Distance to expert care for patients with lysosomal storage disorders enrolled in a real-world data research platform

Ashley N. Leek, PhD, Hayden A. M. Hatch, MS, and Caitlin A. Nichols, PhD; AllStripes Research, San Francisco, CA
Please direct correspondence to ashley@allstripes.com

AllStripes

Introduction

Rare diseases are conditions that affect fewer than 200,000 people in the US (Orphan Drug Act of 1983), although collectively rare diseases impact as much as 10% of the total population (NCBI). Many of these conditions are life-threatening, complicated by a high burden of illness and not well understood. As such, patients and families affected by rare diseases must seek disease-specific expertise, which may be distant from home. Indeed, one study suggests that a greater burden of travel to access healthcare is associated with a higher burden of illness (Wallace et al., 2005). Rare disease patients are geographically dispersed, and few centers have the expertise necessary for adequate care. Therefore, patients and caregivers affected by rare disease face unique challenges to identify and access expert care.

Lysosomal storage disorders (LSDs) are a class of complex rare diseases with a high burden of illness. Altogether, the more than 50 LSDs affect approximately 1 in 5000 to 7500 births (Parenti et al., 2021) or ~750 births per year in the US. While many patients and families affected by LSDs travel widely for care, the travel burden of seeking care for LSDs remains poorly characterized. Likewise, many LSDs do not have established centers of excellence (COEs), which further burdens patients, caregivers and patient advocacy organizations with identifying centers with disease-specific expertise. Characterizing patient travel burden and geographic distribution of expertise is vital to improving patient and caregiver quality of life and understanding transportation-related barriers to effective clinical care and successful site-based studies.

Objectives for this study:

1. Determine potential travel time and distance to common care centers for a cohort of LSD patients
2. Define prospective COEs and the geography of these centers
3. Define patient travel time and distance to prospective COEs

Methods

Data collection: Patients and caregivers of patients were recruited and consented to research participation on the AllStripes research platform. This cohort represented 151 participants in the US with self-reported diagnoses of one of nine LSDs: alpha-mannosidosis (AM), cystinosis, GM1 gangliosidosis, GM2 gangliosidosis, Hunter syndrome (MPS II), Morquio A syndrome (MPS IVA), Morquio B syndrome (MPS IVB), Niemann-Pick disease type C (NPC), or Sanfilippo syndrome (MPS III). Demographic information, such as sex, race, ethnicity and zip code were self-reported by patients. Medical records from patient-reported facilities were collected and digitized. Deidentified facility data was abstracted from the records. A list of 152,746 medical care centers was sourced from the Centers for Medicare & Medicaid Services (CMS.gov) provider databases for evaluation as prospective COEs.

COE determination: We determined whether a facility was a prospective COE based on meeting at least three of the following criteria based on the sources in parentheses (similar criteria to Orphanet): Provider of multidisciplinary care (CMS.gov), participated in >1 LSD clinical trial (ClinicalTrials.gov), published >1 peer-reviewed article on an LSD (PubMed affiliation and article title search), and presence of a metabolic genetics clinic (Google and clinics.acmg.net search).

Analysis: Patient-reported zip code and facility geographic coordinates (latitude and longitude) were obtained using Google's Geocoding API. One-way drive time and distance between patient zip codes and facility coordinates were measured using Google's DistanceMatrix API. Analyses and API calls were performed in R (version 4.1.0).

Results

LSD cohort represents patients from nine conditions across the US

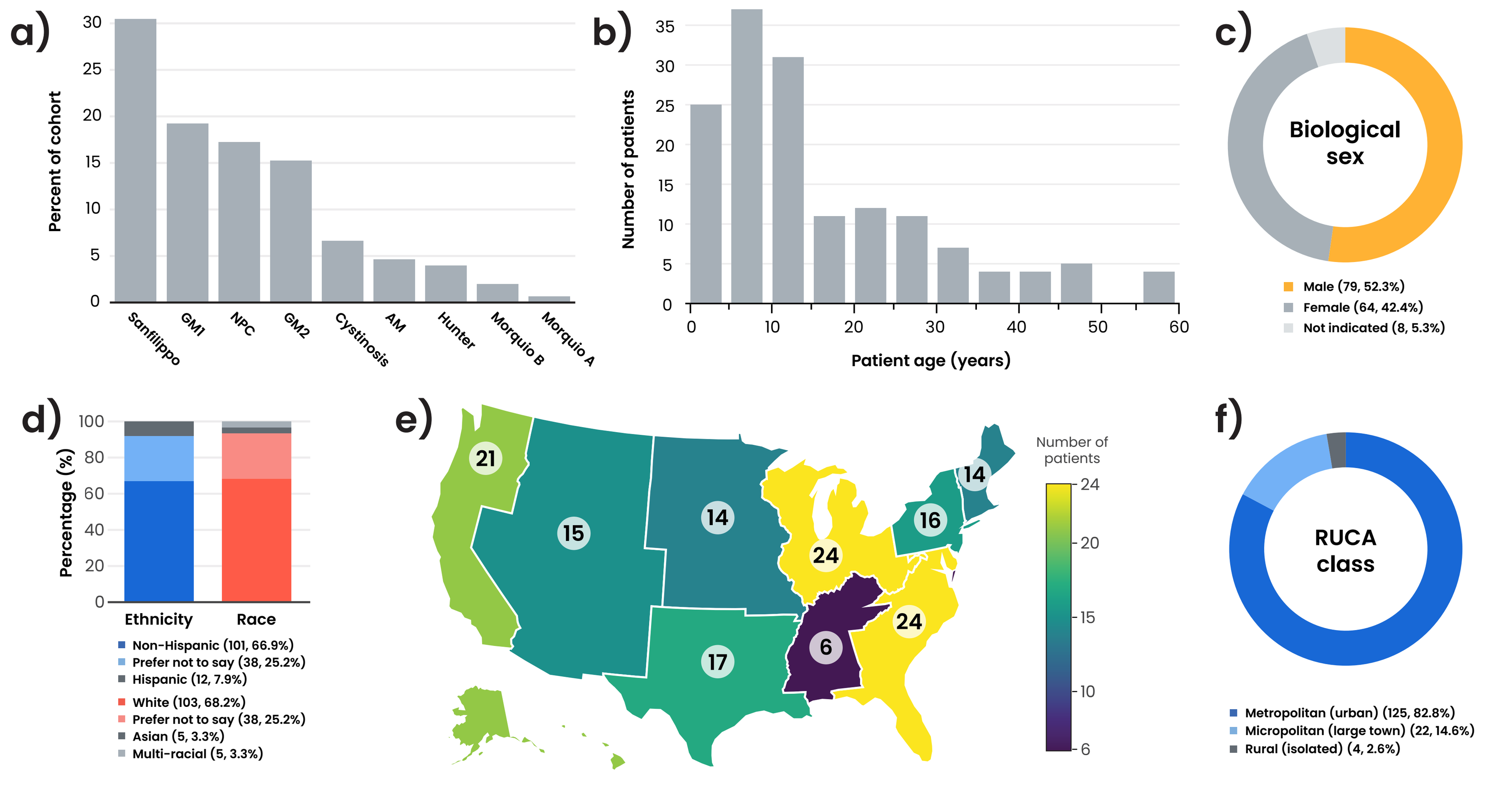
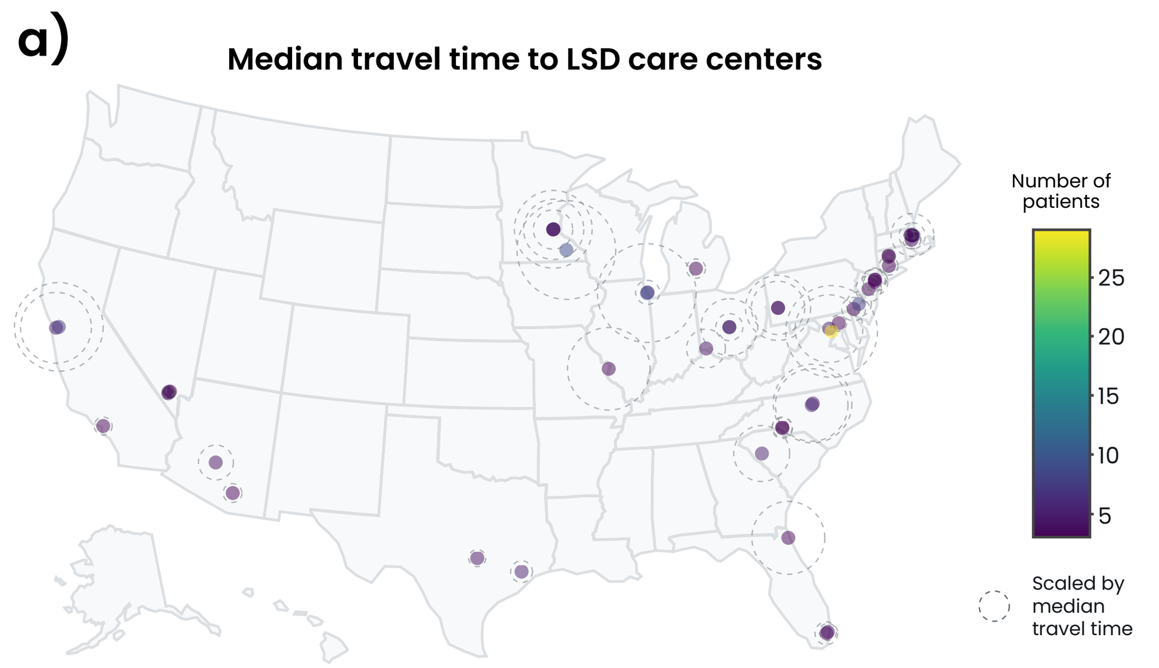

a)
Percent of cohort
Sanfilippo
GM1
NPC
GM2
AM
Cystinosis
Hunter
Morquio B
Morquio A
b)
Number of patients
Patient age (years)
c)
Biological sex
Male (79, 52.3%)
Female (64, 42.4%)
Not indicated (8, 5.3%)
d)
Percentage (%)
Ethnicity
Race
Non-Hispanic (101, 66.9%)
Prefer not to say (38, 25.2%)
Hispanic (12, 7.9%)
White (103, 68.2%)
Prefer not to say (38, 25.2%)
Asian (5, 3.3%)
Multi-racial (5, 3.3%)
e)
Number of patients
f)
RUCA class
Metropolitan (urban) (125, 82.8%)
Micropolitan (large town) (22, 14.6%)
Rural (isolated) (4, 2.6%)

Figure 1. AllStripes LSD cohort represents a variety of conditions, ages and locations across the US. a–b) Distribution of self-reported LSD diagnoses **(a)** and ages **(b)** across a cohort of 151 participants. Median participant age = 11 years. **c)** Distribution of participants' self-reported biological sex. **d)** Distribution of participants' self-reported ethnicity and race. **e)** Geographic distribution of participants by US census divisions. **f)** Distribution of rural vs. urban participants. Participants were designated as residing in metropolitan, micropolitan or rural zip codes using the USDA Economic Research Services' rural-urban commuting area (RUCA) code classifications (which are based on US census tracts).

Patients in the LSD cohort travel extensively for care



b)

Care Center	Number of AllStripes Patients	Median One-way Drive Time (hours)
National Institutes of Health	29 patients	14.7 hours
Nationwide Children's Hospital	10 patients	5.6 hours
Boston Children's Hospital	9 patients	1.2 hours
Mayo Clinic in Rochester, Minnesota	9 patients	17.0 hours
Rush University Medical Center	9 patients	17.0 hours
Children's Hospital of Philadelphia	8 patients	1.1 hours
Massachusetts General Hospital	8 patients	3.2 hours
University of Minnesota Masonic Children's Hospital	8 patients	10.5 hours
UCSF Benioff Children's Hospital	7 patients	13.8 hours
UNC Healthcare	6 patients	9.2 hours

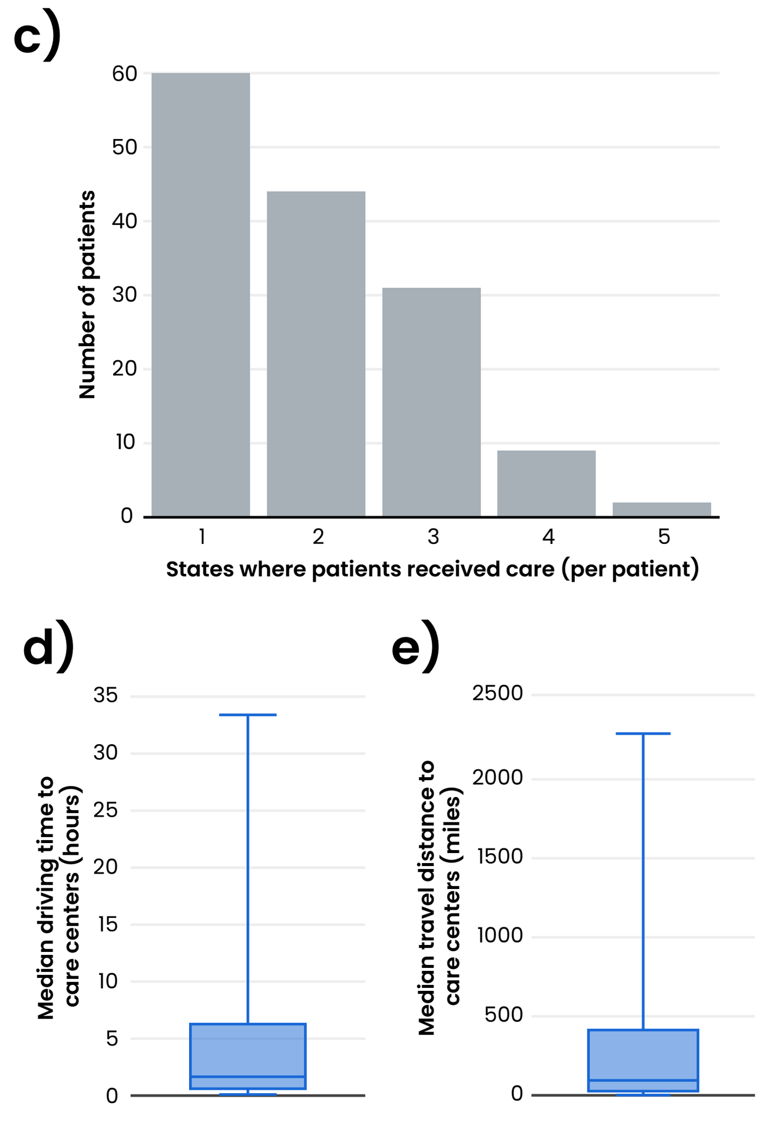
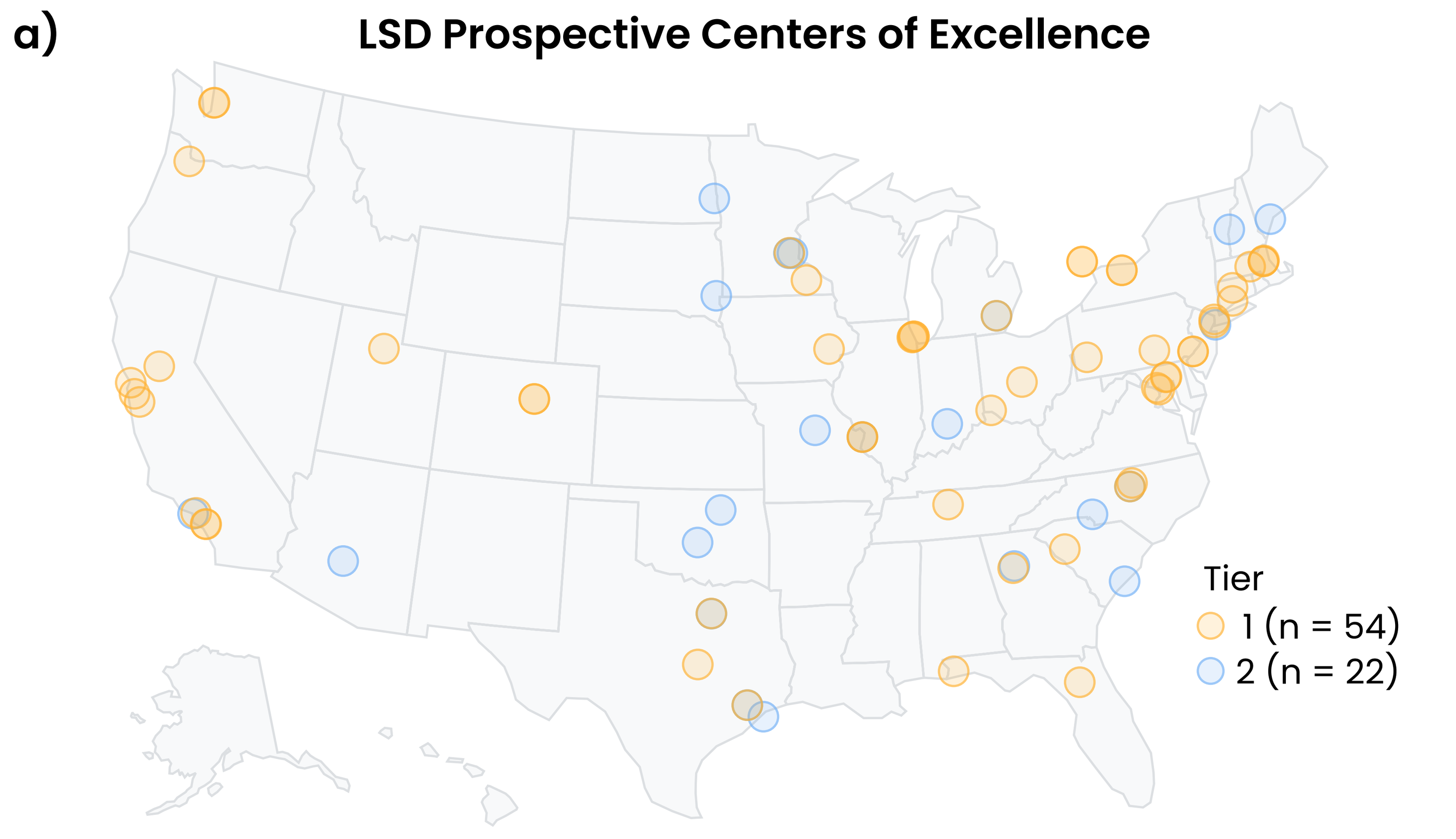


Figure 2. Patients visited care centers at locations across the US, with a high density in the Northeast. a) Patients visited 460 unique care centers across the US. Care centers with visits from more than three patients were plotted and colored according to the number of patients that attended the care center. The dotted circle around each point represents the median one-way drive time from the self-reported zip codes of patients who attended the care center. **b)** The ten care centers with the highest patient attendance across the cohort. **c)** Distribution of the number of states where individual patients received care. Participant records derived from a median (IQR) of 4 (4) care centers across 2 (2) states. **d–e)** Travel time and distance from each participant's self-reported zip code to each facility where they received care were calculated. Box plots show the median travel time **(d)** and travel distance **(e)** for each patient.

Prospective COEs have highest density in the Northeast & California



Tiering was determined by the number of criteria each center met, where meeting all four criteria designated Tier 1 (yellow) and meeting three criteria designated Tier 2 (blue):

1. Provides multidisciplinary care
2. Participated in >1 LSD clinical trial
3. Published >1 peer-reviewed article on an LSD
4. Presence of a metabolic genetics clinic

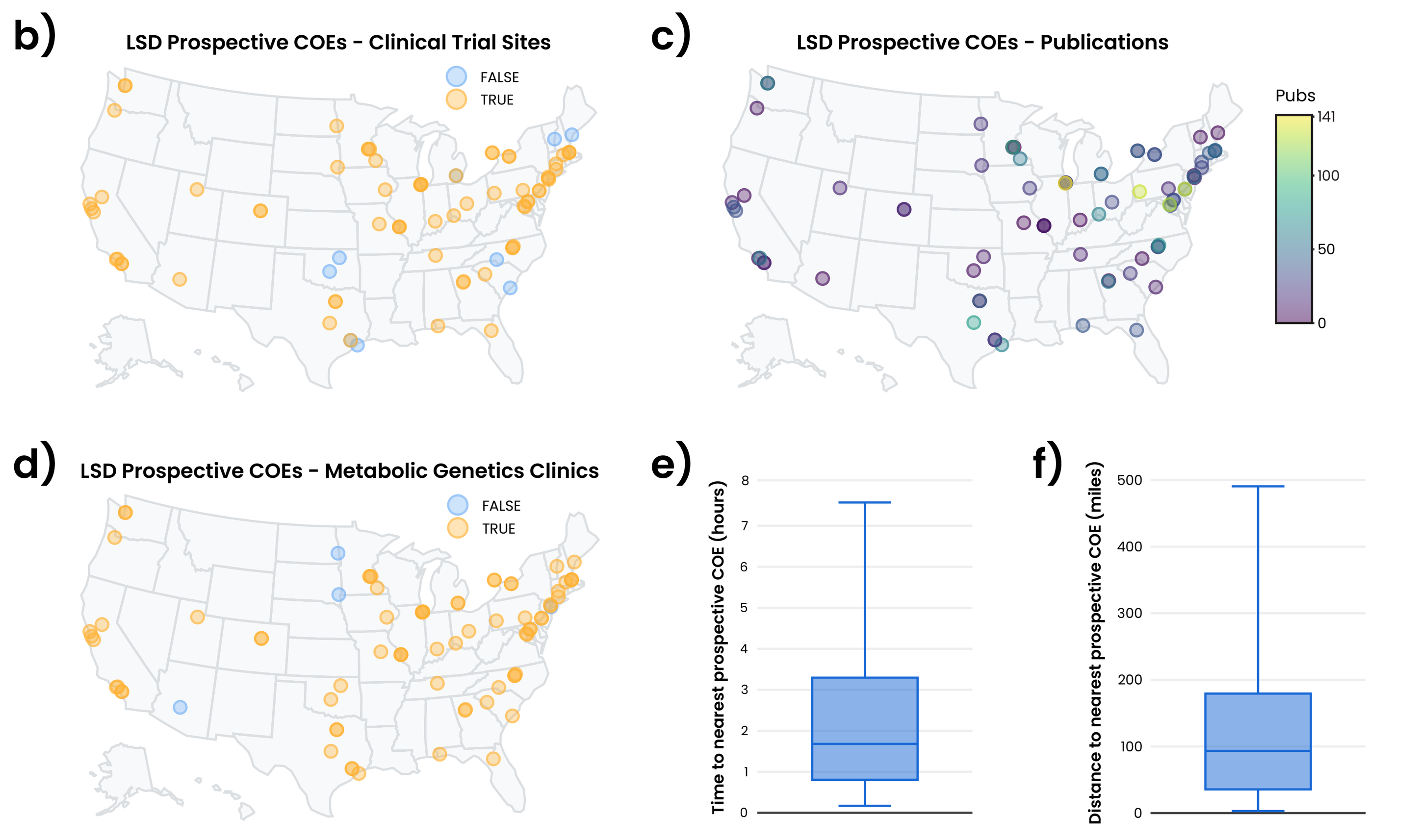

b)
LSD Prospective COEs - Clinical Trial Sites
FALSE
TRUE
c)
LSD Prospective COEs - Publications
Pubs
d)
LSD Prospective COEs - Metabolic Genetics Clinics
FALSE
TRUE
e)
Time to nearest prospective COE (hours)
f)
Distance to nearest prospective COE (miles)

Figure 3. Seventy-six prospective COEs are distributed throughout the US, with noticeable absence in the Rocky Mountain region. a) Care centers were tiered as prospective COEs based on the fulfillment of four criteria outlined below the map. Fifty-four centers met all four criteria (Tier 1; yellow circles), and 22 centers met three of the criteria (Tier 2; blue circles). All centers provided multidisciplinary care. All ten centers with the highest patient attendance across the cohort (Figure 2b) scored as prospective COEs. **b)** Map showing the distribution of prospective COEs that have participated in an LSD clinical trial as reported on ClinicalTrials.gov ("True", shown in yellow). All but nine ("False", blue) of the prospective COEs participated in one or more LSD-related clinical trial. **c)** Map showing the number of PubMed-indexed LSD publications per prospective COE. Mount Sinai Hospital was affiliated with the most LSD publications (141). **d)** Facilities that met criteria 1–3 were evaluated to determine the presence of a metabolic genetics clinic ("True", yellow), which should specialize in treating LSDs. All but four centers ("False", blue) provided a metabolic genetics clinic. **e–f)** One-way drive time **(e)** and distance **(f)** to the nearest prospective COE were measured using patient zip codes and center geographic coordinates. The nearest prospective COEs were a median of 1.68 hours and 93.4 miles from the patients in the cohort.

The LSD cohort represents 151 patients across nine LSDs; 67% of participants were younger than 18 years old (Figure 1b). The cohort is located across the US, with the highest density in metropolitan areas (83%, Figure 1f) and the South Atlantic and East North Central US census divisions, as indicated by the yellow color in Figure 1e. The median (IQR) length of follow-up provided by participant medical records was 6.5 years (8.3).

To estimate the travel burden experienced by patients in this cohort, we measured one-way drive time between patient-provided zip codes and the geographic coordinates of the facilities they attended. We found that patients attended a median of four care centers in a median of two states (Figure 2c), indicating many patients have received care in multiple states. One-way travel time per facility varied widely across the cohort, ranging from two minutes to 46 hours. Per patient, the projected median driving time was 1.66 hours, and the median distance was 94.5 miles (Figures 2d–e). These statistics represent travel 4.5 times as long and 9.2 times as far compared to the 2001 US-wide averages of 22.0 minutes and 10.2 miles for healthcare-related travel (Probst et al., 2007).

In order to identify centers most likely to provide expert care to patients with LSDs, we applied four criteria to US care centers. We identified 76 prospective COEs located across the US that met at least three of the criteria (Figure 3a). Most of the cohort (78%) received care at a prospective COE. To understand the potential burden of travel for patients to access expert care, we measured the one-way drive time and distance from patients to the nearest prospective COE. To reach these expert care centers, patients would need to travel a median of 1.68 hours and a median of 93.4 miles, which is comparable to the estimated median time and distance the cohort travelled to access care during the study period (Figures 3e and 3f).

Conclusions

As anticipated, projected travel time and distance necessary for patients with LSDs to reach their health care facilities dramatically exceeded the US average. This projected travel burden likely also extends specifically to patients seeking care at LSD COEs. Furthermore, we identified a non-uniform distribution of prospective LSD COEs in the US, underscoring the potential burden of accessing care for patients who live outside COE-dense areas, including the Rocky Mountain US census division.

A thorough understanding of patient and COE geography is essential in planning site-based clinical trials, as proper study site selection could increase the chances of successful recruitment and retention by decreasing travel burden. These findings can also help inform and target efforts to increase patient access to expert care, such as through provider education and telehealth resources. In future studies, we plan to assess travel burden, telehealth availability and telehealth value via patient- and caregiver-facing surveys.

Limitations: Calculations of time and distance from participants' home zip codes to their health care facilities were conducted using patient zip codes provided at study enrollment and do not take into account patients who may have resided at multiple addresses during the study period. Additionally, not all prospective COEs may have been identified based on the incomplete nature of the source databases referenced for this study. This study is also limited in its treatment of LSDs as one entity, whereas COEs may differ across conditions. In future studies, we plan to expand this study to identify individual LSD COEs to better serve these patient populations.

1. Wallace R, Hughes-Cromwick P, Mull H, Khasnabis S. Access to health care and nonemergency medical transportation: Two missing links. Transportation Research Record: Journal of the Transportation Research Board. 2005;1924:76–84.
2. Parenti, G., Medina, D. L., & Ballabio, A. (2021). The rapidly evolving view of lysosomal storage diseases. EMBO molecular medicine, 13(2), e12836.
3. Orphanet Inclusion/Exclusion Criteria for COEs: https://www.orpha.net/orphacom/cahiers/docs/GB/eproc_expert_centres_R2_PatCar_Cns_EP_02.pdf
4. Probst JC, Laditka SB, Wang JY, Johnson AO. Effects of residence and race on burden of travel for care: Cross sectional analysis of the 2001 US national household travel survey. BMC Health Services Research. 2007;7:40.

Acknowledgments: We would like to thank several patient advocacy organizations: International Society for Mannosidosis and Related Diseases (ISMRD), Cystinosis Research Network, Cure GM1 Foundation, National Tay-Sachs & Allied Diseases Association, Morquio Community, Priest Family Patient Advocates, Firefly Fund, National Niemann-Pick Disease Foundation, Ara Parseghian Medical Research Fund, and Cure Sanfilippo Foundation, for their partnership in growing these research communities. This study would not have been possible without the patients, families and caregivers who have generously contributed data.