.

CONCLUSION

Unique features of the VHA enable a national rollout of the POP, which VISN 1 successfully piloted. The first of its kind effort for precision medicine within the VA holds the promise of delivering cutting-edge, life-enhancing therapy to cancer patients.

This interdisciplinary program incorporates LHS principles so that delivery of care is accompanied by analytics that can be applied to decision making for future patients. Participation in clinical trials, facilitated by the consortium model, is a cardinal feature of the POP. Opportunity exists to explore novel trial designs that meet the unique challenges presented in precision medicine, where therapeutics tailored to uncommon mutations limit patient availability. ●

Author disclosures

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