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ORIGINAL RESEARCH

Access to Chimeric Antigen Receptor T Cell Therapy for Diffuse Large B Cell Lymphoma

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ABSTRACT

Introduction: Geographic access to novel oncology therapies, and the extent to which it may vary by potential sites of care, regions, and population characteristics, is poorly understood. We examined how expanding access to chimeric antigen receptor (CAR) T cell therapy administration sites impacts patient travel distances and time.

Methods: We used geographic information system techniques to calculate shortest travel distance and time between patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL) and the nearest CAR T cell therapy administration site in three scenarios: academic hospitals; academic and community multispecialty hospitals; and academic and community multispecialty hospitals plus nonacademic specialty oncology network centers. Main outcome measures were differences in travel distance and time among the scenarios and the relationship between travel time and socioeconomic status, race, rural–urban areas, and non-Hodgkin lymphoma clusters. Non-Hodgkin lymphoma incidence, socioeconomic status, and administration centers were derived from governmental/publicly available data sources.

Results: Of 3922 patients eligible for CAR T cell therapy, more than 37% had to travel more than 1 h to the nearest academic hospital. Average travel time and distance were significantly reduced by 23% and 30% ($P < 0.001$), respectively, when access was expanded to include community hospitals plus a broader range of oncology specialty treatment centers. Compared to academic hospitals alone, increasing access to include community hospitals decreased time and distance by 7% and 8% ($P < 0.01$), respectively. In addition, there would be a lower proportion of sites operating as the only care provider within 25 miles if access was expanded outside of academic hospitals only. Longer travel time was associated with lower socioeconomic status.

Conclusion: Many patients with DLBCL have long travel times to an academic hospital that

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administers CAR T cell therapy. Expanding access to care through site-of-care planning will help address regional, rural–urban, and sociodemographic equity in the geographic allocation of CAR T cell therapy.

Keywords: Access to health care; CAR T cell therapy; Diffuse; Economic model; Geographical information systems; Health care inequalities; Lymphoma; Policy

Key Summary Points

Why carry out this study?
Geographic access to novel oncology therapies, and the extent to which it may vary by sites of care, regions, and population characteristics, is poorly understood
Our study assesses how expansion of chimeric antigen receptor (CAR) T cell therapy administration sites impacts patient accessibility in terms of travel distances and time
We hypothesize that expansion of access to CAR T cell therapy administration sites can help to reduce the time and distance burden associated with traveling for CAR T cell therapy in the USA
What was learned from this study?
When access was expanded from academic hospitals to a broader network of specialty oncology treatment centers, average travel time and distance were significantly reduced by 23% and 30% ($P < 0.001$), respectively
Many patients with diffuse large B cell lymphoma have long travel times to an academic hospital that administers CAR T cell therapy
Our study indicates that site-of-care planning should address regional, rural–urban, and sociodemographic equity in the geographic allocation of CAR T cell therapy

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14815686.

INTRODUCTION

Travel distance and time are widely recognized factors impacting patients' access to medical services and their willingness to receive treatment. Residing a long distance from health facilities decreases health service utilization [1–3]—a phenomenon known as the distance decay effect [4]. Extended travel distances to therapy or inconvenient care locations are barriers to patient care, particularly for those receiving later-line oncology therapy who may have poorer performance status. Travel can also greatly increase out-of-pocket therapy costs, making it unfeasible or burdensome for some patients to receive treatment [3, 5–7]. Consequently, longer travel distances may impose socioeconomic and clinical disparities on patients. Information regarding the accessibility of different treatment center types for various population subgroups is crucial for policy- and decision-making.

Chimeric antigen receptor (CAR) T cell therapies have shown promising results in the third-line setting among patients with the non-Hodgkin lymphoma (NHL) subtype diffuse large B cell lymphoma (DLBCL) [8, 9]. However, administration of CAR T cell therapy is currently limited to select cancer centers approved by manufacturers and independent institutions [10, 11]. Patients receiving approved CAR T cell therapies must be closely monitored for treatment-associated adverse events, including cytokine release syndrome (CRS) and neurological events (NEs), and must remain within 0.5–2 h of the treatment site for at least 4 weeks after infusion [12–14]. During this time, a caregiver is also needed to monitor symptoms. These requirements, along with the limited number of treatment sites, impose a travel burden that could limit many patients' access to

this therapy if its administration is restricted to academic hospital settings. To our knowledge, little is known regarding geographic access to CAR T cell therapy and the extent to which it may vary by potential sites of care, regions, and population characteristics. The objective of this study was to estimate the extent to which expanding access to different CAR T cell therapy administration sites impacts patient travel distances and time in the continental United States (US).

METHODS

Data Sources

County-level NHL incidence counts of patients were matched to the nearest ("as the crow flies") potential CAR T cell therapy administration center to analyze variations in travel requirements (in miles and minutes) by site scenario. CAR T cell therapy administration sites included centers with relevant claims activity indicating CAR T cell administration capability and phase 1 oncology clinical trial sponsorship, along with centers approved for administration of currently marketed CAR T cell products. All centers were geocoded in R software (version 3.5.3 [2019-03-11]; R Graphical User Interface system for Windows) [15].

Our analysis considered three types of CAR T cell therapy facilities: academic hospitals, community multispecialty hospitals, and nonacademic specialty oncology network centers (NASONCs) (Fig. S1). Sites were categorized on the basis of publicly available information obtained from facility websites (Table 1) [16–23]. The facilities that administered CAR T cell therapy were classified by certain sites of care type as follows: academic hospitals, community multispecialty hospitals, or NASONCs (Table S1).

The three hypothetical scenarios analyzed were increasingly inclusive of site type and included treatment at (A) academic hospitals only; (B) both academic and community multispecialty hospitals; and (C) any specialized center that included approved inpatient or possible outpatient CAR T cell therapy (academic hospitals, community multispecialty hospitals, and NASONCs) (Table 1). Each patient was assumed to be treated at the nearest center. We used geographic information system techniques for this analysis.

This article does not contain any new studies with human participants or animals performed by any of the authors.

Patient and CAR T Cell Therapy Location and Characteristics

Patients were assigned to US counties with a corresponding US census tract region, level of urbanization, race/ethnicity distribution, and federal poverty level (FPL) based on NHL incidence data from State Cancer Profiles—a data program developed by the National Cancer Institute (NCI) and Centers for Disease Control and Prevention (CDC). Incidence data were extracted from the CDC's National Program of Cancer Registries Cancer Surveillance System and the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. These data represented a 5-year average incidence count from 2011 to 2015 for every county except those in Kansas, Minnesota, and Nevada, as incidence data were not supplied to SEER from these states. Data from Alaska and Hawaii were excluded from analysis because these states had inconsistent road-based travel. The analysis was limited to counties with at least one incident NHL case, on average, from 2011 to 2015. Among counties with available data, limited information was provided in certain Wyoming and Colorado counties because of low NHL incidence or lack of sufficient data.

This analysis used the latest 5-year average (2011–2015) of county-level cancer incidence rate of NHL for all stages, all races (including Hispanic), both sexes, and all ages. Rates were reported as cases per 100,000 population per year; these rates were age adjusted to the 2000 US standard population. In many cases, the CDC suppressed county-level incidence data because of low annual rates. For this analysis, the suppressed county rates were imputed to 1 case per 100,000. The county-level incidence count of patients with DLBCL was estimated as

Table 1 Types of CAR T cell therapy administration sites considered in each scenario

Scenario	Description	No. of sites
A	Academic sites[a]	141
B	Academic sites[a]	179
	Community multispecialty hospitals[b]	
C	Academic sites[a]	262
	Community multispecialty hospitals[b]	
	NASONC[c]	

CAR chimeric antigen receptor, *NASONC* nonacademic specialty oncology network center

[a] Academic (or teaching) hospitals were defined as "hospitals that received payment for Medicare direct graduate medical education, inpatient prospective payment system indirect medical education, or psychiatric hospital indirect medical education programs during the last calendar year for which such information was available" [16]. Academic hospitals, which could be independent or integrated with medical schools, were identified from the Centers for Medicare and Medicaid Services' list of teaching hospitals [17–19]

[b] Nonacademic community multispecialty hospitals were defined as all nonfederal, short-term general and other special hospitals that do not provide teaching, excluding hospitals inaccessible to the general public (e.g., prison hospitals or college infirmaries) [20]

[c] NASONCs were defined as privately owned, community-based oncology centers with office space as a direct cost to the physician and not typically located in hospital outpatient departments. These sites demonstrated the capabilities required to administer CAR T cell therapies and had relationships with inpatient hospitals for adverse event management [21–23]

a uniform percentage (32.5%) of patients with NHL based on published literature that analyzed data from the National Cancer Database [24]. Patients with DLBCL receiving third-line therapy (19.4%) and who were eligible for CAR T cell therapy [12, 13] were estimated on the basis of published findings on response by line of therapy [25–27]. To protect patient confidentiality, county-level geographic details on NHL incidence excluded patient demographics. Accordingly, the incidence data do not contain demographic characteristics of the cases. Thus, separate data on county-level socioeconomic status variables from the US Census Bureau 2011–2015 American Community Survey 5-Year Estimates were linked to the county-level incidence data. Socioeconomic data included county-level information on sex, race/ethnicity, and number of persons above and below the FPL.

Patients' residences were assumed to be at the county population centroid. The centroids were geocoded into latitude and longitude coordinates [28]. For each US county, the number of NHL cases and total county population for the year 2015 were recorded and uploaded to SaTScan (version 9.6; Kulldorff M and Information Management Services, Inc.) and R software. Consistent with payment classification specified by the Centers for Medicare and Medicaid Services, we classified any patient residing within a core-based statistical area (included metropolitan and micropolitan areas) as urban and any patient residing outside of a core-based statistical area as rural [29, 30].

Geographic Access Measures

Travel distance and times were calculated on the basis of the shortest driving route from each county population center to the nearest destination point (academic hospital, community multispecialty hospital, or NASONC) based on a national major and minor road network with associated speed limits and average traffic time (Google's Distance Matrix API) [15]. We computed travel distance and time using a nearest-

neighbor algorithm developed in R. Demographic and rural–urban data were then linked to the county travel distance and times for the three CAR T cell therapy settings (academic hospital, community multispecialty hospital, or NASONC) to evaluate implications across socioeconomic variables.

Travel to a CAR T cell therapy center was defined as the driving distance (miles) and estimated time (minutes; assuming average traffic conditions in the areas) between the geographic center of the patient's residence and the CAR T cell therapy center. Travel distance was categorized, on the basis of literature [31–33], as 0–12.49, 12.5–49.9, 50–149.9, 150–249.9, and $\geq$ 250 miles. Travel time was categorized, on the basis of literature and guidelines [14, 32, 34, 35], as 0–30, 31–60, 61–120, 121–300, and $>$ 300 min. Travel time categories were mapped and summarized in R.

Statistical Analysis

Descriptive analyses were used to investigate the distribution of potential CAR T cell administration sites by each scenario's type of center and by independent variables (race/ethnicity, FPL, and rural–urban). The number of sites by region, rural–urban residencies, and type are shown in Table S2. The base case assumed that patients could only attend academic hospitals (scenario A). This case was compared with the incremental addition of community multispecialty hospitals to academic hospitals (scenario B) and then with the addition of NASONCs (scenario C). Analysis of the differences in the weighted mean travel distance and time was performed using the *t* test after testing for equality of variance. Differences in the proportions of sole providers ("monopoly" providers) were tested using the independent *z* test. Means were weighted by the estimated number of patients with DLBCL in the county. To explore statistical associations between distance and time and sociodemographic characteristics, we conducted nonparametric tests for bivariate correlation using Spearman correlation coefficients. In all statistical tests, $P < 0.05$ was considered statistically significant. All statistical analyses were performed with R.

Cluster Analysis

A geographic cancer cluster is defined as "a greater-than-expected number of cancer cases that occurs within a group of people in a defined geographic area over a period of time" [36]. In this study, SaTScan was used for NHL cluster identification and significance testing. NHL incidence (vs DLBCL incidence) was used for accuracy in the cluster analysis as a result of county-level data availability. The results for patients with DLBCL were assumed to be representative if these patients had similar geographical distribution to patients with NHL. NHL incidence in each county was assumed to be distributed according to a Poisson model, which tests the null hypothesis that the age-adjusted risk of NHL incidence is the same for all counties in the data set. We then compared the top five clusters to the number of available sites to evaluate treatment accessibility for high-density areas with patients with NHL. Lack of overlap would suggest a geographic access disparity in counties that may need it most.

RESULTS

Patients

The analysis included NHL incidence data (2011–2015) from all evaluable states. From these data, 62,339 unique cases of NHL were identified. Patients with DLBCL receiving third-line therapy were estimated to comprise 3922 (6.3%) of the identified patients with NHL [26, 27, 37].

Travel Distance and Time

A shift toward shorter travel distance and time occurred as the scenarios progressed through expanding inclusion of site types. Maps of travel distance by site type and travel time and distance by type of potential CAR T cell therapy site scenario are presented in Fig. 1. Weighted

mean travel distance and time traveled, respectively, were significantly shorter to academic and community multispecialty hospitals for scenario B (54.8 miles and 61.0 min) and were further reduced under scenario C (any specialized treatment center; 41.9 miles and 50.7 min) compared with scenario A (academic hospitals only; 59.7 miles and 65.8 min) (Table 2). For scenario C versus scenario A, this reflected a reduced average travel time and distance of 23% and 30%, respectively. Significance was maintained for travel time between scenarios A and C when stratified by all regions and rural–urban classification; travel distance remained significantly shorter for scenario C versus scenario A when stratified by rural–urban classification and in all regions except the northeast. Numerical improvements were observed between scenarios A and B when stratified by all regions and rural–urban classification; however, statistical significance for both time and distance was seen for only the south region and urban areas. The south region had the longest estimated mean travel distance (71.9 miles) and time (76.3 min)

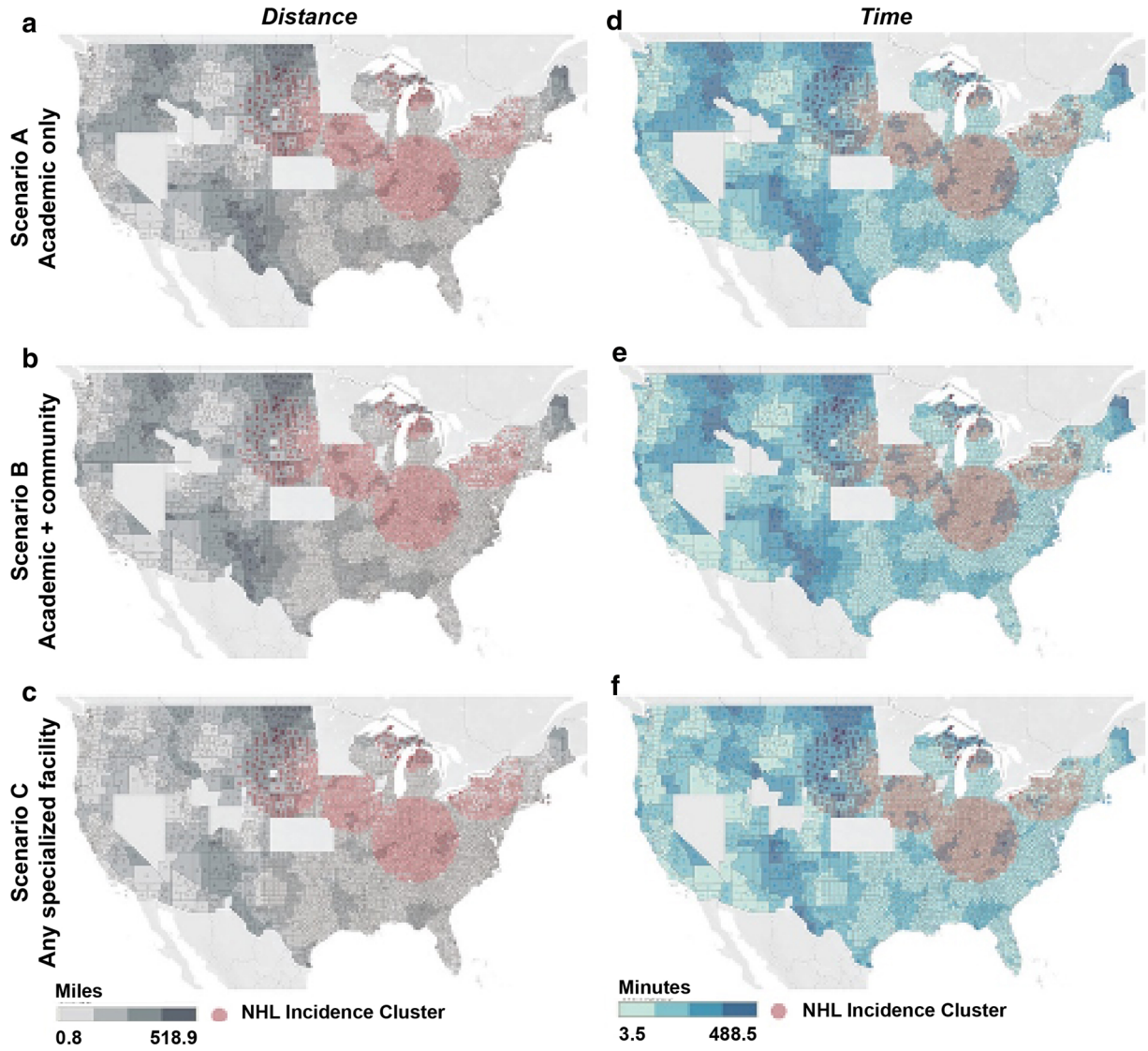

Fig. 1 Map of **a**–**c** distance (miles) and **d**–**f** time (minutes) to the nearest chimeric antigen receptor T cell therapy center by scenario and non-Hodgkin lymphoma (NHL) incidence cluster

Table 2 Weighted mean travel distances and times to CAR T cell therapy administration centers for the third-line DLBCL population (N = 3922) by region and rural–urban classification

	Third-line DLBCL population, *n* (%)	Scenario A (base case): academic hospitals (*n* = 141)	Scenario B: academic and community multispecialty hospitals (*n* = 179)	Scenario C: any specialized treatment center (*n* = 262)
Weighted mean travel distance, miles				
Total (national) population	3922 (100)	59.65 (57.00–62.30) [Ref.]	54.78** (52.57–56.99) [− 4.88]	41.93*** (39.65–44.28) [− 17.73]
Region				
Midwest	803 (21)	57.81 (53.66–61.95) [Ref.]	54.85 (50.75–58.96) [− 2.96]	46.87* (43.03–50.70) [− 10.94]
Northeast	880 (22)	35.71 (29.70–41.72) [Ref.]	33.32 (27.50–39.15) [− 2.39]	26.33 (22.51–30.15) [− 9.38]
South	1441 (37)	71.90 (68.31–75.48) [Ref.]	61.89*** (58.60–65.18) [− 10.01]	46.68*** (44.00–49.36) [− 25.22]
West	798 (20)	65.65 (55.53–75.77) [Ref.]	65.25 (55.13–75.37) [− 0.40]	45.59** (38.15–53.02) [− 20.06]
Rural–urban classification				
Rural	1149 (29)	80.99 (77.16–84.83) [Ref.]	76.45 (72.76–80.14) [− 4.54]	59.92*** (56.82–62.61) [− 21.07]
Urban	2773 (71)	50.95 (47.06–54.84) [Ref.]	45.90* (42.15–49.64) [− 5.05]	34.48*** (31.58–37.38) [− 16.47]
Monopoly, % of centers[a]				
National	–	40.5% [Ref.]	29.2% [− 11.3%]	27.2%** [− 13.3%]
Weighted mean travel time, minutes				
Total (national) population	3922 (100)	65.78 (63.32–68.25) [Ref.]	60.95** (58.63–63.27) [− 4.83]	50.73*** (48.60–52.86) [− 15.05]
Region				
Midwest	803 (21)	63.16 (59.58–66.74) [Ref.]	60.43 (56.85–64.01) [− 2.73]	53.03* (49.45–56.61) [− 10.13]
Northeast	880 (22)	46.55 (42.67–50.43) [Ref.]	43.34 (39.46–47.21) [− 3.21]	36.04* (32.16–39.92) [− 10.51]
South	1441 (37)	76.30 (73.81–78.79) [Ref.]	66.75*** (64.26–69.25) [− 9.55]	53.07*** (50.58–55.57) [− 23.23]
West	798 (20)	70.51 (63.47–77.54) [Ref.]	70.19 (63.16–77.23) [− 0.32]	51.19* (44.15–58.22) [− 19.32]
Rural–urban classification				
Rural	1149 (29)	86.86 (83.21–90.51) [Ref.]	82.46 (78.94–85.98) [− 4.40]	67.10*** (63.98–69.56) [− 19.76]

Table 2 continued

	Third-line DLBCL population, *n* (%)	Scenario A (base case): academic hospitals (*n* = 141)	Scenario B: academic and community multispecialty hospitals (*n* = 179)	Scenario C: any specialized treatment center (*n* = 262)
Urban	2773 (71)	57.19 (53.63–60.74) [Ref.]	52.14* (48.71–55.56) [− 5.05]	41.30*** (38.65–43.96) [− 15.89]

Data are shown as weighted mean (95% confidence interval) [difference vs academic hospitals only] unless otherwise specified

CAR chimeric antigen receptor, *DLBCL* diffuse large B cell lymphoma, *Ref* reference

*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ versus academic hospitals only; nonparametric tests for bivariate correlation using Spearman correlation coefficients

[a] A monopoly was defined as being the sole care provider within a 25-mile range

under scenario A but was reduced to 61.9 miles and 66.8 min ($P < 0.001$), respectively, under scenario B (academic and community multispecialty hospitals) and to 46.7 miles and 53.1 min ($P < 0.001$), respectively, under scenario C (any specialized treatment center). Travel distance for urban areas was 51.0 miles under scenario A versus 34.5 miles under scenario C, and travel time was 57.2 min and 41.3 min, respectively ($P < 0.001$ for both); results were not statistically significant for scenario A versus scenario B.

In scenario A, approximately 60% of potential patients resided less than 50 miles (Fig. 2a) from an academic hospital, and 36%, 63%, and 84% lived within 30 min, 1 h, and 2 h, respectively (Fig. 2b). In scenario B, approximately 64% of patients resided less than 50 miles from the nearest treatment center (P = not significant), and 40%, 67%, and 87% lived within 30 min, 1 h, and 2 h, respectively. In scenario C, approximately 71% of patients resided less than 50 miles from the nearest treatment center ($P < 0.001$), and 46%, 74%, and 92% lived within 30 min, 1 h, and 2 h, respectively. About 15% of patients would have to travel more than 2 h to the nearest academic hospital in scenario A, whereas 13% and 8% of patients would have to travel more than 2 h in scenarios B and C, respectively.

Travel Time, Socioeconomic Status, and Race/Ethnicity

Differences in distance and travel time across the scenarios were apparent for FPL and rural–urban measures (Table 3; Fig. 3). An estimated 42% of patients living below 100% FPL resided at least 50 miles from the nearest academic hospital (scenario A), compared with 39% for academic and community multispecialty hospitals (scenario B) and 31% for any specialized treatment center (scenario C) (both $P < 0.001$; Table 3). Similarly, 64% of patients living below 100% FPL would travel more than 30 min to an academic site, compared with 61% and 55% for academic and community multispecialty hospitals and any specialized treatment center (both $P < 0.001$), respectively. A

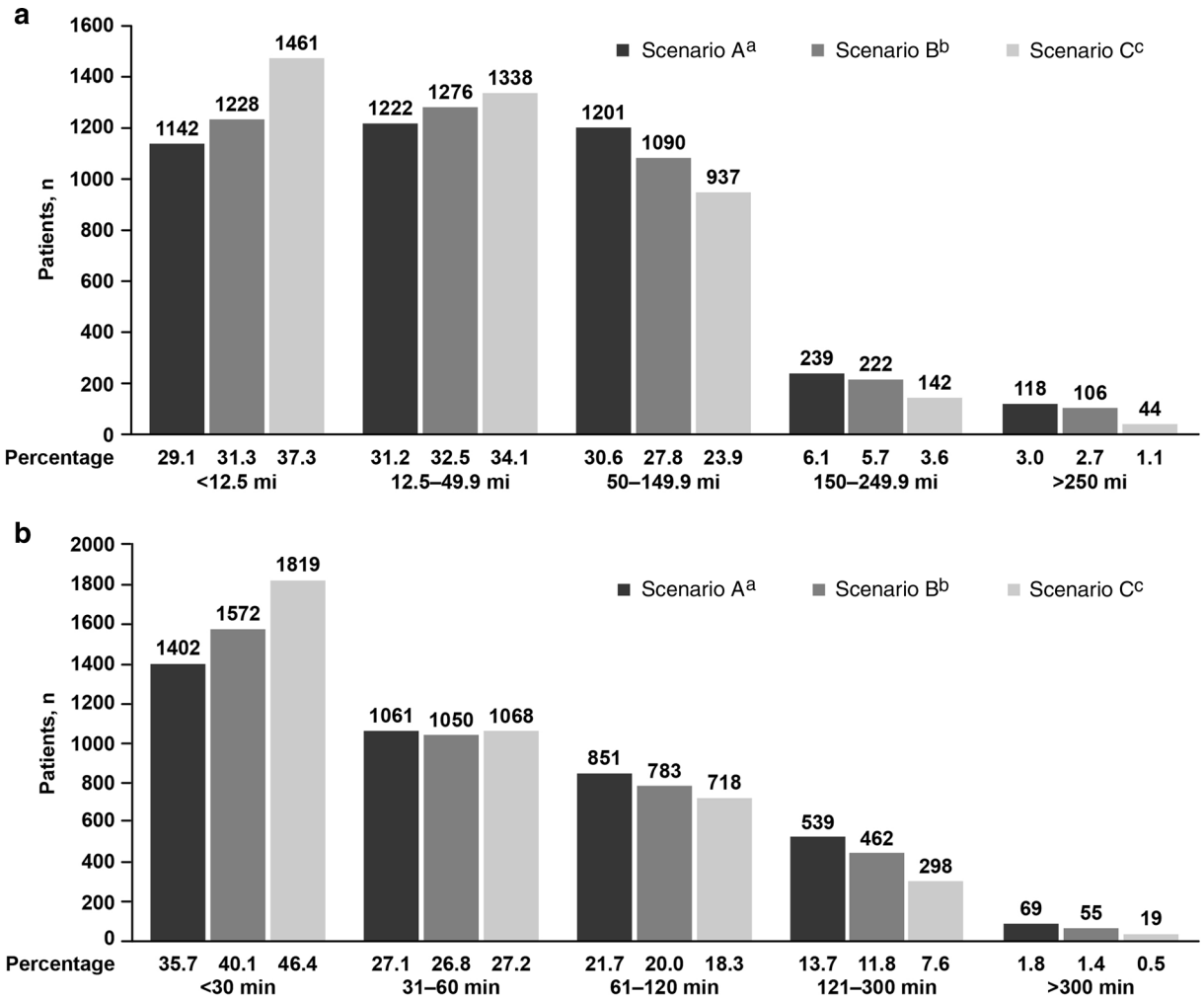

Fig. 2 Number of the diffuse large B cell lymphoma incident population ($N = 3922$) stratified by site type and **a** travel distance and **b** travel time to nearest chimeric antigen receptor (CAR) T cell therapy administration center. [a]Scenario A: academic hospitals only. [b]Scenario B: both academic and community multispecialty hospitals. [c]Scenario C: any specialized center that included approved inpatient or possible outpatient CAR T cell therapy (academic hospitals, community multispecialty hospitals, and nonacademic specialty oncology network centers). mi miles, min minutes

significantly ($P < 0.01$) lower proportion of sites would be the sole care providers for patients (the only provider within 25 miles) if all sites were included compared with academic hospitals only (27% vs 41%, respectively); results were not statistically significant for scenario B (Table 2). Travel distance and time were shorter among both rural and urban areas in scenario C than in scenario A (Fig. 3).

The bivariate analysis of the association between travel time, socioeconomic status, and race/ethnicity showed that longer travel times were significantly ($P < 0.001$) associated with higher poverty rates and particular races/ethnicities (Table S3). Spearman correlation coefficients indicated statistically significant and positive linear associations between time to the nearest CAR T cell therapy site and the percentage of patients living below the FPL, as well as the proportions of Native American and non-Hispanic Whites; for race/ethnicity, the

Table 3 FPL and rural classification within distance and time thresholds by site-of-care scenario

	Scenario A (base case): academic hospitals (n = 141)	Scenario B: academic and community multispecialty hospitals (n = 179)	Scenario C: any specialized treatment center (n = 262)
≥ 50 miles to nearest site			
Population below 100% FPL	42.2% (41.5–42.9)	38.6%** (36.3–40.9)	31.0%** (27.7–34.3)
Rural residents	55.3% (54.7–55.9)	52.6% (50.3–54.9)	44.6%** (41.0–48.2)
> 30 min to nearest site			
Population below 100% FPL	64.4% (63.9–64.9)	60.9%** (60.4–61.5)	55.0%** (54.5–55.5)
Rural residents	74.3% (73.8–74.7)	73.2% (72.7–73.8)	67.9%* (67.4–68.4)

Data are shown as percentage (95% confidence interval)
FPL federal poverty level
*$P < 0.01$ and **$P < 0.001$ versus academic hospitals only

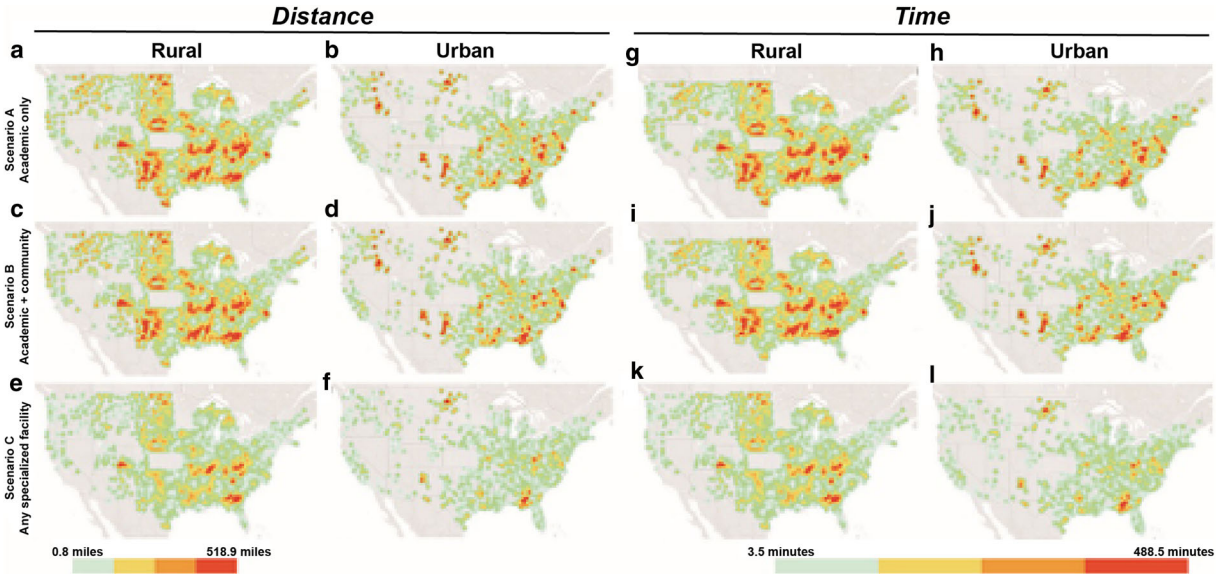

Fig. 3 Map of rural (**a**, **c**, **e**, **g**, **i**, **k**) versus urban (**b**, **d**, **f**, **h**, **j**, **l**) travel distances (**a**–**f**) and travel time (**g**–**l**) to the nearest chimeric antigen receptor T cell therapy administration center based on the three scenarios

proportion of Native Americans showed the strongest positive correlation (Table S3).

Cluster Analysis

The spatial scan identified five areas where observed NHL incidence was significantly greater than the number expected from the distribution in the remaining US areas after adjusting for age (Fig. 1). A heightened need for therapy is expected in these clusters. The cluster analysis revealed a stronger positive correlation between the number of CAR T cell administration sites and NHL patient counts for any specialized treatment center (scenario C) compared with academic hospitals only (scenario A) (Fig. S2).

DISCUSSION

This geospatial analysis showed that increasing the number of administration center options for CAR T cell therapy led to a greater number of patients with shorter travel distance and time to a treatment site. About 74% of patients with DLBCL lived within a travel time of less than 1 h to any specialized treatment center in scenario C compared with only 63% of patients in scenario A, where treatment was limited to the nearest academic hospital. This difference is notable, as CAR T cell therapy requires patients to remain within 0.5–2 h of the site of care for at least 4 weeks after infusion for CRS and NE monitoring [12, 13]. Patients unable to live at home during this monitoring period would need to find lodging near the site of care, making the treatment more costly for patients and caregivers. Travel burden—in terms of distance, time, and costs—is an important factor in access to care. This analysis examines patient access to CAR T cell therapy and reflects on access to future novel oncology therapies.

The results presented here suggest that patients may benefit from administration of CAR T cell therapy in the outpatient setting, as it would allow for more sites to be able to administer CAR T cell therapy. Recent studies have shown that outpatient treatment with CAR T cell therapy is possible with an acceptable safety profile [38]. Because fever is the first presenting symptom of CRS, it has been argued that CAR T cell therapy can be safely administered in the outpatient setting if patients are carefully monitored, with hospital admittance at the time of fever development [39]. Many clinics have the infrastructure and multidisciplinary teams in place to support outpatient stem cell and bone marrow transplant programs [40]. Additionally, differences in safety profiles between CAR T cell therapies and in individual patient risk factors may allow for identification of those patients who can safely be administered CAR T cell therapy at nonacademic centers. Nevertheless, any clinic tasked with administering CAR T cell therapy should be prepared to manage the complexity of administering this therapy and its potential associated adverse effects.

Access to a greater number of qualified administering locations is particularly important for certain geographic areas. In NHL cluster areas, the number of potential administration sites increased under scenario C, resulting in greater proximity to CAR T cell therapy administration sites. In bivariate analyses, patients of Native American race/ethnicity, those living in rural areas, and those with low socioeconomic status had relatively long travel times to CAR T cell therapy administration sites. These findings align with previous studies showing that these groups traveled longer distances to receive care and that longer travel distances were associated with additional patient time burden, cost, and discomfort levels [3, 41–44]. Moreover, lower income has been associated with a reduced likelihood of traveling long distances for therapy [45], potentially decreasing patients' access to appropriate cancer care.

The association between regions and socioeconomic variables with estimated travel distances and times is also concerning, as some health plans may restrict patients' hospital choice. Patients with these plans may need to travel farther from home despite having critical medical conditions and limited resources. Policy- and decision-makers should consider evaluating the geospatial accessibility of CAR T cell therapy

administration and monitoring, along with its impact on patients' care and quality of life.

This study has several strengths and limitations. By developing a detailed geographic information systems database of NHL incidence combined with a specific site of care, we estimated more precise measures of access to novel oncology therapies than those previously described [31–33]. A limitation of this study is that disease incidence was based on county-level NHL patient incidence counts as of 2015. Also, the database from which CAR T cell therapy site locations were extracted is frequently updated. Patients may also be required to travel to a specific site according to provider networks and local oncologist referrals. While this study did not incorporate these possibilities, we analyzed the most optimistic circumstances in that patients were assumed to travel to the nearest location administering CAR T cell therapy.

Actual patient addresses or DLBCL incidence by ZIP code would have refined this analysis; however, these data were not publicly available because of patient confidentiality. Therefore, we were unable to analyze distances traveled by patients living along county borders who may have been closer to potential CAR T cell therapy administration sites than estimated by using the county centroid. However, comparisons across site-of-care scenarios are unlikely to be considerably impacted by increased precision in patient residence data. Additionally, some counties were excluded from the analysis because of insufficient incidence data.

The impact of distance and time on patients' ability to receive therapy may be mitigated by other factors not included in our study, such as the patient–physician relationship, patient preference, physician networks, and patient health status [46, 47]. Further, our study did not address capacity by geographic region, an area of potential concern if NHL and CAR T cell therapy center clusters do not overlap.

It is also critical to note that there are additional costs required to expand CAR T cell therapy to nonacademic hospitals and treatment settings to meet requirements consistent with the Foundation for the Accreditation of Cellular Therapy (FACT) [48, 49]. The CAR T cell therapy process has many steps, including leukapheresis or lymphocyte collection, transportation of the collected cells to a laboratory, cell engineering, patient conditioning or lymphodepleting chemotherapy, infusion, and patient monitoring and follow-up that must not be compromised in order to properly care for patients during and after CAR T cell therapy. Furthermore, investment costs will also require providers in the CAR T cell therapy unit to focus on education. Inpatient units are more likely to have FACT accreditation at the time they establish a CAR T cell therapy program [49], and outpatient facilities must also coordinate with inpatient providers for possible admission to manage adverse events [48]. In this study, the few patients requiring these procedures could potentially affect expansion of CAR T cell therapy to nonacademic hospitals and treatment settings.

The absence of sociodemographic and clinical detail, along with imprecise key patient characteristics, is an inherent limitation of public incidence databases, making association with outcomes unfeasible. As a descriptive study, this research did not attempt to draw causal inferences between geographic access and patient outcomes or receipt of treatment; however, it provides the foundation for this next logical step. Finally, with recent approval of CAR T cell therapies, such as idecabtagene vicleucel, for multiple myeloma, we believe that these study findings have implications outside of DLBCL, and further investigation of access to therapy is warranted. While this study did not include all patient indications for current and future CAR T cell therapies, it provides the basis for such research to be conducted in the future.

CONCLUSION

Our research indicates that patient access to therapy may be limited on the basis of geographic location. Patients with DLBCL who live more than 25 miles from an academic hospital may not have access to the same treatment options as those who live closer. Expanding CAR T cell therapy to nonacademic hospitals and outpatient treatment centers could make

this therapy accessible to a broader patient population.

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