How real is your real-world evidence? Demonstration of the need for comprehensive real-world data to examine patient burden and disease journey in patients with sickle cell disease in the US

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Background

- Randomized controlled trials (RCTs) have historically been prioritized as sources of evidence of efficacy and safety that inform regulatory decisions; however, generalizability of these data to clinical practice is limited because these trials are focused on highly selected populations and conduct their evaluations within highly controlled environments.
  - One evaluation determined that only 4% to 7% of individuals with a condition of interest met eligibility criteria as specified in 30 published RCTs.[1]
- Accordingly, the importance of real-world evidence (RWE) to inform answers to important questions posed by key stakeholders (e.g., payers, clinicians, regulatory agencies) has never been greater.
- RWE is generated from analyses of real-world data (RWD), which comprise a broad set of sources (e.g., healthcare claims, electronic medical records [EMRs], consumer buying habits, disease/vaccine/mortality registers, wearables).
- Many, if not all, RWD sources were not developed to inform RWE generation; moreover, these sources often provide incomplete information on important aspects of disease (e.g., reimbursement, treatment[s] received, social determinants of health [SDOH]) that can jeopardize the ability to generate rigorous, robust, and meaningful RWE.

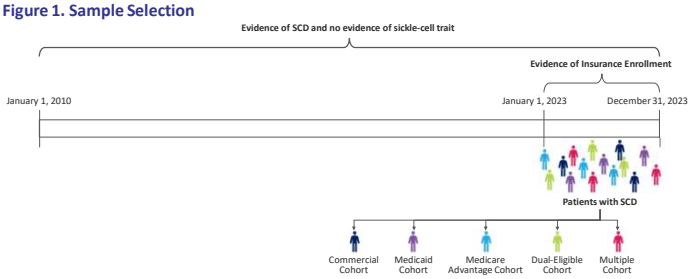
Objectives

- To examine the benefits of using a holistic RWD source in generating RWE on patients' "disease journey," using sickle cell disease (SCD) as an example.

Methods

- Retrospective, observational cohort study based on data from the TriNetX Linked network of de-identified, EMR-derived data linked to closed-claims data:
  - Information available from healthcare encounters include patient demographics, anthropomorphic data, diagnoses, laboratory test results, vital signs, procedures performed during encounters, and prescriptions written; information available from healthcare claims (>150 payers, including commercial, Medicaid, Medicare, and Medicare Advantage plans) include places and dates of service, diagnoses, procedures rendered, prescriptions dispensed by commercial (i.e., retail) and specialty pharmacies (including medications dispensed and accompanying therapy-days and amount dispensed), reimbursed amounts for all medical (inpatient and outpatient) care and prescription therapy dispenses, demographic data, and dates of eligibility.
  - The database is HIPAA-compliant and spanned the period January 1, 2010 to December 31, 2023 ("study period").
- All patients with evidence of SCD at any time during the study period (defined as any encounter resulting in a diagnosis code of sickle-cell disorders (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] code D57) during the study period were identified, with attention focused on those with insurance benefits at some point during calendar-year (CY) 2023 (**Figure 1**):
  - Selected patients were then stratified into payer-based cohorts: Commercial, Medicaid, Medicare Advantage, Dual-Eligible (eligible for Medicaid and Medicare coverage], and Multiple (multiple payers during CY2023).

Figure 1. Sample Selection



Abbreviation: SCD = sickle cell disease

- We assessed demographics, clinical characteristics, and use and cost of healthcare services and prescription pharmacotherapies during CY2023; all analyses were descriptive, as there were no prespecified hypotheses.

Results

- A total of 17,452 patients were identified with evidence of SCD during the study period, of whom 8484 had evidence of insurance coverage in CY2023; the most common insurance types were Medicaid (63.2%) and commercial (25.2%).
- Mean (SD) age was 33.6 (18.4) years; 55.8% were female; and 71.2% were Black:
  - Nominal differences were noted in these variables across cohorts (**Figure 2**).
- Fifty-two percent of patients had ≥1 vaso-occlusive crisis (VOC) during the year, ranging from 48.1% of the commercial cohort to 70.5% of the Medicare cohort (**Table 1**).

Figure 2. Demographic Characteristics

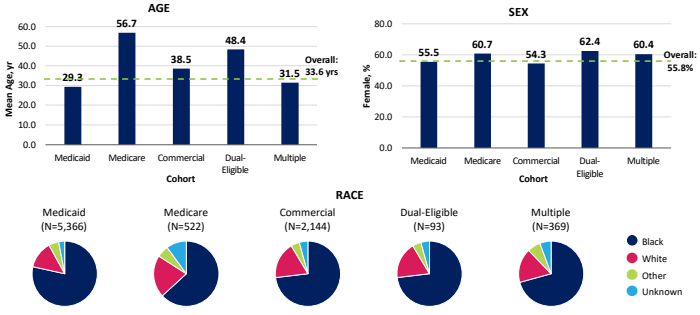


Table 1. Prevalence of VOC, by Cohort*

	Medicaid (N=5366)	Medicare (N=522)	Commercial (N=2144)	Dual-eligible (N=93)	Multiple (N=369)	Overall (N=8,494)
Acute chest syndrome	373 (7.0)	43 (8.2)	105 (4.9)	**14 (15.1)**	19 (5.1)	554 (6.5)
Pain	2,210 (41.2)	**350 (67.0)**	**872 (40.7)**	60 (64.5)	175 (47.4)	3,667 (43.2)
Splenic sequestration	**41 (0.8)**	2 (0.4)	**18 (0.8)**	0 (0.0)	**3 (0.8)**	64 (0.8)
Sickle-cell crisis	1,603 (29.9)	161 (30.8)	**490 (22.9)**	**37 (39.8)**	108 (29.3)	2,399 (28.2)
Priapism	68 (1.3)	6 (1.1)	25 (1.2)	**5 (5.4)**	8 (2.2)	112 (1.3)
Any of above	2,747 (51.2)	**368 (70.5)**	**1,032 (48.1)**	64 (64.8)	203 (55.0)	4,414 (52.0)
Number of VOC events						
Mean (SD)	7.3 (22.4)	13.4 (30.5)	4.2 (13.5)	**17.0 (33.0)**	7.0 (19.8)	7.0 (21.3)
Median (IQR)	1 (0, 4)	3 (0,11)	0 (0, 3)	**4 (0, 17)**	1 (0, 5)	1 (0.4)

*Unless otherwise specified, all values are number of patients (%); percentages estimated using the total number of patients in the relevant cohort as the denominator. Values presented in bold red font denote the minimum prevalence observed; those presented in bold black font, the maximum prevalence; Abbreviation: VOC = vaso-occlusive crisis

Results (cont.)

- Common comorbidities included anemia (25.9% of the study sample), overweight/obesity (25.5%), anxiety (18.4%), depression (16.4%), and asthma (16.0%) (**Table 2**)

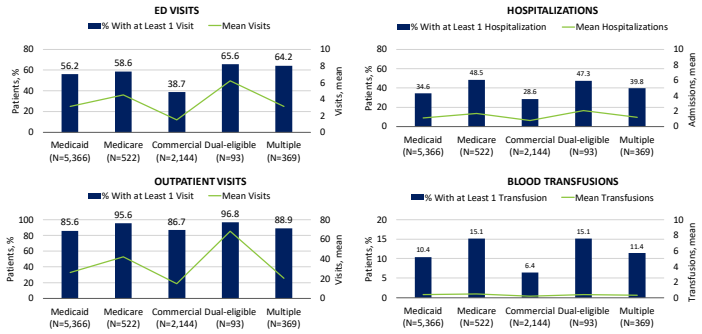
Table 2. Prevalence of Comorbidities of Interest, by Cohort*

	Medicaid (N=5366)	Medicare (N=522)	Commercial (N=2144)	Dual-eligible (N=93)	Multiple (N=369)	Overall (N=8,494)
Anemia	25.3	**44.8**	21.8	46.2	27.1	25.9
Overweight/ obesity	21.4	43.3	30.0	**45.2**	28.7	25.5
Anxiety	17.5	29.1	16.5	**34.4**	24.4	18.4
Depression	15.9	26.2	13.6	**35.5**	20.9	16.4
Asthma	17.3	21.3	10.7	**25.8**	17.6	16.0
Apnea and other sleep disorders	11.6	28.2	14.6	**31.2**	14.9	13.8
Headache/migraine	6.9	10.0	9.1	**15.1**	10.6	7.9
Seizure	5.9	**9.4**	3.7	3.2	5.7	5.5
Stroke	3.7	**11.5**	3.5	10.8	5.1	4.3

*Unless otherwise specified, all values are percentage of patients, and were estimated using the total number of patients in the relevant cohort as the denominator. Values presented in bold red font denote the minimum prevalence observed; those presented in bold black font, the maximum prevalence.

- Most (52.4%) patients had ≥1 emergency department visits during the year; 34.3% had ≥1 hospitalizations; and patients averaged 24.5 outpatient visits in the year (**Figure 3**).

Figure 3. Patterns of Use of Healthcare Services, by Cohort



Abbreviation: ED = emergency department

- Most commonly used prescription therapies included non-opioid analgesics (51.4%), opioids (39.2%), and systemic glucocorticosteroids (28.8%) (**Table 3**).

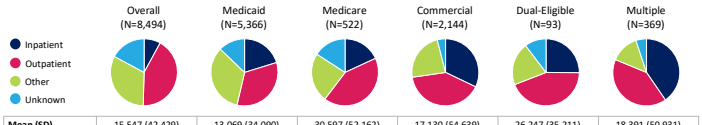
Table 3. Magnitude of Receipt of Selected Prescription Therapies, by Cohort*

	Medicaid (N=5366)	Medicare (N=522)	Commercial (N=2144)	Dual-eligible (N=93)	Multiple (N=369	Overall (N=8,494)
Non-opioid analgesics	52.8	66.9	42.0	**72.0**	59.1	51.4
Opioids	39.0	52.5	34.3	**54.8**	48.0	39.2
Systemic glucocorticoids	26.8	**40.4**	30.0	28.0	35.8	28.8
Antihypertensives	18.6	**60.5**	24.5	44.1	25.2	23.2
Anticoagulants/antithrombotics	16.7	34.7	17.2	**40.9**	19.8	18.3
Hydroxyurea	17.0	16.5	10.8	**17.2**	16.5	15.4

*Unless otherwise specified, all values are percentages of patients, and were estimated using the total number of patients in the relevant cohort as the denominator. Values presented in bold red font denote the minimum prevalence observed; those presented in bold black font, the maximum prevalence.

- Mean (SD) total healthcare costs during CY2023 were $15,547 ($42,429); inpatient, emergency/outpatient, and pharmacy dispenses comprised 19.8%, 36.9%, and 28.3% of total healthcare costs, respectively (**Figure 4**).

Figure 4. Distribution of Total Healthcare Costs, by Cohort



	Overall (N=8,494)	Medicaid (N=5,366)	Medicare (N=522)	Commercial (N=2,144)	Dual-Eligible (N=93)	Multiple (N=369)
Mean (SD)	15,547 (42,429)	13,069 (34,090)	30,597 (52,162)	17,130 (54,639)	26,247 (35,211)	18,391 (50,931)
Median (IQR)	2907 (596, 11,928)	2578 (525, 10137)	11,981 (3,614, 32,007)	2,339 (474, 10,327)	13,083 (3,136, 29,097)	4,064 (1,170, 16,382)

Limitations

- Patients not required to be continuously enrolled during CY2023; accordingly, findings may underestimate patients' journeys through the health system.
- As with all electronic data, there may be errors of omission and/or commission, with unknown impact(s) on findings.
- While our perspective and approach mirrored "typical" analyses conducted by payers, at least some data on those newly diagnosed during CY2023, likely reflect experience prior to clinical recognition of disease.
- Patients often change payers in the US—particularly those with commercial insurance. Accordingly, to the degree patients changed insurers, our analyses fail to capture their complete "journey."

Conclusions

- In the US, the experience of patients with SCD appears to be somewhat dependent on their insurance carrier, including demographics (age, gender, race), comorbidities profile, incidence of VOC and related sequelae, and patterns of use and cost of healthcare services and prescription pharmacotherapies.
  - Those with Medicare insurance and those who were dual-eligible for Medicare and Medicaid appeared in many instances to bear the highest burden of SCD with respect to VOC, levels of comorbidities, use of emergency department visits and hospitalizations, and use of analgesics
- Our findings highlight the need to leverage a data source that provides comprehensive capture on the heterogenous population that comprises SCD to fully understand the "disease journey" experienced by various subgroups.

References

1. Monti S, et al. *Rheumatology*. 2018;57(Suppl 7):vii54-vii58.

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