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Diagnostic delay in histiocytic neoplasms and its association with local resource deprivation

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Histiocytic neoplasms (HN) are rare hematologic malignancies that are frequently multisystemic at presentation and include Erdheim-Chester Disease (ECD), Langerhans Cell Histiocytosis (LCH), and Rosai-Dorfman Disease (RDD).[1] The discovery of *BRAF* and other mitogen-activated protein kinase pathway mutations in HN led to the use of targeted inhibitor therapies with a dramatic decline in mortality.[1] However, because of the heterogeneity of HN, diagnostic delay remains frustratingly common and is associated with increased depression,[2] caregiver anxiety,[3] symptom burden, and organ dysfunction.[4] Limited data exist on how race, age, and local resource availability affect time to diagnosis and other outcomes in HN. We aimed to characterize differences in the diagnosis and treatment of patients with HN with respect to neighborhood resource variation using a national, multi-institutional registry.

This IRB-approved registry-based cohort study (NCT03329274) was led by Memorial Sloan Kettering Cancer Center in conjunction with the University of Michigan and the University of Alabama at Birmingham. Adult and pediatric patients with HN (ECD, LCH, RDD, histiocytic sarcoma, juvenile/adult xanthogranuloma (JXG/AXG), or mixed diagnoses) seen at participating institutions from January 2020-December 2023 were included. Demographic (race, sex, zip code, and age at HN diagnosis), clinical (diagnosis subtype, date of self-reported symptom onset, date of histologic diagnosis, date of first treatment, and *BRAF*V600 mutational status), and treatment information was collected.

The national Area Deprivation Index (ADI) is a validated measure of neighborhood-level resources using income, education, employment, and housing quality and is mapped to 9-digit ZIP code.[5, 6] Higher ADI values indicate fewer neighborhood resources and have been associated with health disparities.[7, 8] The Human Development Index (HDI), a measure of a country's development using life expectancy, education, and standard of living, was also included given a previously reported inverse association between ECD prevalence and HDI.[9]

Descriptive statistics including proportions, medians, and interquartile ranges (IQR) were used to characterize the cohort. Associations for categorical variables were assessed using chi-squared or Fisher's Exact test and for continuous variables using the Kruskal-Wallis test. The primary outcome was time to diagnosis, calculated as the

interval between date of self-reported symptom onset and date of histologic diagnosis, and analyzed as a continuous and binary outcome where delayed diagnosis was ≥1 year from symptom onset to diagnosis. Multivariable linear and logistic regression models were performed to analyze the association of ADI, race, age at diagnosis, and HN diagnosis subtype with time to diagnosis. All statistical tests were two-sided ($\alpha<0.05$) and performed in SAS v9.4[10] and R v4.4.[11]

545 patients with HN from 45 states in the US were included (**Table 1**). Of these, 381 patients (70%) were White. 135 patients (25%) had ECD, 254 (47%) had LCH, and 126 (23%) had RDD. Median age at diagnosis was 41 years (IQR 18-55). Median time from presentation to diagnosis was 0.41 years (IQR 0.14-1.13). Of 486 patients (89%) with available ADI data, 158 (33%) were from ADI tertile 1, 163 (34%) from ADI tertile 2, and 165 (34%) from ADI tertile 3. 129 patients (24%) were pediatric with mostly LCH (**Supplementary Table 1**).

Patients from resource-poor areas were older at diagnosis (median 45 years for ADI tertile 3, 30 years for tertile 1, $p<0.001$). White patients were more likely to reside in resource-rich areas (35% in ADI tertile 1, 30% in tertile 3, $p=0.004$) while non-White patients were more likely to live in resource-poor areas (28% in ADI tertile 1, 48% in tertile 3, $p=0.004$).

HN diagnosis subtype varied significantly with respect to ADI. Patients with RDD largely lived in resource-poor areas (66% in ADI tertile 3, 24% in tertile 2, 10% in tertile 1, $p<0.001$). Patients with LCH more often lived in resource-rich areas (46% in ADI tertile 1, 19% in tertile 3, $p<0.001$).

Patients from resource-poor areas had a significantly longer time from symptom onset to diagnosis than those from resource-rich areas (median 0.63 years for ADI tertile 3 versus 0.22 years for tertile 1, $p<0.001$) (**Table 1**). Patients diagnosed early were more often from resource-rich areas (36% from tertile 1, 29% from tertile 3, $p=0.009$), while those with delayed diagnosis were more often from resource-poor areas (26% from tertile 1, 44% from tertile 3, $p=0.009$).

Time to treatment also varied with patients from resource-poor areas having a shorter interval from symptom onset to first treatment than those from resource-rich areas (median 1.4 years for ADI tertile 3, 3.0 years for tertile 1, $p=0.03$) and a shorter

interval from diagnosis to first treatment (median 0.25 years for ADI tertile 3, 0.45 years for tertile 1, p=0.002) (**Table 1**). Patients from resource-poor areas were more likely to receive all treatment modalities including immunomodulatory therapy, chemotherapy, and targeted therapy.

Table 2 depicts time from symptom onset to diagnosis as continuous and binary outcomes. After multivariable adjustment, patients older at diagnosis were more likely to experience delayed diagnosis [odds ratio (OR) 1.02; 95% confidence interval (CI) 1.01-1.03, p<0.001]. Patients with ECD had a longer time from symptom onset to diagnosis than patients with RDD (mean 1.53 years longer; 95%CI 0.27-2.79, p=0.02) or other HN subtypes (mean 1.36 years longer; 95%CI 0.34-2.39, p=0.009) and experienced more delayed diagnosis (OR_{RDD} 0.50; 95%CI 0.25-0.98, p=0.04). Those from resource-poor areas also had higher odds of delayed diagnosis (OR 1.80; 95%CI 0.99-3.30, p=0.05).

Variations in time from symptom onset to diagnosis (**Supplementary Table 2**) and from diagnosis to treatment (**Supplementary Table 3**) were also observed within each HN subtype after multivariable analysis. Non-White patients with ECD and LCH, patients with LCH from resource-poor areas, and older patients with RDD were all more likely to experience delayed diagnosis. All patients from resource-poor areas received treatment sooner after diagnosis. Delayed diagnosis did not differ among treating centers (**Supplementary Table 1**).

Our findings demonstrate that neighborhood resource level is significantly associated with the clinical trajectory of patients with HN. Patients from resource-poor areas are more likely to experience delayed diagnosis, receive treatment sooner after diagnosis, and receive treatment across all modalities. Additionally, patients with ECD are more likely to experience delayed diagnosis compared to patients with other HN subtypes.

Race and age at diagnosis were also associated with delayed diagnosis within HN subtypes. For patients with ECD and LCH, non-White patients were more likely to experience delayed diagnosis than White patients. Among patients with LCH and RDD, older age at diagnosis was associated with delayed diagnosis.

While the association between resource deprivation and diagnostic delay has been reported in other cancers, our findings are the first in kind across all HN.[12] This

may be compounded by the rarity and heterogeneity of HN, where timely diagnosis requires expert care that may be more accessible for patients from resource-rich areas. Patients diagnosed after longer delays might also have more severe disease at diagnosis, necessitating earlier and/or more intensive treatment. Though data to support this hypothesis is lacking from our cohort, it has been reported for other hematologic malignancies, including lymphoma and multiple myeloma.[13, 14]

Time from symptom onset to diagnosis also differed among HN disease subtypes. Patients with ECD experienced more diagnostic delay than those with RDD or other HN diagnoses after adjusting for race, ADI, and age at diagnosis, with non-White patients with ECD experiencing the largest diagnostic delays. This suggests that patients with ECD, particularly non-White patients, remain most vulnerable to delayed diagnosis and its downstream effects, possibly because of its especially heterogenous and elusive pathology.[15]

Limitations of this study include the lack of granular clinical data, including disease severity at diagnosis and specific disease sites, which may be associated with both HN subtype and diagnostic delay. In addition, the substantial heterogeneity in presentation and clinical course across HN subtypes is not fully captured in the current analysis and warrants further investigation in future work. Although we assembled a large and geographically diverse cohort representing patients from 45 states, individuals living outside the collaborative institutions' catchment areas may be underrepresented. The relatively small number of non-White individuals in the cohort also precluded subgroup analyses and necessitated dichotomization of race. Data from countries outside the US may help to distinguish disease-specific disparities from those compounded by the US healthcare system. Finally, while the ADI is a neighborhood-level measure of resource disadvantage, it does not capture individual-level resource limitations, and demographic differences across ADI strata may reflect factors beyond resource availability alone.

This study provides the first comprehensive examination of associations between ADI, diagnostic delay, and treatment patterns among patients with HN. Our findings suggest that individuals living in resource-poor areas are more likely to experience diagnostic delay and to receive more treatment. We also observed that patients with

ECD are more likely to experience diagnostic delay compared with patients with other HN subtypes. These results provide a strong rationale for initiatives to improve timely diagnosis and access to specialized care for patients with HN. Educational efforts among clinicians and patients through patient advocacy groups may help reduce diagnostic delays and promote more equitable care delivery for patients with HN.

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Table 1. Cohort Characteristics Overall and by ADI National Tertile.

Characteristic	Overall N=545[a]	ADI National Tertile 1 (N=158)[a]	ADI National Tertile 2 (N=163)[a]	ADI National Tertile 3 (N=165)[a]	p-value[b]
Symptom onset to diagnosis (years)	0.41 (0.14, 1.13)	0.22 (0.10, 0.88)	0.41 (0.13, 0.98)	0.63 (0.23, 1.84)	<0.001
Symptom onset to diagnosis (no.)					0.009
<1 year	362 (100)	116 (36)	115 (35)	93 (29)	
≥1 year	134 (100)	33 (26)	38 (30)	55 (44)	
Symptom onset to first treatment (years)	1.6 (0.7, 4.1)	3.0 (0.8, 6.3)	1.8 (0.8, 3.6)	1.4 (0.5, 3.8)	0.03
Diagnosis to first treatment (years)	0.35 (0.11, 1.24)	0.45 (0.14, 2.61)	0.45 (0.15, 1.52)	0.25 (0.04, 0.87)	0.002
Age at diagnosis (years)	41 (18, 55)	30 (7, 52)	43 (20, 55)	45 (29, 58)	<0.001
Race (no.)					0.004
White	381 (100)	122 (35)	122 (35)	107 (30)	
Non-White	112 (100)	30 (28)	26 (24)	51 (48)	
Black	76 (100)	15 (20)	11 (15)	49 (65)	
Asian	25 (100)	11 (46)	11 (46)	2 (8.3)	
Other	11 (100)	4 (50)	4 (50)	0 (0)	
Sex (no.)					0.04
Female	290 (100)	84 (32)	77 (29)	101 (39)	
Male	255 (100)	74 (33)	86 (38)	64 (29)	
Insurance (no.)					<0.001
Commercial	313 (57)	107 (36)	104 (35)	84 (28)	
Medicaid	74 (14)	24 (35)	22 (32)	23 (33)	
Medicare	83 (15)	14 (18)	20 (26)	44 (56)	
Other, self-pay, union	21 (4)	2 (13)	5 (33)	8 (53)	
Diagnosis (no.)					<0.001
ECD	110 (100)	20 (22)	41 (45)	30 (33)	
HS	9 (100)	1 (13)	4 (50)	3 (38)	
JXG	21 (100)	8 (42)	5 (26)	6 (32)	
LCH	254 (100)	106 (46)	80 (35)	45 (19)	
RDD	117 (100)	10 (10)	25 (24)	69 (66)	
Mixed ECD/LCH	17 (100)	9 (53)	5 (29)	3 (18)	
Mixed ECD/RDD	8 (100)	3 (38)	3 (38)	2 (35)	
Mixed RDD/LCH	1 (100)	0 (0)	0 (0)	1 (100)	
Other	7 (100)	1 (17)	0 (0)	5 (83)	
Driver Mutations (no.)					0.50
No driver mutation	149 (100)	37 (28)	46 (35)	48 (37)	
BRAFV600E only	121 (100)	38 (36)	35 (33)	32 (30)	
Driver other than BRAF	119 (100)	28 (26)	39 (36)	42 (39)	
Immunotherapy (no.)					<0.001
No immunotherapy	456 (100)	151 (37)	134 (33)	120 (30)	
Immunotherapy	88 (100)	7 (9)	29 (36)	44 (55)	
Chemotherapy (no.)					<0.001
No chemotherapy	417 (100)	133 (36)	129 (35)	110 (30)	
Chemotherapy	127 (100)	25 (22)	34 (30)	54 (48)	
Targeted Therapy (no.)					0.01
No targeted therapy	325 (100)	108 (37)	96 (33)	86 (30)	
Targeted therapy	219 (100)	50 (26)	67 (34)	78 (40)	

Abbreviations: N: Number; ADI: Area Deprivation Index; ECD: Erdheim-Chester Disease, HS: Histiocytic Sarcoma, JXG: Juvenile Xanthogranuloma; LCH: Langerhans Cell Histiocytosis; RDD: Rosai-Dorfman Disease.

[a] n (row %); median (Q1, Q3)

[b] For comparisons with categorical variables: Chi-squared test or Fisher's Exact test with simulated p-value. For comparisons with continuous variables: Kruskal-Wallis Rank Sum test.

Table 2. Multivariable Associations with Time from Symptom Onset to Diagnosis.

Characteristic	Outcome: Continuous Time to Diagnosis (years)			Outcome: Binary Time to Diagnosis (≥1/<1 year)		
	Beta[a]	95% CI[a]	p-value[a]	OR[a]	95% CI[a]	p-value[a]
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Non-White	1.01	-0.01, 2.03	0.05	1.53	0.87, 2.68	0.14
ADI National Tertiles						
Tertile 1	Ref	Ref	Ref	Ref	Ref	Ref
Tertile 2	0.29	-0.67, 1.24	0.56	0.97	0.55, 1.70	0.90
Tertile 3	0.90	-0.19, 2.00	0.11	1.80	0.99, 3.30	0.05
HDI (scaled 0-100)	0.24	-0.06, 0.55	0.11	1.02	0.87, 1.20	0.80
Age at Diagnosis (years)	0.02	0.00, 0.04	0.11	1.02	1.01, 1.03	<0.001
Diagnosis						
ECD or ECD mixed	Ref	Ref	Ref	Ref	Ref	Ref
RDD or RDD mixed	-1.53	-2.79, -0.27	0.02	0.50	0.25, 0.98	0.04
Other or Unknown	-1.36	-2.39, -0.34	0.009	0.66	0.39, 1.14	0.13

Abbreviations: CI: Confidence interval; OR: Odds Ratio; Ref: Reference; ADI: Area Deprivation Index; HDI: Human Development Index; ECD: Erdheim-Chester Disease; RDD: Rosai-Dorfman Disease.

[a] All estimates mutually adjusted for all other variables in the table.

Supplementary Table 1: Cohort Characteristics by Adult/Pediatric Cohorts and by Treating Institution

Characteristic	Adult (N=416)[1]	Pediatric (N=129) [1]	p-value[2]		MSK (N=446) [1]	UAB (N=44) [1]	UMich (N=55) [1]	p-value[2]
Race			0.03					<0.001
White	279 (73%)	102 (27%)			328 (86%)	21 (5.5%)	32 (8.4%)	
Non-White	93 (83%)	19 (17%)			74 (62%)	23 (19%)	15 (19%)	
Sex			0.03					0.07
Female	232 (80%)	58 (20%)			227 (78%)	29 (10%)	34 (12%)	
Male	184 (72%)	71 (28%)			219 (86%)	15 (5.9%)	21 (8.2%)	
Institution			<0.001					
MSK	324 (73%)	122 (27%)						
UAB	41 (93%)	3 (6.8%)						
UMich	51 (93%)	4 (7.3%)						
Age								<0.001
Adult					324 (78%)	41 (9.9%)	51 (12%)	
Pediatric					122 (95%)	3 (2.3%)	4 (3.1%)	
Time from symptom onset to diagnosis, con't. (years)	0.58 (0.19, 1.68)	0.15 (0.08, 0.27)	<0.001		0.41 (0.13, 1.06)	0.34 (0.13, 1.80)	0.52 (0.28, 1.08)	0.31
Time from symptom onset to diagnosis, binary			<0.001					0.43
<1 year	263 (73%)	99 (27%)			308 (85%)	23 (6.4%)	31 (8.6%)	
1+ year	128 (96%)	6 (4.5%)			109 (81%)	13 (9.7%)	12 (9.0%)	
ADI national rank (1-100)	28 (13, 54)	10 (4, 22)	<0.001		17 (7, 34)	63 (43, 88)	68 (45, 82)	<0.001
Diagnosis			<0.001					
ECD/Mixed ECD	134 (99%)	1 (1%)						
RDD/Mixed RDD	117 (95%)	6 (5%)						
LCH	132 (52%)	122 (48%)						
HS	9 (100%)	0 (0%)						
JXG	21 (100%)	0 (0%)						

Abbreviations: MSK: Memorial Sloan Kettering Cancer Center; UAB: University of Alabama at Birmingham; UMich: University of Michigan; ADI: Area Deprivation Index; ECD: Erdheim-Chester Disease; LCH: Langerhans Cell Histiocytosis; RDD: Rosai-Dorfman Disease.

[1] n (%); Median (Q1, Q3)

[2] Pearson's Chi-squared test; Kruskal-Wallis rank sum test; Fisher's exact test; Fisher's Exact Test for Count Data with simulated p-value (based on 2000 replicates)

Supplementary Table 2. Multivariable Associations with Binary Time to Diagnosis (<1/≥1 year) by Diagnosis

Characteristic	ECD or ECD-mixed			LCH			RDD or RDD-mixed		
	OR[a]	95% CI[a]	p-value[a]	OR[a]	95% CI[a]	p-value[a]	OR[a]	95% CI[a]	p-value[a]
Race									
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Non-White	3.38	0.93, 13.95	0.07	2.75	1.04, 7.08	0.04	1.14	0.40, 3.30	0.81
ADI National Tertiles									
Tertile 1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Tertile 2	0.86	0.33, 2.26	0.75	1.30	0.54, 3.16	0.55	1.76	0.30, 14.65	0.55
Tertile 3	1.37	0.45, 4.21	0.58	3.34	1.23, 9.18	0.02	2.36	0.42, 19.22	0.36
HDI (scaled 0-100)	1.10	0.77, 1.60	0.63	0.93	0.70, 1.24	0.60	1.13	0.83, 1.56	0.45
Age at Diagnosis (years)	1.00	0.98, 1.03	0.93	1.03	1.01, 1.05	<0.001	1.03	1.00, 1.06	0.05

Abbreviations: ECD: Erdheim-Chester Disease; LCH: Langerhans Cell Histiocytosis; RDD: Rosai-Dorfman Disease; OR: Odds Ratio; CI: Confidence interval; Ref: Reference; ADI: Area Deprivation Index; HDI: Human Development Index.

[a] All estimates mutually adjusted for all other variables in the table.

Supplementary Table 3. Multivariable Associations with Time from Diagnosis to Treatment in those Treated

Characteristic	Beta[a]	95% CI[a]	p-value[a]
Race			
White	—	—	
Non-White	-0.15	-0.73, 1.02	0.74
ADI National Tertiles			
ADI Natl: Tertile 1	—	—	
ADI Natl: Tertile 2	-0.95	-1.87, -0.03	0.04
ADI Natl: Tertile 3	-1.29	-2.25, -0.34	0.008
HDI (scaled 0-100)	0.17	-0.06, 0.40	0.14
Driver Mutations			
No driver mutation	—	—	
BRAFV600E mutation only	0.08	-0.96, 1.12	0.88
Driver mutation other than BRAF	-0.51	-1.43, 0.41	0.27
Not sequenced	-0.76	-1.99, 0.46	0.22
Diagnosis			
ECD or ECD mixed	—	—	
RDD or RDD mixed	0.57	-0.47, 1.61	0.28
Other or Unknown	-0.22	-1.07, 0.64	0.62
Age at Diagnosis (years)	-0.02	-0.04, 0.00	0.06

Abbreviations: CI: Confidence interval; Ref: Reference; ADI: Area Deprivation Index; HDI: Human Development Index; ECD: Erdheim-Chester Disease; Rosai-Dorfman Disease.

[a] All estimates mutually adjusted for all other variables in the table.