Mediators of Racial and Ethnic Inequities in Access to Front-Line Therapies for Chronic Lymphocytic Leukemia in the United States: A Real-World Evidence Study

Joanna M. Rhodes,[1] Adam S. Kittai,[2] Paul J. Hampel,[3] Xiaoliang Wang,[4] Qianhong Fu,[4] Danni Zhao,[5] Smriti Karwa,[5] Olive Mbah,[5] Ahmed Sawas,[5] Benji Wagner,[5] Rachel Myers,[5] Derrick van Beuge,[4] Gregory A. Maglinte,[4] Erlene K. Seymour,[4] Jacqueline C. Barrientos[6]

[1]Rutgers Cancer Institute, New Brunswick, NJ, USA; [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Department of Medicine, Mayo Clinic, Rochester, MN, USA; [4]BeOne Medicines Ltd, San Carlos, CA, USA; [5]Flatiron Health, New York, NY, USA; [6]Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, USA

CONCLUSIONS

- In this real-world study, Black and Hispanic patients with CLL were less likely than White patients to receive 1L NCCN guideline-preferred novel therapies
- A significant proportion of these disparities was explained by area-level SDOH, particularly residential segregation
- These findings underscore the need to address structural barriers to ensure equitable access to emerging, guideline-recommended treatments

INTRODUCTION

- The treatment landscape for chronic lymphocytic leukemia (CLL) has evolved over the past decade, shifting from chemoimmunotherapy (CIT) and first-generation Bruton tyrosine kinase (BTK) inhibitors (eg, ibrutinib) to novel therapies, including next-generation BTK inhibitors (eg, acalabrutinib and zanubrutinib) and B-cell lymphoma 2 (BCL2) inhibitors[1-3]
- While these novel therapies are now National Comprehensive Cancer Network® (NCCN) guideline–preferred,[2,3] we previously showed that patients from different racial/ethnic groups may not have equitable access to novel therapies[4,5]
- Social determinants of health (SDOH) factors have also been associated with differences in CLL prescribing patterns and treatment outcomes.[6] However, few real-world studies have examined whether SDOH factors explained the association between race/ethnicity and treatment choices in CLL

Aim

- This study examined racial/ethnic inequities in front-line (1L) novel therapy utilization among US patients with CLL and potential SDOH drivers of these inequities

METHODS

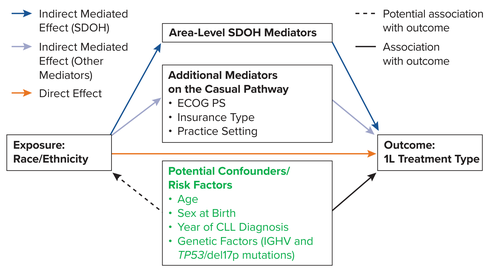
Data Source and Study Population

- This retrospective cohort study utilized the US-based, electronic health record–derived deidentified Flatiron Health Research Database,[7] linked to neighborhood (US Census track or block group) data from the American Community Survey and the Agency for Healthcare Research and Quality
- Eligible patients included adults with CLL who started 1L treatment between January 1, 2019 and July 31, 2024

Study Design and Statistical Analysis

- Receipt of 1L therapy was the primary outcome, and included: CIT, ibrutinib, and NCCN guideline–preferred novel therapies (acalabrutinib, zanubrutinib, and BCL2-based regimens),[2,3] with novel therapies as a reference
- Associations between race/ethnicity (White, Black, Hispanic) and 1L treatment types were assessed using logistic regressions, adjusting for age, sex, year of 1L start, immunoglobulin heavy chain variable region (IGHV) status, and del17p/*TP53* status
- Mediation analysis was performed using Multiple Mediation Analysis implemented through nonlinear multiple additive regression tree models[8]
  - Under the proposed conceptual framework (**Figure 1**), individual-level (Eastern Cooperative Oncology Group performance status [ECOG PS], practice type, insurance) and 20 area-level SDOH factors measuring social deprivation (defined as limited access to economic, social, neighborhood, physical, or healthcare resources) were assessed as potential mediators
  - Only factors that met the conditions for mediators were included in the final model
  - Based on the National Academy of Medicine healthcare disparities definition, most clinical factors were considered confounders a priori

Figure 1. Framework for Mediation Analysis



RESULTS

Patient Characteristics

- A total of 4452 patients were included in the study (**Table 1**)

Table 1. Patient Demographic and Clinical Characteristics Overall and By Race/Ethnicity

	Overall N=4452	White n=3717	Black n=371	Hispanic n=209	Other[a] n=155
Age[b], years, n (%)					
18-49	271 (6.1)	211 (5.7)	29 (7.8)	24 (11.5)	<10
50-64	1552 (34.9)	1291 (34.7)	139 (37.5)	72 (34.4)	50 (32.3)
65-74	1572 (35.3)	1309 (35.2)	133 (35.8)	69 (33.0)	61 (39.4)
≥75	1057 (23.7)	906 (24.4)	70 (18.9)	44 (21.1)	37 (23.9)
Gender, n (%)					
Female	1731 (38.9)	1429 (38.4)	160 (43.1)	79 (37.8)	63 (40.6)
Male	2721 (61.1)	2288 (61.6)	211 (56.9)	130 (62.2)	92 (59.4)
ECOG PS at 1L, n (%)					
0-1	3110 (69.9)	2618 (70.4)	244 (65.8)	143 (68.4)	105 (67.7)
2-4	354 (8.0)	298 (8.0)	32 (8.6)	14 (6.7)	10 (6.5)
Unknown	988 (22.2)	801 (21.5)	95 (25.6)	52 (24.9)	40 (25.8)
***TP53* status, n (%)**					
Not tested/Unknown or not documented	3279 (73.7)	2725 (73.3)	268 (72.2)	160 (76.6)	126 (81.3)
Tested	1173 (26.3)	992 (26.7)	103 (27.8)	49 (23.4)	29 (18.7)
Ever *TP53*-positive at 1L	167 (14.2)	142 (14.3)	14 (13.6)	<10	<10
TP53-negative/Unknown or not documented[c]	1006 (85.8)	850 (85.7)	89 (86.4)	44 (89.8)	23 (79.3)
FISH testing status, n (%)					
Not tested/Unknown or not documented	775 (17.4)	645 (17.4)	72 (19.4)	39 (18.7)	19 (12.3)
Tested	3677 (82.6)	3072 (82.6)	299 (80.6)	170 (81.3)	136 (87.7)
Del17p-positive[d]	379 (10.3)	317 (10.3)	26 (8.7)	20 (11.8)	16 (11.8)
Del17p-negative[d]	3008 (81.8)	2505 (81.5)	259 (86.6)	137 (80.6)	107 (78.7)
IGHV status, n (%)					
Not tested/Not documented	1916 (43.0)	1587 (42.7)	160 (43.1)	97 (46.4)	72 (46.5)
Tested	2536 (57.0)	2130 (57.3)	211 (56.9)	112 (53.6)	83 (53.5)
Mutated	977 (38.5)	854 (40.1)	35 (16.6)	46 (41.1)	42 (50.6)
Unmutated	1328 (52.4)	1091 (51.2)	149 (70.6)	55 (49.1)	33 (39.8)
Unsuccessful/Indeterminate	231 (9.1)	185 (8.7)	27 (12.8)	11 (9.8)	<10
Insurance type, n (%)					
Commercial	1856 (41.7)	1575 (42.4)	150 (40.4)	64 (30.6)	67 (43.2)
Medicare	1764 (39.6)	1517 (40.8)	117 (31.5)	66 (31.6)	64 (41.3)
Medicaid	68 (1.5)	42 (1.1)	10 (2.7)	16 (7.7)	<10
Other	224 (5.0)	173 (4.7)	29 (7.8)	16 (7.7)	<10
Unknown/Not documented	540 (12.1)	410 (11.0)	65 (17.5)	47 (22.5)	18 (11.6)
Practice type, n (%)					
Academic	942 (21.2)	829 (22.3)	65 (17.5)	27 (12.9)	21 (13.5)
Community	3331 (74.8)	2738 (73.7)	293 (79.0)	178 (85.2)	122 (78.7)
Both	179 (4.0)	150 (4.0)	13 (3.5)	<10	12 (7.7)
Year of index (1L start), n (%)					
2019	895 (20.1)	736 (19.8)	83 (22.4)	39 (18.7)	37 (23.9)
2020	916 (20.6)	759 (20.4)	83 (22.4)	40 (19.1)	34 (21.9)
2021	885 (19.9)	727 (19.6)	76 (20.5)	48 (23.0)	34 (21.9)
2022	773 (17.4)	651 (17.5)	53 (14.3)	41 (19.6)	28 (18.1)
2023	690 (15.5)	605 (16.3)	44 (11.9)	26 (12.4)	15 (9.7)
2024	293 (6.6)	239 (6.4)	32 (8.6)	15 (7.2)	<10

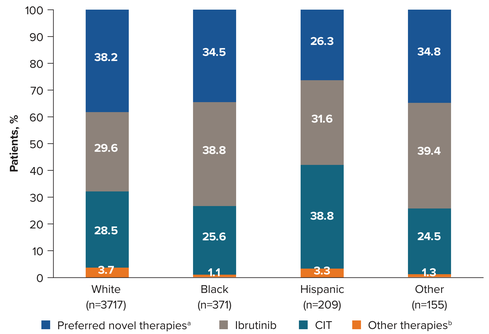
Due to decimal rounding, percentages may not add up to 100. [a]Includes Asian, American Indian/Alaskan Native, Native Hawaiian/Other Pacific Islander, and people reporting multiple races. [b]Age categories are inclusive of the upper bound. [c]Negative/Unknown results for *TP53* test results are inclusive of results that are negative, equivocal, results pending, Unsuccessful/indeterminate test, or Unknown. [d]Percentages calculated among patients with FISH testing for del17p.
FISH, fluorescence in situ hybridization.

- Black and Hispanic patients were more likely to live in neighborhoods with higher social deprivation, such as residential segregation (predominant race/ethnicity in the area: White, Black, Hispanic, Diverse), with no internet access, no vehicle ownership, and no health insurance coverage

Treatment Access by Race/Ethnicity

- Rates of the receipt of preferred novel therapies differed by race/ethnicity (**Figure 2**)
- Overall, 37% of patients received a preferred novel therapy, which was highest among White (38.2%) patients, followed by Black (34.5%) and Hispanic (26.3%) patients

Figure 2. Treatment Patterns by Race/Ethnicity



[a]Preferred novel therapies included acalabrutinib, zanubrutinib, BCL2-based regimens. [b]Other therapies included ibrutinib + venetoclax, lenalidomide-based therapies, CAR-T, bortezomib-based therapies, clinical trial drugs, stem cell transplant (autologous, allogenic). CAR-T, chimeric antigen receptor T cell.

- Compared with White patients, Hispanic patients were more likely to receive CIT than preferred novel therapies (adjusted odds ratio [aOR]: 2.12; 95% confidence interval [CI]: 1.46-3.09) (**Table 2**)
- Black patients (aOR: 1.44; 95% CI: 1.05-1.97) and Hispanic patients (aOR: 1.83; 95% CI: 1.17-2.85) were more likely to receive ibrutinib than preferred novel therapies

Table 2. Unadjusted and Adjusted ORs of 1L Treatment Type by Race/Ethnicity

	Ibrutinib versus Preferred Novel Therapies		CIT versus Preferred Novel Therapies	
Race/Ethnicity	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
White (referent)	-	-	-	-
Black	1.45 (1.13-1.87)	1.44 (1.05-1.97)	1.00 (0.75-1.31)	1.00 (0.74-1.35)
Hispanic	1.55 (1.07-2.24)	1.83 (1.17-2.85)	1.98 (1.39-2.82)	2.12 (1.46-3.09)
Other	1.46 (1.00-2.12)	1.27 (0.81-2.00)	0.94 (0.62-1.44)	0.81 (0.51-1.27)

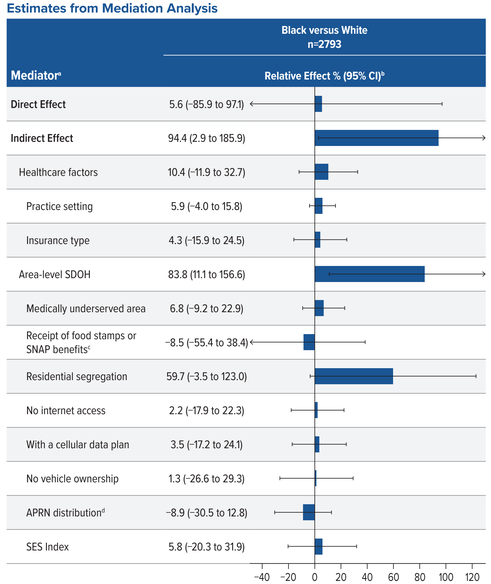
Treatment Access by Area-Level SDOH Factors

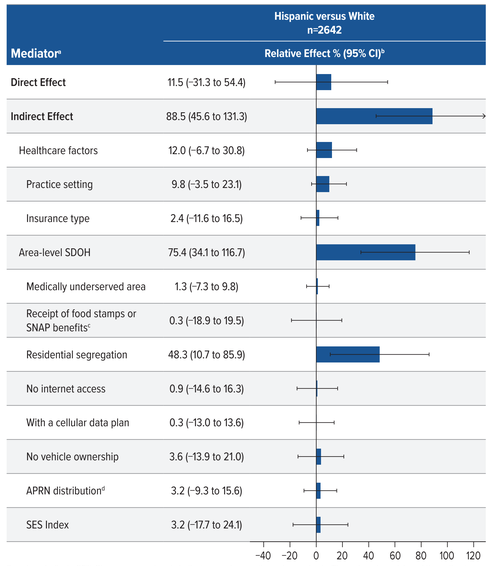
- In general, compared with patients living in areas with the lowest social deprivation, those residing in areas with the highest social deprivation appeared less likely to receive preferred novel therapies
  - In total, 25.8% and 26.7% of any patients residing in predominantly Black or Hispanic neighborhoods, respectively, received a preferred novel therapy versus 38.6% of patients residing in predominantly White neighborhoods
- Lower preferred novel therapy use was associated with residence in areas with the lowest levels of internet access (31.9% vs 39.3% in areas with highest levels of internet access), vehicle ownership (32.5% vs 39.25% in areas with highest vehicle ownership), and health insurance coverage (34.1% vs 40.7% in areas with the most health insurance coverage)
- This trend was consistently observed across nearly all SDOH factors (**Supplemental Table 1. Treatment Access by SDOH**; scan QR code to the right to access)

Mediation Analysis of Racial and Ethnic Inequities in Treatment Access

- In the mediation analysis, individual- and area-level SDOH factors explained 94.4% (95% CI: 2.9-185.9) of the observed Black–White inequity in receipt of ibrutinib versus preferred novel therapies; residential segregation appeared to be the most important mediator (59.7%; 95% CI: −3.5 to 123.0) (**Table 3**)
- Similarly, the Hispanic–White inequity in receipt of preferred novel therapies was driven by the combined effect of area-level SDOH and individual-level variables (88.5%; 95% CI: 45.6-131.3), with residential segregation as the main driver (48.3%; 95% CI: 10.7-85.9), followed by practice setting (9.8%; 95% CI: −3.5 to 23.1)

Table 3. Association Between Race/Ethnicity and 1L Treatment Category Among Patients Receiving Ibrutinib versus Preferred Novel Therapies: Estimates from Mediation Analysis

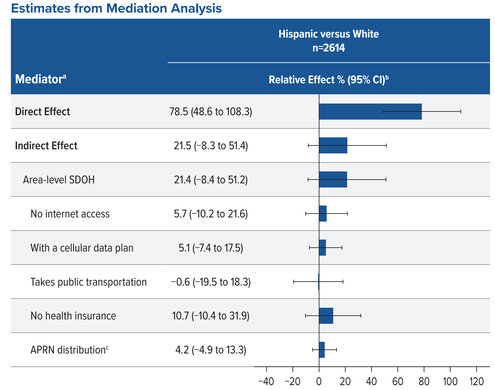




Error bars indicate 95% CIs; < or > arrowheads indicate error bar continues beyond axis. The reduced precision of the estimates for certain relative effects (95% CIs) likely reflects the limited study sample size and the resulting possible instability in the mediation estimates from the Multiple Mediation Analysis. [a]Three variables were excluded from the analysis: households with no computing device, area-level private health insurance, and area-level Medicaid coverage. [b]Represents the proportion of overall effect of race and ethnicity on 1L treatment type attributed to both direct and indirect pathways (ie, effects through mediators). The correlations and overlapping influences among mediators are captured in the total indirect effect, and the sum of the relative effects from each mediator might not match the total indirect effects. [c]Households that received food stamps or SNAP benefits in the past 12 months. [d]Total number of advanced practice registered nurses with NPI per 1000 population.
APRN, advanced practice registered nurses; NPI, National Provider Identifier; SNAP, Supplemental Nutrition Assistance Program; SES, socioeconomic status.

- In contrast, measured SDOH factors did not explain the inequity in receipt of CIT versus preferred novel therapies between Hispanic and White patients (21.5%; 95% CI: −8.3 to 51.4), suggesting that other factors may contribute to the observed inequities (**Table 4**)

Table 4. Association Between Race/Ethnicity and 1L Treatment Category Among Patients Receiving CIT versus Preferred Novel Therapies: Estimates from Mediation Analysis



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DISCUSSION

- The results of this study revealed differences in receipt of treatment for patients with CLL based on race/ethnicity and SES
- These patterns highlight potential inequities in the adoption of guideline-recommended treatments, underscoring the need for research to better understand barriers leading to these inequities and tailored interventions to promote equitable treatment access

Limitations

- Generalizability of the results to patients outside of the Flatiron Health database and outside of the US may be limited
- Because the Flatiron Health database is derived from electronic health records, patient data may be incomplete or missing

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ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines Ltd. Medical writing and editorial support was provided by Emily Mercadante, PhD, of Amiculum, and supported by BeOne Medicines Ltd.

CORRESPONDENCE: Jacqueline C. Barrientos, jacqueline.barrientos@msmc.com

Presented at the 67th Annual Meeting and Exposition of the American Society of Hematology; December 6-9, 2025; Orlando, FL, USA