DOI: 10.1111/jrh.12773

THE JOURNAL OF RURAL HEALTH

ORIGINAL ARTICLE

Veterans with blood cancers: Clinical trial navigation and the challenge of rurality

Daphne R. Friedman MD[1,2] | Thomas D. Rodgers MD[1,2] | Courtney Kovalick PA-C[1] | Sarvari Yellapragada MD[3,4,5] | Leah Szumita MS, RN, ACNS-BC[6] | Elisa S. Weiss PhD[6]

[1]Durham VA Health Care System, Durham, North Carolina, USA

[2]Duke University School of Medicine, Durham, North Carolina, USA

[3]Michael E. DeBakey VA Medical Center, Houston, Texas, USA

[4]Baylor College of Medicine, Houston, Texas, USA

[5]Dan L. Duncan Comprehensive Cancer Center

[6]The Leukemia & Lymphoma Society, Rye Brook, New York, USA

Correspondence
Daphne R. Friedman, Hematology-Oncology, Durham VA Health Care System, 508 Fulton Street (111G), Durham, NC 27705.
Email: Daphne.Friedman@va.gov, Daphne.Friedman@duke.edu

Abstract

Purpose: The proportion of cancer patients who participate in clinical trials (CTs) remains low, despite an understanding of barriers to enrollment. The barrier of rural residence is relevant to Veterans, who more commonly live in rural areas than non-Veterans. In this exploratory study, we aimed to examine geographic factors that could impede CT enrollment and to improve access to CTs for Veterans.

Methods: To assess the influence of rurality on the availability of CTs, we performed simulated searches using The Leukemia & Lymphoma Society's Clinical Trial Support Center (LLS CTSC) database. The LLS CTSC provides free CT education and navigation. In the second part of this study, we offered Veterans with blood cancers who received care at the Durham, Salem, Clarksburg, Sioux Falls, and Houston Veterans Administration (VA) Medical Centers referral to the LLS CTSC.

Findings: In simulated searches, we found significantly lower numbers of CTs open to enrollment in rural areas, compared to urban areas. In actual referrals, 33 Veterans were referred to the LLS CTSC, of which 15 (45%) lived in rural areas. Three Veterans enrolled in CTs. Patients declined referral or did not enroll in CTs for various reasons, including a desire to maintain care within the VA and/or to initiate therapy quickly.

Conclusions: We identified "clinical trial deserts," which might hinder access and reduce CT participation for rural Veterans. Referral to the LLS CTSC promoted CT education and enrollment among a highly rural cohort of Veterans receiving care in the VA system.

KEYWORDS
clinical trial, hematologic neoplasms, patient navigation, rural health

INTRODUCTION

Rural residence is associated with higher rates of cancer diagnoses and inferior cancer outcomes. The rural-urban divide in cancer is attributed to various factors, including oncology infrastructure, insurance, geographic access and transportation, health behaviors, access to medical providers, health literacy, and access to clinical trials (CTs).[1]

The Veterans Administration (VA) is a large integrated health care system, and approximately 3% of cancer patients in the United States are diagnosed or receive cancer care in the VA.[2] The VA is known for providing high-quality cancer care to Veterans, with equivalent or better outcomes than the private sector.[3] Veterans who receive their medical care in the Veterans Health Administration (VA) are more likely to live in rural areas, compared to the general population,[4] have higher

TABLE 1 Characteristics of VA facilities used in LLS CTSC simulations.

VA facility	Location	Region	% Rural	% Urban	Rurality assignment for simulated searches
Eastern Colorado	Denver	Midwest	9.57%	90.43%	Urban
Edward Hines	Chicago	Midwest	4.15%	95.85%	Urban
James A Haley	Tampa	East	6.94%	93.06%	Urban
John D Dingell	Detroit	Midwest	2.91%	97.09%	Urban
Long Beach	California	West	1.85%	98.15%	Urban
Philadelphia	Pennsylvania	East	2.31%	97.69%	Urban
Providence	Rhode Island	East	8.12%	91.88%	Urban
Jack C Montgomery	Oklahoma	Midwest	93.51%	6.49%	Rural
Louis A Johnson	West Virginia	East	91.88%	8.12%	Rural
Fort Harrison	Montana	West	92.55%	7.45%	Rural
Lake City	North Florida	East	91.36%	8.64%	Rural
Oscar G Johnson	N Michigan	Midwest	97.21%	2.79%	Rural
White River Junction	Vermont	East	95.59%	4.41%	Rural

Abbreviations: LLS CTSC, The Leukemia & Lymphoma Society's Clinical Trial Support Center; VA, Veterans Administration.

level of comorbidities,[5] and often find that transportation is a barrier for accessing health care.[6,7] Reaching out to and providing high-quality health care to rural Veterans is a priority to the VA, for example, using tele-oncology services to care for Veterans with cancer.[8,9]

Cancer CTs offer high-quality care while collecting essential data that advances medical knowledge. Despite this, only 2%-8% of cancer patients in the United States participate in CTs, and these rates are even lower among ethnic and racial minorities.[10–12] Factors associated with lower CT participation have been studied in the general population.[10–12] Patient, provider, and institutional barriers to CT enrollment have previously been described.[12–14] Specific factors associated with lower CT enrollment that are most applicable to the Veteran population who receive care in the VA include: rurality, racial and ethnic minority status, lower education, insufficient transportation, lower income, and/or presence of comorbidities that render them ineligible to participate due to restrictive eligibility criteria.[5,15]

While it is known that rural patients are less likely to participate in CTs, the factors that contribute to this disparity are not fully understood.[12,16,17] We used data from The Leukemia & Lymphoma Society (LLS) Clinical Trial Support Center (CTSC)[18] to describe geographic barriers to CT enrollment, and we offered referral to the LLS CTSC to Veterans with blood cancers, who constitute approximately 8% of Veterans with cancer in the VA system.[2] In this exploratory study, we aimed to overcome barriers to CT participation and address the rural-urban divide in cancer clinical research.

METHODS

Examination of available CTs: Rural versus urban

In the first part of this work, in May 2021, using the LLS CTSC proprietary CTs database, we performed simulated searches for CTs in 13 geographic areas (centered on 6 rural and 7 urban VA facilities), in 6 blood cancer types (acute myeloid leukemia—AML, myelodysplastic syndrome—MDS, diffuse large B-cell lymphoma—DLBCL, follicular lymphoma—FL, chronic lymphocytic leukemia—CLL, and multiple myeloma—MM), and in 2 disease states (newly diagnosed or relapsed/refractory). We searched for the number of CTs available using these parameters within a radius of 100 or 200 miles from each VA facility (Table 1).

VA facilities referred to as "urban" served a Veteran population that was 90.43%-98.15% urban, and VA facilities referred to as "rural" served a Veteran population that was 91.36%-97.21% rural.[19] These facilities were in the Eastern United States (n = 6), Midwest United States (n = 5), and Western United States (n = 2), with urban and rural facilities in each region. Western United States facilities had less representation among the selected facilities because most served highly urban Veteran populations and there were fewer VA facilities that served rural Veterans in this region. To evaluate the effect of rurality on distance to CTs, we selected VA facilities that served almost exclusively urban or rural populations for these initial dichotomized analyses.

Referrals to the LLS CTSC

In the second part of this work, between September 2020 and January 2022, 4 hematology-oncology providers asked Veterans who required initial therapy or a change in treatment for blood cancers if they were interested in learning more about CT options for treatment. The VA oncology providers treated patients served by the Durham North Carolina, Houston Texas, Clarksburg West Virginia, Salem Virginia, and Sioux Falls South Dakota VA Medical Centers. Veterans received care through in-person traditional VA oncology clinics or tele-oncology

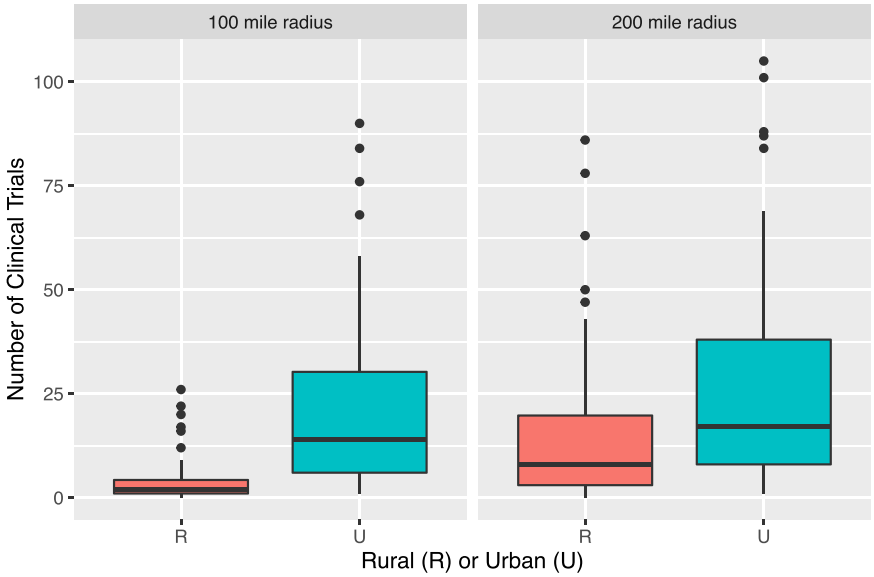

FIGURE 1 Comparison of the number of clinical trials for blood cancers in a 100- or 200-mile radius of VA facilities located in rural or urban areas. Abbreviation: VA, Veterans Administration.

visits through the VA National TeleOncology Service. If a patient wanted to learn more, the providers obtained verbal consent to share the patient's contact information and personal health information with the LLS CTSC. The LLS CTSC is a free CT nurse navigation and education service assisting patients with blood cancers and their oncology providers.[18] The provider then entered the patient's information in the LLS CTSC online referral form (https://lls-forms.careboxhealth.com). Once patient information was received, an LLS CTSC nurse navigator contacted the patient, conducted comprehensive nursing, educational and psychosocial assessments, and discussed the patient's understanding of available treatment options and their treatment goals. Using this information, the LLS CTSC nurse navigator performed a CT search using its own database, which contains information from clinicaltrials.gov and other proprietary data. Thereafter, the patient and their provider were sent an individualized list of potential CT options, as well as education and support resources as needed. The patient and provider were able to use the provided list and resources in shared decision-making about treatment options.

For patients who agreed to an LLS CTSC referral, age at the time of referral, race, ethnicity, gender, disease type, and disease status were recorded by the LLS CTSC nurse navigators. Rurality of the patient's home address was calculated using ZIP codes and RUCA codes from the referred patients' mailing address, using the R package ruca.

When patients required therapy, but the provider did not complete a referral to the LLS CTSC, or the patient declined LLS CTSC referral, the reason was recorded by the provider. Providers did not use standardized response options to code the reason for lack of referral or patients' reason(s) for declining referral; rather, free text was recorded. For patients who agreed to the referral but did not enroll on a CT, the referring providers and the LLS CTSC recorded information about the final decision for therapy and, if available, the reasons for not proceeding with enrollment on a CT.

Statistical analyses

Descriptive data analysis was performed to calculate medians and ranges. Wilcoxon rank sum test was used to compare data obtained from the simulated searches. Unadjusted *P*-values of $< .05$ were considered significant because these analyses were exploratory. Analyses were performed using RStudio, R version 4.0.5.

RESULTS

Findings from simulation searches for CTs

In simulation searches, there were significantly lower numbers of CTs open to enrollment in a 100- or 200-mile radius from rural VA facilities compared to urban VA facilities (Figure 1, Table S1 $P_{unadj} < .001$). In a 100-mile radius, there was a median of 2 trials near rural VA facilities (range: 0-26 trials), compared to a median of 14 trials near urban VA facilities (range: 1-90 trials). Similarly, in a 200-mile radius, there was a median of 8 trials near rural VA facilities (range: 0-86 trials), compared to a median of 17 trials near urban VA facilities (range: 1-105 trials) (Supporting Information).

For each disease type (AML, CLL, DLBCL, FL, MDS, and MM), there were significantly fewer CTs near rural VA facilities, compared to urban VA facilities ($P_{unadj} \leq .001$, Figure 2). In a 100-mile radius, comparing rural to urban VA facilities, the median number of CTs for AML was 3.5 compared to 25, respectively, for CLL, the median was 2.5 compared to 10.5, for FL, the median was 1 compared to 9, for DLBCL, the median was 1 compared to 10.5, for MDS, the median was 2 compared to 12.5, and for MM, the median was 2 compared to 16.5. The same pattern was seen with a 200-mile radius.

The proximity of trials for initial therapy or for relapsed/refractory disease followed a similar pattern as well (Figure 3). For example, at a 100-mile radius, there was a median of 1.5 (range: 0-6) CTs near rural

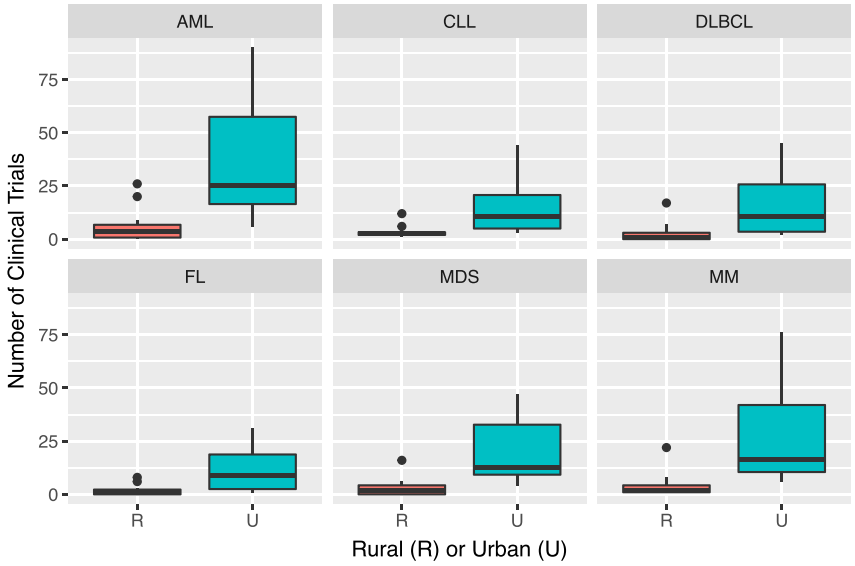

FIGURE 2 Comparison of the number of clinical trials for specific blood cancers in a 100-mile radius of VA facilities located in rural or urban areas. Abbreviations: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; VA, Veterans Administration.

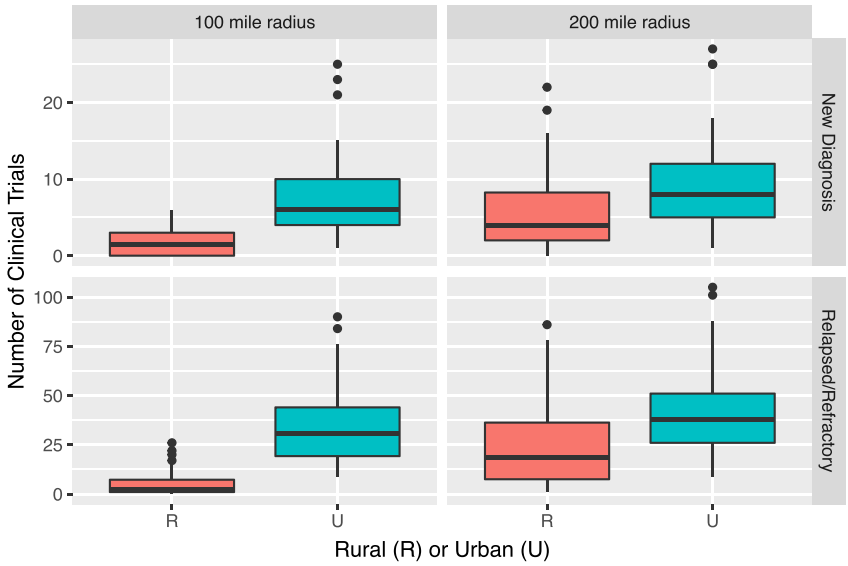

FIGURE 3 Comparison of the number of clinical trials for newly diagnosed or for relapsed/refractory blood cancers in a 100- or 200-mile radius of VA facilities located in rural or urban areas. Abbreviation: VA, Veterans Administration.

VA facilities and 6 (range: 1-25) CTs near urban VA facilities for initial therapy ($P_{unadj} < .001$). At a 200-mile radius, there was a median of 2.5 (range: 0-26) CTs near rural VA facilities and 30.5 (range: 9-90) CTs near urban VA facilities for relapsed/refractory disease ($P_{unadj} < .001$).

Characteristics and outcomes of Veterans referred to the LLS CTSC

Thirty-three Veterans were referred to the LLS CTSC by 4 VA oncology providers. As seen in Table 2, all referred Veterans were male, reflecting the skewed gender breakdown among Veterans. In addition, 9 Veterans (27%) self-identified as a racial minority, and 15 Veterans (45%) lived in rural areas across 8 different states. The majority of referred Veterans had relapsed or refractory cancers, representing a wide variety of hematologic malignancies.

Three of the 33 (9%) referred Veterans ultimately enrolled in CTs. Of these, 2 patients had myelofibrosis and 1 had chronic lymphocytic leukemia. Two of these Veterans lived in rural areas and 1 Veteran lived in an urban area. Twenty-two referred Veterans did not enroll in CTs, and the reasons that patients provided included: preferred standard of care (n = 17), did not meet eligibility criteria (n = 2), no trials in geographic area/lack of transportation (n = 1), condition deteriorated rapidly (n = 1), and chose off-label treatment (n = 1). Of the Veterans who did not enroll in CTs, 12 lived in urban areas and 10 lived in rural areas. The remaining 8 Veterans were lost to follow-up, decided not to pursue a trial search, or had a search in progress with the LLS CTSC at the time data were analyzed.

Providers' and Veterans' reasons for not referring or agreeing to referral to the LLS CTSC

Providers documented reasons for not referring Veterans who needed therapy to the LLS CTSC (n = 15). The reasons provided by hematology-oncology providers included: local VA facility restrictions

TABLE 2 Demographics of Veterans referred to the LLS CTSC (N = 33).

Race (n, %)	
White	24 (73%)
Black or African American	8 (24%)
American Indian or Alaska Native	1 (3%)
Ethnicity (n, %)	
Non-Hispanic	29 (88%)
Hispanic	2 (6%)
NA	2 (6%)
Gender (n, %)	
Male	33 (100%)
Female	0 (0%)
Age at the time of referral (years)	
Range	41-92
Median	71
States of residence (n, %)	
North Carolina	11 (33%)
South Dakota	7 (21%)
Virginia	5 (15%)
Minnesota	3 (9%)
Iowa	2 (6%)
West Virginia	2 (6%)
New York	1 (3%)
Texas	1 (3%)
Rurality (n, %)	
Urban	18 (55%)
Rural	15 (45%)
Cancer type (n, %)	
Chronic lymphocytic leukemia/small lymphocytic lymphoma	6 (18%)
Multiple myeloma	4 (12%)
Myelofibrosis	4 (12%)
Diffuse large B-cell lymphoma	3 (9%)
Myelodysplastic syndrome (MDS)	3 (9%)
Acute myeloid leukemia	2 (6%)
Chronic myeloid leukemia	1 (3%)
Follicular lymphoma	1 (3%)
Hairy cell leukemia	1 (3%)
Hodgkin lymphoma	1 (3%)
Mantle cell lymphoma	1 (3%)
Marginal zone lymphoma	1 (3%)
MDS/myeloproliferative neoplasm overlap	1 (3%)
Peripheral T-cell lymphoma	1 (3%)
Primary mediastinal B-cell lymphoma	1 (3%)
Richter's transformation	1 (3%)
Waldenstrom's macroglobulinemia/ lymphoplasmacytic lymphoma	1 (3%)
Cancer state (n, %)	
Initial therapy	12 (36%)
Relapsed	12 (36%)
Refractory	9 (27%)

Abbreviation: LLS CTSC, The Leukemia & Lymphoma Society's Clinical Trial Support Center.

on approving out-of-VA care, need for immediate cancer therapy, patient comorbidities that would likely lead to ineligibility, patient preference for standard care already known, or other circumstances that would preclude participation in a CT (eg, the patient was not compliant with standard care, the patient was a caregiver for an ill family member). Patients who were offered but were not interested in a referral to the LLS CTSC provided feedback to their oncologist about why the referral was refused (n = 21). The reasons provided by patients included: wanting to keep their care within the integrated VA network, wanting standard therapy, wanting to limit additional appointments, wanting to start therapy urgently, and lack of transportation.

DISCUSSION

Despite the interest and commitment of the oncology community to CTs, enrollment and participation are low, particularly among ethnic and racial minorities and patients who live in rural areas.[10–12,16] Barriers identified for rural cancer patients' enrollment in CTs have focused on inadequate transportation and greater travel time, insufficient specialists, and underfunded research infrastructure.[1] A prior study found that CTs for selected solid cancers were greater than a 60-minute drive-time for approximately half of Americans.[20]

Here, we demonstrate that there are fewer CTs for hematologic malignancies accessible to patients living in rural areas compared to urban areas, across disease types and state of the disease trajectory. This finding of such "clinical trial deserts" may be a significant barrier to Veterans' access to CTs, since Veterans more often live in rural areas than non-Veterans.[4] The lower number of CTs in rural areas is consistent with the previously observed rural-urban disparity in trial enrollment,[14,16,17] although there also are likely patient- or facility-specific reasons not evaluated in this work that have been summarized in other publications.[10,13,14,16]

When asked, Veterans in both rural and urban areas often agreed to a referral to the LLS CTSC, with information subsequently provided to patients and to their providers. This supports prior literature indicating that when patients are asked if they are interested in enrolling in a CT—including patients from underserved groups—the majority say yes.[21] Three (9%) of the referred patients described here ultimately enrolled in CTs, which is just above the historical rates of enrollment on CTs among cancer patients in general. However, this cohort included a relatively high percentage of patients who reside in rural locations (45%)

and who identify as racial minorities (27%), groups that historically are not well represented in CTs, and who are less frequently referred or considered for enrollment in CTs. While the number of patients in this study was small, to our knowledge, this is the first report that documents the percentage of Veterans who are interested in learning about CTs as a treatment option and who participate in oncology CTs when provided with information and education.

Limitations of this study include the short duration of time and small sample size for LLS CTSC referrals described here, which limit the generalizability of our findings. In addition, the simplified, dichotomized nature of the simulated searches (rural vs urban) limits the ability to understand how our findings fit within the known complexity of barriers to CT enrollment.

Educating Veterans with blood cancers who require therapy about CTs and providing them and their oncology providers with regional CT options is one step toward the goal of increasing access to and enrollment in CTs. Greater participation in cancer CTs from a heterogenous population will enhance the rapid evaluation of promising emerging treatments and will increase the applicability of results to cancer patients in general. Our efforts to address the problem of low CT enrollment demonstrate the ease and feasibility of using the LLS CTSC clinical trial navigation service. Future efforts to increase CT referral and participation by Veterans include developing and using informatics tools to help VA Hematology-Oncology providers identify appropriate patients, increasing referrals to the LLS CTSC for Veterans with blood cancers, and providing VA-specific CT navigation to connect Veterans with appropriate CTs for any cancer. In addition, designing CTs that are inclusive, accessible, and patient-centric (eg, incorporating virtual modalities, minimizing therapy frequency and study visits, and reducing the burden of toxicity monitoring) would align with the needs of rural cancer patients and lower barriers to participation (Supporting Information).

FUNDING INFORMATION

The study was funded by Veterans Administration and The Leukemia & Lymphoma Society.

DISCLOSURES

Leah Szumita and Elisa S. Weiss are employees of The Leukemia & Lymphoma Society.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

REFERENCES

1. Bhatia S, Landier W, Paskett ED, et al. Rural-urban disparities in cancer outcomes: opportunities for future research. *J Natl Cancer Inst*. 2022;114(7):940-952.
2. Zullig LL, Sims KJ, McNeil R, et al. Cancer incidence among patients of the U.S. Veterans Affairs Health Care System: 2010 update. *Mil Med*. 2017;182(7):e1883-e1891.
3. Landrum MB, Keating NL, Lamont EB, et al. Survival of older patients with cancer in the Veterans Health Administration versus fee-for-service Medicare. *J Clin Oncol*. 2012;30(10):1072-1079.
4. National Center for Veterans Analysis and Statistics (NCVAS). Characteristics of Rural Veterans: 2014. 2016. Accessed June 23, 2021 https://www.va.gov/vetdata/docs/SpecialReports/Rural_Veterans_ACS2014_FINAL.pdf
5. Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM. Are patients at Veterans Affairs medical centers sicker? A comparative analysis of health status and medical resource use. *Arch Intern Med*. 2000;160(21):3252-3257.
6. Jazowski SA, Sico IP, Lindquist JH, et al. Transportation as a barrier to colorectal cancer care. *BMC Health Serv Res*. 2021;21(1):332.
7. Parikh DA, Ragavan M, Dutta R, et al. Financial toxicity of cancer care: an analysis of financial burden in three distinct health care systems. *JCO Oncol Pract*. 2021;17(10):e1450-e1459.
8. Jiang CY, El-Kouri NT, Elliot D, et al. Telehealth for cancer care in Veterans: opportunities and challenges revealed by COVID. *JCO Oncol Pract*. 2021;17(1):22-29.
9. Jiang CY, Strohbehn GW, Dedinsky RM, et al. Teleoncology for Veterans: high patient satisfaction coupled with positive financial and environmental impacts. *JCO Oncol Pract*. 2021;17(9):e1362-e1374.
10. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291(22):2720-2726.
11. Tejeda HA, Green SB, Trimble EL, et al. Representation of African-Americans, Hispanics, and Whites in National Cancer Institute cancer treatment trials. *J Natl Cancer Inst*. 1996;88(12):812-816.
12. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. *J Natl Cancer Inst*. 2019;111(3):245-255.
13. Hamel LM, Penner LA, Albrecht TL, Heath E, Gwede CK, Eggly S. Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. *Cancer Control*. 2016;23(4):327-337.
14. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. *Cancer*. 2008;112(2):228-242.
15. Meffert BN, Morabito DM, Sawicki DA, et al. US Veterans who do and do not utilize Veterans Affairs health care services: demographic, military, medical, and psychosocial characteristics. *Prim Care Companion CNS Disord*. 2019;21(1):18m02350. doi: 10.4088/PCC.18m02350
16. Baquet CR, Commiskey P, Daniel Mullins C, Mishra SI. Recruitment and participation in clinical trials: socio-demographic, rural/urban, and health care access predictors. *Cancer Detect Prev*. 2006;30(1):24-33.
17. Zullig LL, Fortune-Britt AG, Rao S, Tyree SD, Godley PA, Carpenter WR. Enrollment and racial disparities in cancer treatment clinical trials in North Carolina. *C Med J*. 2016;77(1):52-58.
18. Sae-Hau M, Disare K, Michaels M, et al. Overcoming barriers to clinical trial participation: outcomes of a national clinical trial matching and navigation service for patients with a blood cancer. *JCO Oncol Pract*. 2021;17(12):e1866-e1878.
19. Cowper Ripley DC, Ahern JK, Litt ER, Wilson LK. Rural Veterans Health Care Atlas 1st edition FY-2014. Washington, DC: Veterans Rural Health Resource Center-Eastern Region, VHA Office of Rural Health, Department of Veterans Affairs; 2015. Accessed June 23, 2021. https://www.ruralhealth.va.gov/docs/atlas/Core_Chapters_508_compressed.pdf
20. Galsky MD, Stensland KD, McBride RB, et al. Geographic accessibility to clinical trials for advanced cancer in the United States. *JAMA Intern Med*. 2015;175(2):293-295.
21. Unger JM, Hershman DL, Till C, et al. "When offered to participate": a systematic review and meta-analysis of patient agreement to

participate in cancer clinical trials. *J Natl Cancer Inst*. 2021;113(3):244-257.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Friedman DR, Rodgers TD, Kovalick C, Yellapragada S, Szumita L, Weiss ES. Veterans with blood cancers: Clinical trial navigation and the challenge of rurality. *J Rural Health*. 2023;1-7. https://doi.org/10.1111/jrh.12773