Nationwide Genomic Surveillance and Response to COVID-19: The VA SEQFORCE and SEQCURE Consortiums

Jay Krishnan, MD[a,b]; Christopher W. Woods, MD, MPH[a,b]; Mark Holodniy, MD[c,d]; Bradly P. Nicholson, PhD[b,e]; Vincent C. Marconi, MD[f,g]; Mary Cloud B. Ammons, PhD[h]; Chetan Jinadatha, MD, MPH[i,j]; Saiju Pyarajan, PhD[k]; Jessica Wang-Rodriguez, MD[l]; Amanda P. Garcia, MPH[m]; Jane K. Battles, PhD[m]

Background: The US Department of Veterans Affairs (VA) has dedicated significant resources toward countering the COVID-19 pandemic. Sequencing for Research Clinical and Epidemiology (SeqFORCE) and Sequencing Collaborations United for Research and Epidemiology (SeqCURE) were developed as clinical and research consortiums, respectively, focused on the genetic COVID-19 surveillance.

Observations: Through genetic sequencing, VA SeqFORCE and SeqCURE collaborations contributed to the COVID-19 pandemic response and scientific understanding. Future directions for each program include the assessment of the unique impact of COVID-19 on the veteran population, as well as the adaptation of these

programs to future infectious disease threats. We foresee the use of these established platforms beyond infectious diseases.

Conclusions: VA SeqFORCE and SeqCURE were established as clinical and research programs dedicated to sequencing COVID-19 as part of ongoing clinical and surveillance efforts. In the future, we anticipate that having these programs embedded within the largest integrated health care system in the US will enable the study of pathogens and pandemics beyond COVID-19 and at an unprecedented scale. The investment in these programs will form an integral part of our nation's response to emerging infectious diseases, with future applications to precision medicine and beyond.

Author affiliations can be found at the end of this article.

Correspondence:
Jay Krishnan
(jay.krishnan@duke.edu);
Christopher W. Woods
(christopher.woods2@va.gov)

The COVID-19 virus and its associated pandemic have highlighted the urgent need for a national infrastructure to rapidly identify and respond to emerging pathogens. The importance of understanding viral population dynamics through genetic sequencing has become apparent over time, particularly as the vaccine responses, clinical implications, and therapeutic effectiveness of treatments have varied substantially with COVID-19 variants.[1,2]

As the largest integrated health care system in the US, the US Department of Veterans Affairs (VA) is uniquely situated to help with pandemic detection and response. This article highlights 2 VA programs dedicated to COVID-19 sequencing at the forefront of pandemic response and research: VA Sequencing for Research Clinical and Epidemiology (SeqFORCE) and VA Sequencing Collaborations United for Research and Epidemiology (SeqCURE) (Table).

VA SEQFORCE

VA SeqFORCE was established March 2021 to facilitate clinical surveillance of COVID-19 variants in the US veteran population and in VA employees. VA SeqFORCE consists of 9 Clinical Laboratory Improvement Amendment (CLIA)–certified laboratories in VA medical centers, including the VA Public Health Reference Laboratory in Palo Alto, California, and 8 Veterans Health Administration (VHA) clinical laboratories (Los Angeles, California; Boise, Idaho; Iowa City, Iowa; Bronx, New York; West Haven, Connecticut; Indianapolis, Indiana; Denver, Colorado; and Orlando, Florida).[3] Specimen standards (eg, real-

time polymerase chain reaction [RT-PCR] cycle threshold [Ct] $\leq$ 30, minimum volume, etc) and clinical criteria (eg, COVID-19–related deaths, COVID-19 vaccine escape, etc) for submitting samples to VA SeqFORCE laboratories were established, and logistics for sample sequencing was centralized, including providing centralized instructions for sample preparation and to which VA SeqFORCE laboratory samples should be sent.

These laboratories sequenced samples from patients and employees with COVID-19 to understand patterns of variant evolution, vaccine, antiviral and monoclonal antibody response, health care–associated outbreaks, and COVID-19 transmission. As clinically relevant findings, such as monoclonal antibody treatment failure, emerged with novel viral variants, VA SeqFORCE was well positioned to rapidly detect the emergent variants and inform better clinical care of patients with COVID-19. Other clinical indications identified for sequencing within VA SeqFORCE included outbreak investigation, re-infection with COVID-19 > 90 days but < 6 months after a prior infection, extended hospitalization of > 21 days, death due to COVID-19, infection with a history of recent nondomestic travel, rebound of symptoms after improvement on oral antiviral therapy, and epidemiologic surveillance.

VA SeqFORCE laboratories use a variety of sequencing platforms, although a federated system was developed that electronically linked all laboratories using a software system (PraediGene, Bitscopic) for sample management, COVID-19 variant analytics, and automated re-

TABLE VA Surveillance Programs Overview

	VA SeqFORCE	VA SeqCURE
Objective	Clinical surveillance, rapid response to COVID-19 variants	COVID-19 sequencing data resource
VA offices	Pathology and Laboratory Medicine Program, Public Health	Office of Research and Development, VA SHIELD
Data usage	Clinical management and epidemiologic studies; results stored in VA Computerized Patient Record System	Broader epidemiologic studies and other research applications; results not stored in VA Computerized Patient Record System
Inclusion criteria	COVID-19 samples with cycle threshold values ≤ 30	COVID-19 samples with cycle threshold values > 30
Applications	COVID-19 variant evaluations among infected individuals with recent nondomestic travel, COVID-19 vaccine breakthrough, treatment rebound, and outbreak	COVID-19 vaccine effectiveness; rural vs urban impact of COVID-19 variants
Key participating locations	Palo Alto, California (reference laboratory); Los Angeles, California; Denver, Colorado; West Haven, Connecticut; Orlando, Florida; Iowa City, Iowa; Boise, Idaho; Indianapolis, Indiana; Bronx, New York	Iowa City, Iowa; Boise, Idaho; Durham, North Carolina Bronx, New York; Cleveland, Ohio; Temple, Texas

Abbreviations: SeqCURE, Sequencing Collaborations United for Research and Epidemiology; SeqFORCE, Sequencing for Research Clinical and Epidemiology; SHIELD, VA Science and Health Initiative to Combat Infectious and Emerging Life Threatening Diseases; VA, US Department of Veterans Affairs.

sult reporting of clade and lineage into the Veterans Health Information Systems and Technology Architecture (VistA) Computerized Patient Record System. In addition, generated nucleic acid sequence alignment through FASTA consensus sequence files have been archived for secondary research analyses. By archiving the consensus sequences, retrospective studies within the VA have the added benefit of being able to clinically annotate investigations into COVID-19 variant patterns. As of August 2023, 43,003 samples containing COVID-19 have been sequenced, and FASTA file and metadata upload are ongoing to the Global Initiative on Sharing Avian Influenza Data, which houses > 15 million COVID-19 files from global submissions.

VA SeqFORCE's clinical sequencing efforts have created opportunities for multicenter collaboration in variant surveillance. In work from December 2021, investigators from the James J. Peters VA Medical Center in Bronx, New York, collaborated with the VHA Pathology and Laboratory Medicine Services and Public Health national program offices in Washington, DC, to develop an RT-PCR assay to rapidly differentiate Omicron from Delta variants.[4] Samples from VA hospitals across the nation were used in this study.

Lessons from VA SeqFORCE have also been cited as inspiration to address COVID-19 clinical problems, including outbreak investigations in hospital settings and beyond. Researchers at the Iowa City VA Health Care System, for example, proposed a novel probabilistic quantitative method for determining genetic-relatedness among COVID-19 viral strains in an outbreak setting.[5] They extended the scope of work to develop COVID-19 outbreak screening tools combining publicly available algorithms with targeted sequencing data to identify outbreaks as they arise.[6] We expect VA SeqFORCE, in conjunction with its complement VA SeqCURE, will continue to further pandemic surveillance and response.

VA SEQCURE

As the research-focused complement to VA SeqFORCE, VA SeqCURE is dedicated to a broader study of the COVID-19 genome through sequencing. Established January 2021, the VA SeqCURE network consists of 6 research laboratories in Boise, Idaho; Bronx, New York; Cleveland, Ohio; Durham, North Carolina; Iowa City, Iowa; and Temple, Texas.

Samples are collected as a subset of the broader VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD) biorepository sweep protocol for discarded blood and nasal swab specimens of VHA patients hospitalized with COVID-19, as described by Epstein and colleagues.[7-9] While VA SeqFORCE sequences samples positive for COVID-19 by RT-PCR with a Ct value of ≤ 30 for diagnostic purposes, VA SeqCURE laboratories sequence more broadly for nondiagnostic purposes, including samples with a Ct value > 30. The 6 VA SeqCURE laboratories generate sequencing data using various platforms, amplification kits, and formats. To ensure maximum quality and metadata on the sequences generated across the different laboratories, a sequence intake pipeline has been developed, adapting the ViralRecon bioinformatics platform.[10] This harmonized analysis pipeline accommodates different file formats and performs quality control, alignment, variant calling, lineage assignment,

clade assignment, and annotation. As of August 2023, VA SeqCURE has identified viral sequences from 24,107 unique specimens. Annotated COVID-19 sequences with the appropriate metadata will be available to VA researchers through VA SHIELD.

Research projects include descriptive epidemiology of COVID-19 variants in individuals who receive VHA care, COVID-19 vaccine and therapy effectiveness, and the unique distribution of variants and vaccine effectiveness in rural settings.[3] True to its core mission, members of the VA SeqCURE consortium have contributed to the COVID-19 viral sequencing literature over the past 2 years. Researchers also are accessing VA SeqCURE to study COVID-19 persistence and rebound among individuals with mild disease taking nirmatrelvir/ritonavir compared with other COVID-19 therapeutics and untreated controls. Finally, COVID-19 samples and their sequences are stored in the VA SHIELD biorepository, which leverages these samples and data to advance scientific understanding of COVID-19 and future emerging infectious diseases.[7-9]

Important work from investigators at the Central Texas Veterans Health Care System confronted the issue of whole genome sequencing data from COVID-19 samples with low viral loads, a common issue with COVID-19 sequencing. They found that yields of 2 sequencing protocols, which generated high-sequence coverage, were enhanced further by combining the results of both methods.[11] This project, which has potentially broad applications for sequencing in research and clinical settings, is an example of VA SeqCURE's efforts to address the COVID-19 pandemic. The VA SeqCURE program has substantial potential as a large viral sequencing repository with broad geographic and demographic representation, such that future large-scale sequencing analyses may be generated from preexisting nested cohorts within the repository.

NEXT STEPS

Promising new directions of clinical and laboratory-based research are planned for VA SeqFORCE and VA SeqCURE. While the impact of COVID-19 and other viruses with epidemic potential is perhaps most feared in urban settings, evidence suggests that the distribution of COVID-19 in rural settings is unique and associated with worse outcomes.[12,13] Given the wide catchment areas of VA hospitals that encompass both rural and urban settings, the VA's ongoing COVID-19 sequencing programs and repositories are uniquely positioned to understand viral dynamics in areas of differing population density.

While rates of infection, hospitalization, and death resulting from COVID-19 have substantially dropped, the long-term impact of the pandemic is just beginning to be recognized in conditions such as long COVID or postacute COVID-19 syndrome. Long COVID has already proven to be biologically multifaceted, difficult to diagnose, and unpredictable in identifying the most at-risk patients.[14-16] Much remains to be determined in our understanding of long COVID, including a unified definition that can effectively be used in clinical settings to diagnose and treat patients. However, research indicates that comorbidities common in veterans, such as diabetes and cardiovascular disease, are associated with worse long-term outcomes.[17,18] Collaborations between VA scientists, clinicians, and national cooperative programs (such as a network of VHA long COVID clinics) create an unmatched opportunity for VA SeqFORCE and VA SeqCURE programs to provide insight into a disease likely to become a chronic disease outcome of the pandemic.

With VA SeqFORCE and VA SeqCURE programs, the VA now has infrastructure ready to respond to new infectious diseases. During the mpox outbreak of 2022, the VA Public Health Reference Laboratory received > 80% of all VA mpox samples for orthopox screening and mpox confirmatory testing. A subset of these samples underwent whole genome sequencing with the identification of 10 unique lineages across VA, and > 200 positive and 400 negative samples have been aliquoted and submitted to VA SHIELD for research. Furthermore, the VA SeqFORCE and VA SeqCURE sequencing processes might be adapted to identify outbreaks of multidrug-resistant organisms among VA patients trialed at other institutions.[19] We are hopeful that VA SeqFORCE and VA SeqCURE will become invaluable components of health care delivery and infection prevention at the hospital level and beyond.

Finally, the robust data infrastructure and associated repositories of VA SeqFORCE and VA SeqCURE may be leveraged to study noninfectious diseases. Research groups are starting to apply these programs to cancer sequencing. We anticipate that these efforts may have a substantial impact on our understanding of cancer epidemiology and region-specific risk factors for malignancy, given the size and breadth of VA SeqFORCE and VA SeqCURE. Common oncogenic mutations identified through these programs could be targets for precision oncology therapeutics. Similarly, we envision applications of the VA SeqFORCE and VA SeqCURE data infrastructures and repositories toward other precision medicine fields, including

pharmacogenomics and nutrition, to tailor interventions to meet the specific individual needs of veterans.

CONCLUSIONS

The productivity of VA SeqFORCE and VA SeqCURE programs over the past 2 years continues to increase in response to the COVID-19 pandemic. We anticipate that they will be vital components in our nation's responses to infectious threats and beyond.

Author affiliations

[a]Duke University School of Medicine, Durham, North Carolina; [b]Durham Veterans Affairs Medical Center, North Carolina; [c]Public Health National Program Office, Department of Veterans Affairs, Washington, DC; [d]Stanford University, California; [e]Institute for Medical Research, Durham Veterans Affairs Medical Center, North Carolina; [f]Atlanta Veterans Affairs Medical Center, Decatur, Georgia; [g]Emory University School of Medicine and Rollins School of Public Health, Atlanta, Georgia; [h]Idaho Veterans Research and Education Foundation & Boise Veterans Affairs Medical Center; [i]Central Texas Veterans Health Care System, Temple; [j]Texas A&M University School of Medicine, Bryan; [k]Center for Data and Computational Sciences, Veterans Affairs Boston Healthcare System, Massachusetts; [l]National Pathology and Laboratory Medicine Service, Department of Veterans Affairs, Washington, DC; [m]Office of Research and Development, Department of Veterans Affairs, Washington, DC

Author disclosures

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies.

Ethics and consent

Not applicable

References

1. Iuliano AD, Brunkard JM, Boehmer TK, et al. Trends in disease severity and health care utilization during the early Omicron variant period compared with previous SARS-CoV-2 high transmission periods - United States, December 2020-January 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):146-152. Published 2022 Jan 28. doi:10.15585/mmwr.mm7104e4

2. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399(10332):1303-1312. doi:10.1016/S0140-6736(22)00462-7

3. Veterans Health Administration. Coronavirus Disease 2019 (COVID-19) response report - annex C. December 5, 2022. Accessed August 28, 2023. https://www.va.gov/HEALTH/docs/VHA-COVID-19-Response-2022-Annex-C.pdf

4. Barasch NJ, Iqbal J, Coombs M, et al. Utilization of a SARS-CoV-2 variant assay for the rapid differentiation of Omicron and Delta. *medRxiv*. Preprint posted online December 27, 2021. doi:10.1101/2021.12.22.21268195

5. Bilal MY. Similarity Index-probabilistic confidence estimation of SARS-CoV-2 strain relatedness in localized outbreaks. *Epidemiologia (Basel)*. 2022;3(2):238-249. doi:10.3390/epidemiologia3020019

6. Bilal MY, Klutts JS. Molecular Epidemiological investigations of localized SARS-CoV-2 outbreaks-utility of public algorithms. *Epidemiologia (Basel)*. 2022;3(3):402-411. doi:10.3390/epidemiologia3030031

7. Veterans Health Administration, Office of Research & Development. VA Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD). Updated November 23, 2022. Accessed August 28, 2023. https://www.research.va.gov/programs/shield/about.cfm

8. Harley JB, Pyarajan S, Partan ES, et al. The US Department of Veterans Affairs Science and Health Initiative to Combat Infectious and Emerging Life-Threatening Diseases (VA SHIELD): a biorepository addressing national health threats. *Open Forum Infect Dis*. 2022;9(12):ofac641. doi:10.1093/ofid/ofac641

9. Epstein L, Shive C, Garcia AP, et al. VA SHIELD: a biorepository for our veterans and the nation. *Fed Pract*. 2023;40(suppl 5):S48-S51. doi:10.12788/fp.0424

10. Patel H, Varona S, Monzón S, et al. Version 2.5. nf-core/viralrecon: nf-core/viralrecon v2.5 - Manganese Monkey (2.5). Zenodo. July 13, 2022. doi:10.5281/zenodo.6827984

11. Choi H, Hwang M, Navarathna DH, Xu J, Lukey J, Jinadatha C. Performance of COVIDSeq and swift normalase amplicon SARS-CoV-2 panels for SARS-CoV-2 genome sequencing: practical guide and combining FASTQ strategy. *J Clin Microbiol*. 2022;60(4):e0002522. doi:10.1128/jcm.00025-22

12. Cuadros DF, Branscum AJ, Mukandavire Z, Miller FD, MacKinnon N. Dynamics of the COVID-19 epidemic in urban and rural areas in the United States. *Ann Epidemiol*. 2021;59:16-20. doi:10.1016/j.annepidem.2021.04.007

13. Anzalone AJ, Horswell R, Hendricks BM, et al. Higher hospitalization and mortality rates among SARS-CoV-2-infected persons in rural America. *J Rural Health*. 2023;39(1):39-54. doi:10.1111/jrh.12689

14. Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*. 2022;185(5):881-895.e20. doi:10.1016/j.cell.2022.01.014

15. Pfaff ER, Girvin AT, Bennett TD, et al. Identifying who has long COVID in the USA: a machine learning approach using N3C data. *Lancet Digit Health*. 2022;4(7):e532-e541. doi:10.1016/S2589-7500(22)00048-6

16. Subramanian A, Nirantharakumar K, Hughes S, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med*. 2022;28(8):1706-1714. doi:10.1038/s41591-022-01909-w

17. Munblit D, O'Hara ME, Akrami A, Perego E, Olliaro P, Needham DM. Long COVID: aiming for a consensus. *Lancet Respir Med*. 2022;10(7):632-634. doi:10.1016/S2213-2600(22)00135-7

18. Thaweethai T, Jolley SE, Karlson EW, et al. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA*. 2023;329(22):1934-1946. doi:10.1001/jama.2023.8823

19. Sundermann AJ, Chen J, Kumar P, et al. Whole-genome sequencing surveillance and machine learning of the electronic health record for enhanced healthcare outbreak detection. *Clin Infect Dis*. 2022;75(3):476-482. doi:10.1093/cid/ciab946