Diagnostic disparities in inborn errors of immunity: From clinical suspicion to diagnosis

Karen M. Gilbert, PhD,[a] Robert F. LeCates, MA,[a] Alison A. Galbraith, MD, MPH,[b] Paul J. Maglione, MD, PhD,[c] Stephanie Argetsinger, MPH,[a] Nicholas L. Rider, DO,[d] Jocelyn R. Farmer, MD, PhD,[e] and Mei-Sing Ong, PhD[a,f] *Boston and Burlington, Mass; and Roanoke, Va*

Background: Emerging evidence suggests that inborn errors of immunity (IEI) are underdiagnosed among underserved populations. However, there remains a lack of national studies evaluating diagnostic disparities in IEI.

Objective: We examined disparities in the timely IEI diagnosis and related health outcomes.

Methods: A retrospective analysis was performed of a US national claims database (years 2007 to 2021). Participants included patients diagnosed with an "unspecified immune deficiency" (uID) and presented with IEI-related symptoms, who later received an IEI diagnosis (n = 1429). We quantified the diagnostic interval from clinical suspicion (uID) to IEI diagnosis and examined its association with sociodemographic factors and related health outcomes.

Results: The median (interquartile range) diagnostic interval was 369 (126-808) days. Diagnostic interval was 14% longer among patients residing in predominantly non-White neighborhoods, compared with those in predominantly White neighborhoods ($P = .04$), despite having more severe IEI-related symptoms at uID diagnosis and significantly more health care encounters for pneumonia (incidence rate ratio, 2.24; 95% confidence interval, 1.40-3.70) and sepsis (incidence rate ratio, 2.15; 95% confidence interval, 1.21-3.99) in the year after uID diagnosis. Residence in neighborhoods with greater deprivation was also associated with more severe IEI-related symptoms and greater health care utilization in the year after uID diagnosis. Older age was associated with longer diagnostic interval ($P < .001$). Longer diagnostic interval was associated with a longer interval to receiving IgR therapy (hazard ratio, 0.64; 95% confidence interval, 0.49-0.83).

Conclusion: We observed significant racial and socioeconomic disparities in the timeliness of IEI diagnosis and IEI-related outcomes. Further studies are needed to address the underlying factors contributing to diagnostic inequity. (J Allergy Clin Immunol Global 2025;4:100407.)

Key words: *Inborn errors of immunity, primary immune deficiency, diagnostic delay, racial disparities, socioeconomic disparities, diagnosis*

Inborn errors of immunity (IEI) comprise nearly 500 rare and potentially life-threatening conditions of inherited immune dysregulation.[1] IEI are diagnostically challenging due to heterogeneity of clinical manifestations and the rarity of each individual underlying etiology.[2-5] Delays in IEI diagnosis are therefore pervasive and are associated with an increased risk of mortality and morbidity, including life-threatening infections and chronic organ damage.[6-11] In patients with common variable immune deficiency, the most common symptomatic IEI worldwide, mortality risk increased by 1.7% for each year of diagnostic delay, and a 4.5% increased risk of mortality was observed for each year of increased age at diagnosis.[12] Among patients with undiagnosed IEI, recurrent infections may also lead to lasting organ damage, including the development of terminal lung disease.[13-15]

Emerging evidence suggests that IEI may be underdiagnosed among historically marginalized populations.[16-19] Notably, before the implementation of newborn screening for severe combined immune deficiency (SCID), the majority (90%) of patients referred to transplant centers were non-Hispanic White,[20] which was disproportionately higher than in the general population. However, a long-term follow-up study of newborn screening for SCID in California found no significant racial or ethnic group differences in SCID occurrence, suggesting potential disparities in diagnosis before the implementation of newborn screening.[21,22] In another single-center study, an objective scoring algorithm based on International Classification of Disease (ICD)-9 codes was developed to identify patients with undiagnosed IEI using electronic health record data. The study showed that patients with undiagnosed IEI were more likely to be Hispanic or Black and more likely to be insured by Medicaid.[19] Whether diagnostic disparities occurred across different IEI nationally remains unknown. Here, we examined racial and socioeconomic disparities in the timeliness of IEI diagnosis and the associated disease outcomes and health care utilization in a national cohort of IEI patients.

METHODS

Study design and data source

We performed a retrospective cohort analysis of health care claims data from the Optum deidentified Clinformatics Datamart database between January 2007 and September 2021. Clinformatics Datamart

From [a]the Department of Population Medicine, Harvard Pilgrim Health Care Institute, Boston; [b]the Pulmonary Center and Section of Pulmonary, Allergy, Sleep and Critical Care, [c]the Boston University Chobanian and Avedisian School of Medicine and Boston Medical Center, Boston; [d]the Department of Health Systems & Implementation Science, Virginia Tech Carilion School of Medicine, Roanoke; [e]the Program in Clinical Immunodeficiency, Division of Allergy & Immunology, Beth Israel Lahey Health, Burlington; and [f]Harvard Medical School, Boston.

The last 2 authors contributed equally to this article, and both should be considered senior author.

Received for publication June 13, 2024; revised September 23, 2024; accepted for publication November 16, 2024.

Available online January 11, 2025.

Corresponding author: Karen Gilbert, PhD, Department of Population Medicine, Harvard Pilgrim Health Care Institute, 401 Park Dr, Suite 401 East, Boston, MA 02215. E-mail: karenmgilbert@gmail.com.

2772-8293

https://doi.org/10.1016/j.jacig.2025.100407

Abbreviations used
ADI: Area deprivation index
CI: Confidence interval
ED: Emergency department
HR: Hazard ratio
ICD: International Classification of Disease
IEI: Inborn errors of immunity
IgR: Immunoglobulin replacement
IQR: Interquartile range
IRR: Incidence rate ratio
PAD: Predominantly antibody deficiency
SCID: Severe combined immune deficiency
uID: Unspecified immune deficiency

is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans across the United States. The study was approved by the Harvard Pilgrim Health Care institute institutional review board.

Study participants

Study participants included both pediatric and adult patients diagnosed with an unspecified disorder of the immune mechanism (ie, unspecified immune deficiency [uID]) who were subsequently diagnosed with IEI (Fig 1). ICD diagnostic codes in the first and second diagnosis positions were used to identify uID (ICD-9 279.9, ICD-10 D89.9) and IEI (ICD-9 279.0x-279.3x, 279.8, ICD-10 D80-D84) diagnoses (see Table E1 in this article's Online Repository available at www.jaci-global.org). We restricted our cohort to patients who presented with at least one IEI symptom in the annual year of the first (index) uID diagnosis during the study period. IEI symptoms were identified using a previously validated algorithm that enumerates relevant diagnostic and pharmacy codes to assess IEI risk.[23] Given these inclusion criteria, patients in our cohort represented individuals who had received medical attention for suspected IEI-related symptoms but had not yet received a more definitive clinical diagnosis of IEI.

To ensure adequate follow-up, we confined the study cohort to patients with continuous enrollment for >12 months before and after index uID diagnosis. To form an incident cohort (ie, a cohort of patients with newly diagnosed IEI), we further confined our study cohort to those who did not have an IEI diagnosis at least a year before the index uID diagnosis. We included both pediatric and adult patients. Individuals aged ≥65 years were only included if they were enrolled onto Medicare Advantage health plans; those enrolled onto Medicare alone were excluded because data from these individuals may not be completely captured in our dataset. To exclude patients with secondary immune deficiency, we applied a previously published algorithm[24] and excluded patients with human immunodeficiency virus, patients with immune deficiency due to drugs or external causes, and patients diagnosed with uID who also had a diagnosis of leukemia or lymphoma. Table E2, in the Online Repository available at www.jaci-global.org, lists the ICD codes we used for identifying these conditions, and Fig 2 provides the selection criteria.

Assessments and study end points

The primary outcomes of interest were: (1) diagnostic interval, defined as the time between a uID diagnosis and a specific IEI diagnosis, representing the period from clinical suspicion to an IEI diagnosis; (2) the association between diagnostic interval and sociodemographic factors (including age, sex, neighborhood race, and socioeconomic status); and (3) the association between diagnostic interval and disease outcomes and health care utilization. Additionally, as secondary outcomes, we examined the association of sociodemographic factors with IEI symptom severity at the time of uID diagnosis, as well as with disease outcomes and health care utilization.

IEI symptom severity was categorized into low, medium, or high according to a previously validated claims-based score calculation.[23] Disease outcomes were assessed using 3 variables: IEI symptom severity at uID diagnosis, number of health care encounters with a diagnosis of pneumonia, and number of health care encounters with a diagnosis of sepsis in the year after index uID diagnosis (see Table E3 in the Online Repository available at www.jaci-global.org). Sepsis and pneumonia are indicators of severe disease among patients with an undiagnosed or untreated IEI.[10,25] Health care utilization was assessed using 3 variables: number of emergency department (ED) visits, days of hospitalization for any cause in the year after uID diagnosis, and time to initiation of immunoglobulin replacement (IgR) therapy after uID diagnosis.

We extracted patients' age, sex, and zip code of residence. We linked patients' zip code with zip code–level race composition, area deprivation index (ADI), and rural/urban status, derived from the US Census Bureau American Community Survey's 2014-2018 5-Year Estimates. Neighborhood race was categorized as predominantly White (≥66% White) or non-White (≤34% White). ADI is a composite measure of a region's socioeconomic disadvantage based on income, education, employment, and housing quality, with higher ADI indicating greater socioeconomic disadvantage. Rural/urban status was determined using rural–urban commuting area codes and categorized as urban (≤3) or rural (>3).[26]

Statistical analysis

Descriptive statistics described the study demographics and the diagnostic interval between uID and IEI diagnoses. Multivariate generalized linear models with gamma distribution and log link function were developed to identify sociodemographic factors associated with diagnostic interval. In these models, diagnostic interval was the dependent outcome, represented as a continuous variable in days. Cumulative link models (ie, ordinal regression)[27,28] were developed to investigate the association between sociodemographic factors and IEI symptom severity at diagnosis. In these analyses, IEI symptom severity at uID diagnosis was the dependent variable, defined as an ordinal score with 3 ordered categories (ie, low, medium, or high severity). We used multivariate negative binomial regression models to explore the association between diagnostic interval and disease outcomes and health care utilization in the year after index uID diagnosis while adjusting for sociodemographic factors. This modeling approach accounts for overdispersed count outcome variables.[29,30] Separate models were developed to predict the number of health care encounters related to pneumonia, the number of health encounters related to sepsis, the number of ED visits, and days of hospitalization. Finally, we performed Cox regression analysis to examine the association of diagnostic interval with time to initiation of IgR therapy from the time of uID diagnosis while adjusting for IEI symptom severity at diagnosis and sociodemographic factors. Data of patients who did

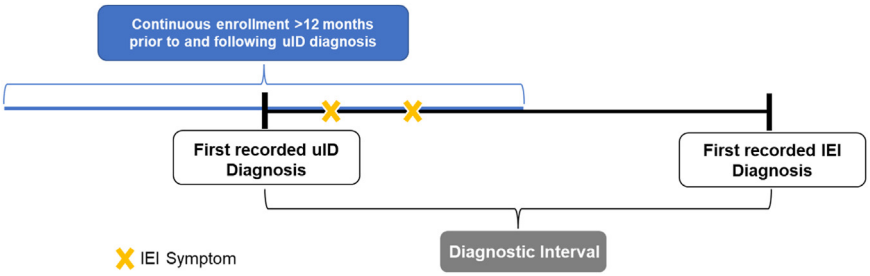

FIG 1. Study cohort definition.

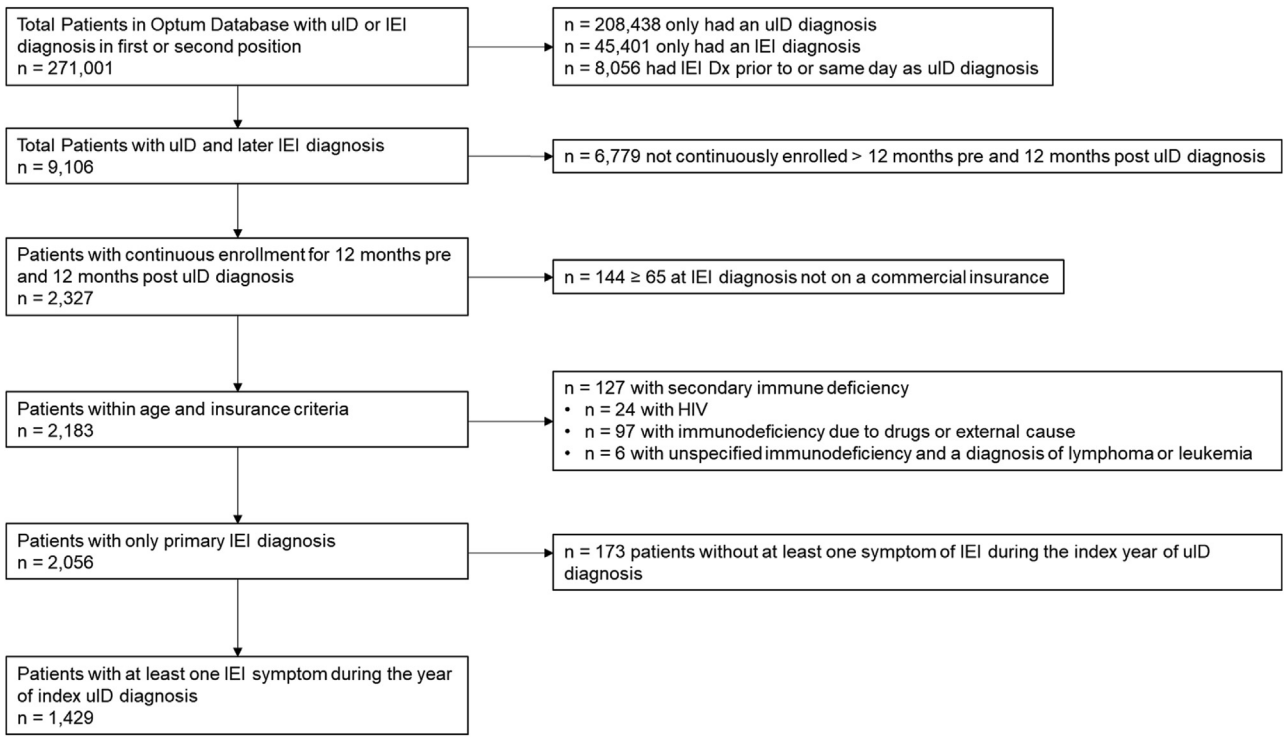

FIG 2. Study cohort selection criteria.

not receive IgR therapy during the study period were censored at the end of insurance enrollment. In all analyses, univariate analyses were first performed, and variables with $P \leq .2$ were retained for multivariate analysis. We used R v4.3.1 statistical software (R Project; www.r-project.org). All tests of statistical significance were 2 sided and used an α level of $P < .05$.

Sensitivity analysis

IEI diagnoses can vary in their presentation, pathogenesis, and demographics. As a sensitivity analysis, we compared the diagnostic interval of patients with predominantly antibody deficiency (PAD)—the most common IEI—residing in predominantly White neighborhoods against those in predominantly non-White neighborhoods.

RESULTS

A total of 1429 individuals were included in our study, 55.6% (n = 795) of whom were female and 14.9% (n = 213) children (<18 years old) (Table I). The median age at index uID diagnosis was 53 years. Most study participants resided in predominantly White neighborhoods (n = 1031; 72.1%) and urban areas (n = 1301; 91.0%). The median (interquartile range [IQR]) diagnostic interval from uID to IEI diagnoses was 369 (126-808) days. In the year after the index uID diagnosis, 214 patients (15.0%) and 148 patients (10.4%) had one or more health care encounters for pneumonia and sepsis, respectively. During this period, 47.4% of patients had one or more ED visits, 35.3% had one or more day of hospitalization, and 10.1% received IgR therapy (Table II). The median (IQR) follow-up period after uID diagnosis was 864 (557-1402) days.

Sociodemographic factors associated with diagnostic interval

In multivariate analysis examining the association between sociodemographic factors and diagnostic interval, individuals residing in predominantly non-White neighborhoods experienced a longer diagnostic interval compared with those in

TABLE I. Demographic characteristics of study population (N = 1429)

Characteristic	Value
Sex, no. (%)	
Female	795 (55.6)
Male	893 (43.6)
Age (years) at uID diagnosis, median (IQR)	53.0 (25.0, 69.0)
Min, max	1.0, 89.0
Rural/urban status, no. (%)	
Urban	1,301 (91.0)
Rural	126 (8.8)
Missing	2 (0.1)
ADI, median (IQR)	39.0 (21.7, 57.7)
Min, max	1.0, 99.0
Neighborhood race, no. (%)	
Predominantly White	1,031 (72.1)
Predominantly non-White	396 (27.7)
Missing	2 (0.1)
Symptom severity at uID, no. (%)	
Low	686 (27.6)
Medium	108 (7.6)
High	635 (44.4)

predominantly White neighborhoods (median, 391 vs 364 days; exp(β) = 1.14; 95% confidence interval [CI], 1.00, 1.30; P = .044). Increasing age was associated with a longer diagnostic interval (exp(β) = 1.15; 95% CI, 1.08, 1.22; P < .001). In contrast, high IEI symptom severity was associated with a shorter diagnostic interval (exp(β) = 0.76; 95% CI, 0.68, 0.86; P < .001). ADI was not associated with diagnostic interval (Table III). Although patients residing in rural areas experienced a longer diagnostic interval compared with those in urban areas (median, 402 vs 366 days), the difference did not reach statistical significance (see Table E4 in the Online Repository available at www.jaci-global.org).

Association of diagnostic interval and sociodemographic factors with disease outcomes, health care utilization, and treatment

Diagnostic interval was not associated with disease outcomes (ie, number of health care encounters related to pneumonia or sepsis) or number of ED visits (see Tables E4-E7 in the Online Repository available at www.jaci-global.org). However, we observed that patients residing in predominantly non-White neighborhoods (odds ratio, 1.28; 95% CI, 1.02, 1.60; P = .034) and patients residing in neighborhoods with greater ADI (odds ratio, 1.15; 95% CI, 1.04, 1.28; P = .006) had greater IEI symptom severity at uID diagnosis after adjusting for other sociodemographic factors (Table IV). We further observed that residence in non-White neighborhoods was associated with more health care encounters related to pneumonia (incidence rate ratio [IRR], 2.24; 95% CI, 1.40, 3.70) and sepsis (IRR, 2.15; 95% CI, 1.21, 3.99) in the year after the uID diagnosis (Fig 3, Table E5). Similarly, residence in neighborhoods with higher ADI was associated with more health care encounters related to pneumonia (IRR, 1.28; 95% CI, 1.02, 1.62) and sepsis (IRR, 1.74; 95% CI, 1.32, 2.32) in the year after the uID diagnosis (Fig 3, Table E6). Older patients (IRR, 1.43; 95% CI, 1.17, 1.74) and patients

TABLE II. Disease outcomes and health care utilization in year after uID diagnosis, and IgR therapy after uID diagnosis (n = 1429)

Characteristic	No. (%)*
Pneumonia-related health care encounter	214 (15.0)
Sepsis-related health care encounter	148 (10.4)
ED visit	678 (47.4)
Days of hospitalization	505 (35.3)
Received IgR therapy	145 (10.1)

*Patients with ≥1 health care encounters related to outcome of interest.

living in rural counties (IRR, 2.56; 95% CI, 1.21, 6.15) also had more health care encounters related to pneumonia in the year after the uID diagnosis. Finally, residence in neighborhoods with higher ADI was also associated with a greater number of ED visits (IRR, 1.14; 95% CI, 1.05, 1.24) and days of hospitalization (IRR, 1.18; 95% CI, 1.02, 1.37) in the year after the uID diagnosis (Fig 3, and see Tables E7 and E8 in the Online Repository).

Finally, we observed that longer diagnostic interval was associated with a longer interval to receiving IgR therapy from uID diagnosis (hazard ratio [HR], 0.64; 95% CI, 0.49, 0.83; P = .001). Furthermore, patients residing in predominantly non-White neighborhoods (HR, 0.54; 95% CI, 0.31, 0.97; P = .040) and neighborhoods with greater ADI (HR, 0.54; 95% CI, 0.31, 0.97; P = .040) had a longer interval to receipt of IgR therapy (Table V).

Sensitivity analysis

In a sensitivity analysis of PAD patients, individuals residing in predominantly non-White neighborhoods had a longer median diagnostic interval compared with those in predominantly White neighborhoods (318 vs 278 days) (see Table E9 in the Online Repository available at www.jaci-global.org). However, this difference did not reach statistical significance (see Table E10 in the Online Repository).

DISCUSSION

In this retrospective cohort analysis of IEI patients suspected by a clinician to have immune deficiency, as indicated by an initial diagnosis of uID, we found substantial delay in the diagnosis of IEI. The median diagnostic interval from uID diagnosis to IEI diagnosis was more than a year. Notably, individuals in predominantly non-White neighborhoods experienced longer diagnostic intervals compared with those in predominantly White neighborhoods, despite presenting with more severe IEI symptoms at uID diagnosis. Moreover, residence in predominantly non-White or high-deprivation neighborhoods were predictive of worse disease outcomes.

Our findings add to existing evidence demonstrating substantial delay in the diagnosis of IEI. In the United States, the median interval from IEI symptom onset to diagnosis is 4.7 years,[11] with similar rates reported in Europe.[31,32] The average interval from symptom onset to diagnosis for common variable immune deficiency ranges from 4 to 9 years.[10,31-33] Our study reported a shorter diagnostic interval likely due to differences in methodology. Published studies measured diagnostic interval from symptom onset to IEI diagnosis, whereas we quantified diagnostic interval between uID and IEI diagnoses. Because onset of IEI symptoms likely preceded uID diagnosis by months or years,

TABLE III. Regression analyses of factors associated with diagnostic interval

	Univariate analysis			Multivariable analysis*		
Characteristic	**exp(β)**	**95% CI**	***P***	**exp(β)**	**95% CI**	***P***
Sex						
Female	Ref	Ref	Ref			
Male	0.94	0.84, 1.05	.3			
Age	1.15	1.08, 1.22	<.001	1.15	1.08, 1.22	<.001
Rural/urban status						
Urban	Ref	Ref	Ref			
Rural	1.03	0.85, 1.25	.8			
ADI	1.03	0.98, 1.09	.3			
Neighborhood race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Non-White	1.10	0.97, 1.24	.14	1.14	1.00, 1.30	.044
Symptom severity at uID						
Low	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	0.99	0.80, 1.24	.9	1.05	0.84, 1.32	.7
High	0.76	0.67, 0.85	<.001	0.76	0.68, 0.86	<.001

*Included only variables found to have significance of $P < .2$ in univariate analyses.

TABLE IV. Regression analyses of factors associated with IEI symptom severity in year of uID diagnosis

	Univariate analysis			Multivariable analysis*		
Characteristic	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.39	1.14, 1.70	.001	1.39	1.14, 1.71	.001
Age	0.90	0.82, 1.00	.044	0.89	0.81, 0.99	.030
Rural/urban status						
Urban	Ref	Ref	Ref			
Rural	1.03	0.72, 1.46	.9			
ADI	1.13	1.03, 1.25	.014	1.15	1.04, 1.28	.006
Neighborhood race						
Predominantly White	Ref	Ref	Ref	Ref	Ref	Ref
Predominantly non-White	1.28	1.02, 1.61	.031	1.28	1.02, 1.60	.034

OR, Odds ratio.
*Included only variables found to have significance of $P < .2$ in univariate analyses.

our reported diagnostic interval was likely much shorter than the total interval from symptom onset to IEI diagnosis, which includes the diagnostic cascade in which symptoms are brought to medical attention and recognized. While published works were inclusive of IEI patients with or without a uID diagnosis, we focused on a subgroup of IEI patients who were initially diagnosed with uID. Our study therefore provides unique insights into the diagnostic journey of IEI patients who were already suspected and documented by their health care providers to have immune deficiency. We showed that despite repeated health care encounters for IEI-related symptoms and strong clinical suspicion for an underlying immune deficiency, many patients continued to experience delay in IEI diagnosis.

We found that patients residing in predominantly non-White neighborhoods experienced significantly longer diagnostic intervals compared with those in predominantly White neighborhoods, even after controlling for IEI symptom severity at uID diagnosis (Table III). Moreover, patients in predominantly non-White neighborhoods were more likely to experience more severe IEI symptoms and greater number of health care encounters related to pneumonia and sepsis in the year after uID diagnosis. These findings are consistent with prior studies demonstrating disparities in IEI outcomes among historically marginalized racial populations. For example, a study conducted at a safety net hospital found higher rates of pneumonia and bronchiectasis among Black patients with PAD compared with other racial groups.[34] A national study further showed substantial mortality disparities among historically underserved racial groups diagnosed with an IEI, especially among Black patients.[35]

Several factors may contribute to diagnostic delay among underserved racial populations. Genetic testing is a critical tool in IEI diagnosis, but barriers such as cost, access, awareness, and medical distrust in the use of genetic testing could exacerbate inequity.[36-39] Disparities may also arise from lack of access to specialized immunology care—a well-documented challenge, particularly in historically marginalized patients.[40-43] A national survey of 1250 primary care physicians found that physicians serving marginalized populations were significantly less likely to perform laboratory testing when a possible IEI case was identified, and Black physicians were least likely to refer patients with suspected IEI to a specialist.[40] Interestingly, we did not observe an association between diagnostic interval and residence in higher-deprivation areas (measured by the ADI), suggesting that the relationship between race and prolonged diagnostic interval was

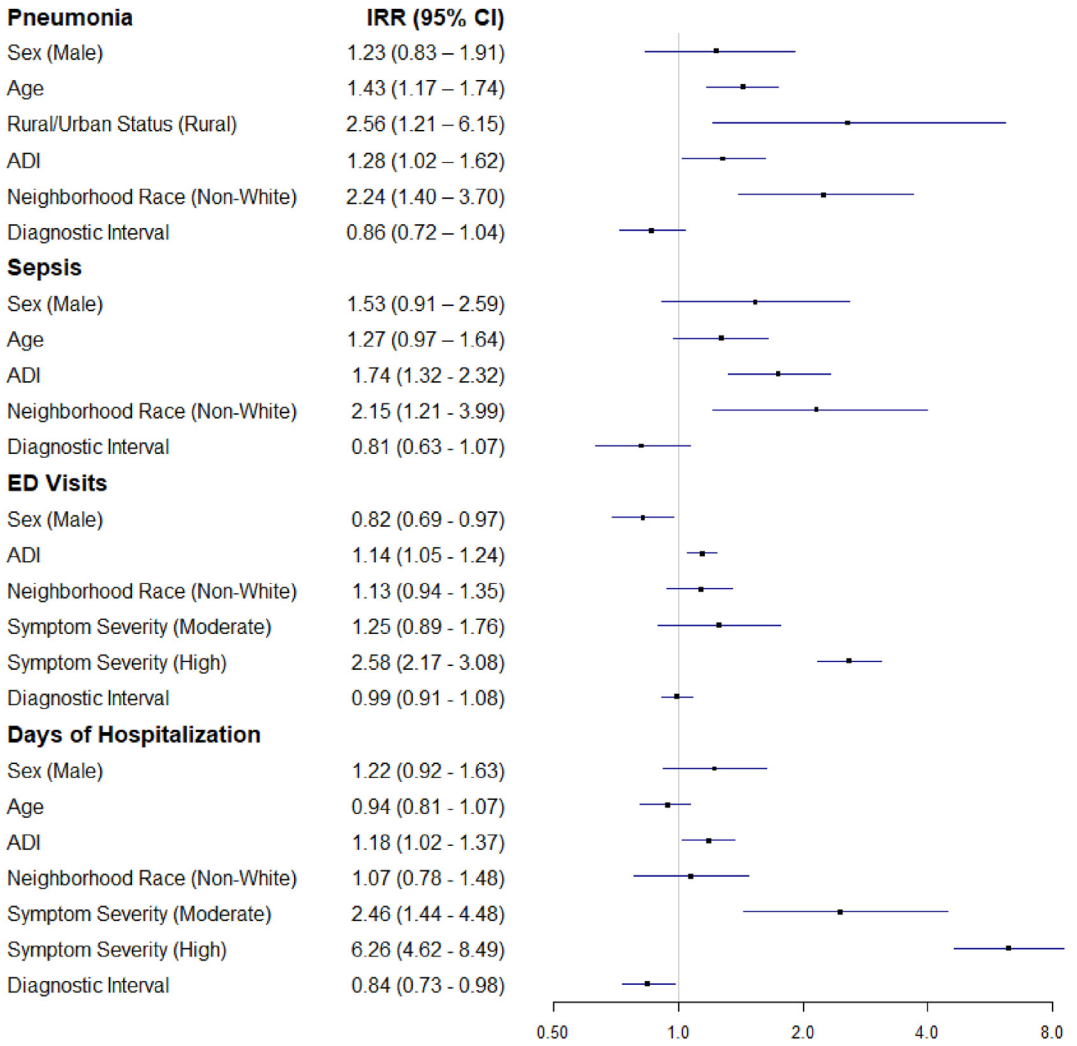

FIG 3. Multivariate analyses of factors associated with disease outcomes and health care utilization in year after uID diagnosis. Only variables with $P < .2$ in univariate analyses were included (Tables E5-E8).

driven by factors beyond those related to socioeconomic status. Nonetheless, residence in higher-deprivation areas was associated with worse IEI symptom severity, more ED visits, and more days of hospitalization in the year after uID diagnosis. Residence in rural areas was also not associated with diagnostic interval but was associated with more pneumonia-related health care encounters in the year after uID diagnosis.

Our analysis further showed that greater diagnostic interval was associated with a greater interval from uID diagnosis to the receipt of IgR therapy, after adjusting for IEI symptom severity, suggesting that delay in diagnosis potentially led to delay in treatment. Importantly, consistent with a prior study,[34] we found that patients living in non-White neighborhoods or in areas of greater deprivation had a longer interval to receiving IgR therapy. Together, these results point to racial and socioeconomic disparities in IEI diagnosis and treatment.

We observed that prolonged diagnostic interval was more pervasive in older patients, likely as a result of milder disease in older patients. As observed in our study and other published data,[44,45] IEI diagnosed in childhood tend to have a more severe disease course than those diagnosed later in life (Table IV). However, our analysis showed that the relationship between age and diagnostic interval persisted after adjusting for IEI symptom severity, suggesting that other factors may be involved (Table III). Atypical clinical and immunologic presentations of IEI may lead to delayed diagnosis of IEI in adulthood.[46,47] An overall paucity of prevailing knowledge of IEI among adult health care providers may also be a contributing factor.[40] A study reported that pediatricians were significantly more likely to refer suspected cases of IEI to specialist care. Heightened awareness of IEI and increase in clinical exposure might have led to a greater index of suspicion for IEI and earlier diagnosis of IEI in children. Older patients are also more likely to have other chronic diseases, complicating the diagnosis of IEI.[48,49]

We did not observe an association between diagnostic interval and disease outcomes in the year after uID diagnosis, as measured by the number of health care encounters related to pneumonia and sepsis. These findings stand in contrast with the extensively documented adverse health consequences linked to diagnostic delay in IEI.[6-8,11-14] Several factors may explain this discrepancy. First, we found that greater IEI symptom severity at uID diagnosis was associated with a shorter diagnostic interval, suggesting that

TABLE V. Cox regression analyses examining factors associated with receiving IgR therapy

	Univariate analysis			Multivariable analysis*		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Sex						
Female	Ref	Ref	Ref			
Male	0.95	0.59, 1.53	.8			
Age	0.96	0.76, 1.21	.7			
Rural/urban status						
Urban	Ref	Ref	Ref			
Rural	0.89	0.41, 1.94	.8			
ADI	0.80	0.64, 1.00	.048	0.77	0.61, 0.98	.031
Neighborhood race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Non-White	0.64	0.37, 1.12	.12	0.54	0.31, 0.97	.040
Symptom severity at uID						
Low	Ref	Ref	Ref	Ref	Ref	Ref
Moderate	1.22	0.45, 3.31	.7	1.16	0.42, 3.20	.77
High	1.90	1.09, 3.32	.024	1.49	0.83, 2.70	.19
Diagnostic interval	0.59	0.45, 0.77	<.001	0.64	0.49, 0.83	.001

*Included only variables found to have significance of $P < .2$ in univariate analyses.

patients with more severe disease were more likely to seek care and were therefore more likely to be diagnosed sooner. Indeed, our analysis showed that longer diagnostic interval was associated with fewer days of hospitalization in the year after index uID diagnosis. Second, as discussed above, our definition of diagnostic interval does not account for the time that lapses between symptom onset and uID diagnosis. Given that delay in the treatment of IEI is known to result in more severe IEI symptoms,[7,50-52] our analysis may have systematically underestimated the diagnostic interval of patients with prolonged delay from symptom onset. The difficulty in discerning the exact timing of IEI symptom onset in retrospective claims data precluded our ability to assess diagnostic interval from symptom onset. Third, due to difficulty in distinguishing IEI-related ED visits and hospitalization from those unrelated to IEI, our analysis assessed all-cause ED visits and hospitalizations. This may have limited our ability to detect associations between diagnostic delay and specific IEI-related health care encounters.

Our study was limited by the availability and granularity of information captured in claims data. Of note, our dataset did not capture patient-level race and socioeconomic status; instead, we leveraged neighborhood-level socioeconomic data. Thus, the observed disparities may be attributable to differences in the spectrum of IEI present in specific groups of patients separated by zip code. However, given that our prior analysis of national, individual-level mortality data demonstrated stark survival disparities among Black versus White patients with IEI across most IEI diagnoses,[35] we believe that the diagnostic disparities observed in the current study could not have been driven by geographical differences alone. Furthermore, published studies have validated neighborhood-level characteristics as measures of health disparities.[53-56] We relied on ICD diagnostic codes to identify our cohort; therefore, coding inaccuracy or variability in coding practices may skew our study findings. To maximize the specificity of our case identification, we chose a stringent case definition that included both uID and IEI diagnoses, as well as occurrence of IEI-related symptoms in the year after uID diagnosis. We also restricted our cohort to those continuously enrolled for at least a year before and after uID diagnosis, potentially biasing our cohort toward patients who received more consistent care. Furthermore, our cohort was primarily composed of individuals who were privately insured. Diagnostic delays and disparities are likely to be much more pervasive among publicly insured and uninsured individuals.[18,19,57,58] Given the rarity of individual IEI diagnoses and the lack of granularity of ICD codes, we could not investigate diagnostic disparities for specific IEI diagnoses. A sensitivity analysis including only PAD patients showed that those in non-White neighborhoods experienced longer diagnostic intervals than those in predominantly White neighborhoods, although the difference was not statistically significant, likely as a result of the small sample size. Finally, there may also be residual confounding by unmeasured factors. While there are limitations to claims data, the availability of information on a large number of patients makes it possible to study rare diseases such as IEI. Furthermore, claims data are systematically collected and provide longitudinal information that crosses facilities, geography, and demographics, thereby enhancing the generalizability of research and limiting selection biases.

Taken together, our findings provide evidence for significant racial and socioeconomic disparities in timeliness of diagnosis, disease outcomes, and health care utilization in IEI. These patterns suggest potential biases and barriers in the diagnostic process of IEI in the US health care system, and further studies are needed to explore and address the underlying factors contributing to diagnostic inequity.

DISCLOSURE STATEMENT

Research reported in this publication was supported by funding from the National Institute on Minority Health and Health Disparities (NIMHD) of the National Institutes of Health (NIH) under award R01MD017816. J.R.F. was supported by a faculty development award from the American Academy of Allergy Asthma & Immunology and NIMHD-NIH under award R01MD017816. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The funding sources were not involved in the collection, analysis, or interpretation of data, preparation of the report, or decision to submit the report for publication.

Disclosure of potential conflict of interest: N. L. Rider received funding from the Jeffrey Modell Foundation (58293-I), the NIH (R21AI164100), and Takeda Pharmaceuticals; is a consultant for Takeda, Pharming Healthcare, and CSL Behring; and receives royalties from Wolters Kluwer and UpToDate. M.-S. Ong has received funding from Pfizer through an investigator-initiated grant with no direct relation to the work presented. J. R. Farmer is an ongoing consultant for Pharming and has received investigator-initiated research grants from Pfizer, Bristol Myers Squibb, and Pharming with no direct relation to the work presented. P. J. Maglione has consulted for Takeda and Pharming Healthcare. The rest of the authors declare that they have no relevant conflicts of interest.

Key messages

- **Delays in diagnosis of IEI are pervasive and have significant consequences for patients; however, racial and/or socioeconomic disparities in diagnostic delay have not been previously studied.**
- **Compared with patients living in predominantly White neighborhoods, those living in predominantly non-White neighborhoods experienced a longer delay in IEI diagnosis and IgR therapy, and worse disease outcomes, despite presenting with more severe symptoms before diagnosis. Older patients were also more likely to experience prolonged diagnostic interval after clinical suspicion for immune deficiency.**
- **These findings highlight the need to address barriers to timely diagnosis and treatment of IEI among historically underserved populations and older patients with IEI.**

REFERENCES

1. Akalu YT, Bogunovic D. Inborn errors of immunity: an expanding universe of disease and genetic architecture. Nat Rev Genet 2024;25:184-95.
2. Branch A, Modi B, Bahrani B, Hildebrand KJ, Cameron SB, Junker AK, et al. Diverse clinical features and diagnostic delay in monogenic inborn errors of immunity: a call for access to genetic testing. Pediatr Allergy Immunol 2021;32:1796-803.
3. O'Keefe AW, Halbrich M, Ben-Shoshan M, McCusker C. Primary immunodeficiency for the primary care provider. Paediatr Child Health 2016;21:e10-4.
4. Gruber C, Bogunovic D. Incomplete penetrance in primary immunodeficiency: a skeleton in the closet. Hum Genet 2020;139:745-57.
5. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppänen MR, Fischer A, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol 2021;148:1332-41.
6. Graziano V, Pecoraro A, Mormile I, Quaremba G, Genovese A, Buccelli C, et al. Delay in diagnosis affects the clinical outcome in a cohort of CVID patients with marked reduction of IgA serum levels. Clin Immunol 2017;180:1-4.
7. Seymour B, Miles J, Haeney M. Primary antibody deficiency and diagnostic delay. J Clin Pathol 2005;58:546-7.
8. Blore J, Haeney MR. Primary antibody deficiency and diagnostic delay. BMJ 1989;298(6672):516.
9. Wood P, Stanworth S, Burton J, Jones A, Peckham DG, Green T, et al. Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review. Clin Exp Immunol 2007;149:410-23.
10. Oksenhendler E, Gérard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 2008;46:1547-54.
11. Joshi AY, Iyer VN, Hagan JB, Sauver JLSt, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc 2009;84:16-22.
12. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134:116-26.
13. Slade CA, Bosco JJ, Binh Giang T, Kruse E, Stirling RG, Cameron PU, et al. Delayed diagnosis and complications of predominantly antibody deficiencies in a cohort of Australian adults. Front Immunol 2018;9:694.
14. Ameratunga R, Jordan A, Cavadino A, Ameratunga S, Hills T, Steele R, et al. Bronchiectasis is associated with delayed diagnosis and adverse outcomes in the New Zealand Common Variable Immunodeficiency Disorders cohort study. Clin Exp Immunol 2021;204:352-60.
15. van de Ven AA, van Montfrans JM, Terheggen-Lagro SW, Beek FJ, van Konijnenburg DPH, Kessels OA, et al. A CT scan score for the assessment of lung disease in children with common variable immunodeficiency disorders. Chest 2010;138:371-9.
16. Rubin Z, Pappalardo A, Schwartz A, Antoon JW. Prevalence and outcomes of primary immunodeficiency in hospitalized children in the United States. J Allergy Clin Immunol Pract 2018;6:1705-10.
17. Barlogis V, Mahlaoui N, Auquier P, Fouyssac F, Pellier I, Vercasson C, et al. Burden of poor health conditions and quality of life in 656 children with primary immunodeficiency. J Pediatr 2018;194:211-7.
18. Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001-2007. J Clin Immunol 2014;34:954-61.
19. Cunningham-Rundles C, Sidi P, Estrella L, Doucette J. Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. J Allergy Clin Immunol 2004;113:747-55.
20. Railey MD, Lokhnygina Y, Buckley RH. Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis. J Pediatr 2009;155:834-40.
21. Kwan A, Church JA, Cowan MJ, Agarwal R, Kapoor N, Kohn DB, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California: results of the first 2 years. J Allergy Clin Immunol 2013;132:140-50.
22. Amatuni GS, Currier RJ, Church JA, Bishop T, Grimbacher E, Nguyen AAC, et al. Newborn screening for severe combined immunodeficiency and T-cell lymphopenia in California, 2010-2017. Pediatrics 2019;143:e20182300.
23. Rider NL, Miao D, Dodds M, Modell V, Modell F, Quinn J, et al. Calculation of a primary immunodeficiency "risk vital sign" via population-wide analysis of claims data to aid in clinical decision support. Front Pediatr 2019;7:70.
24. Resnick ES, Bhatt P, Sidi P, Cunningham-Rundles C. Examining the use of ICD-9 diagnosis codes for primary immune deficiency diseases in New York State. J Clin Immunol 2013;33:40-8.
25. Rayzan E, Mirbeyk M, Pezeshki PS, Mohammadpour M, Yaghmaie B, Hassani SA, et al. Whole-exome sequencing to identify undiagnosed primary immunodeficiency disorders in children with community-acquired sepsis, admitted in the pediatric intensive care unit. Pediatr Allergy Immunol 2023;34:e14066.
26. Zahnd WE, Del Vecchio N, Askelson N, Eberth JM, Vanderpool RC, Overholser L, et al. Definition and categorization of rural and assessment of realized access to care. Health Serv Res 2022;57:693-702.
27. Ning Y, Ho PJ, Støer NC, Lim KK, Wee HL, Hartman M, et al. A new procedure to assess when estimates from the cumulative link model can be interpreted as differences for ordinal scales in quality of life studies. Clin Epidemiol 2021;13:53-65.
28. Agresti A, Kateri M. Ordinal probability effect measures for group comparisons in multinomial cumulative link models. Biometrics 2017;73:214-9.
29. Gardner W, Mulvey EP, Shaw EC. Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models. Psychol Bull 1995;118:392-404.
30. Byers A, Allore H, Gill T, Peduzzi P. Application of negative binomial modeling for discrete outcomes. J Clin Epidemiol 2003;56:559-64.
31. Gathmann B, Goldacker S, Klima M, Belohradsky BH, Notheis G, Ehl S, et al. The German national registry for primary immunodeficiencies (PID). Clin Exp Immunol 2013;173:372-80.
32. Edgar JDM, Buckland M, Guzman D, Conlon NP, Knerr V, Bangs C, et al. The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008-2012. Clin Exp Immunol 2014;175:68-78.
33. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007;27:308-16.
34. Wallace LJ, Ware MS, Cunningham-Rundles C, Fuleihan RL, Maglione PJ. Clinical disparity of primary antibody deficiency patients at a safety net hospital. J Allergy Clin Immunol Pract 2021;9:2923-5.
35. Ong MS, Rider NL, Stein S, Maglione PJ, Galbraith A, DiGiacomo DV, et al. Racial and ethnic disparities in early mortality among patients with inborn errors of immunity. J Allergy Clin Immunol 2024;153:335-40.e1.

36. Suther S, Kiros GE. Barriers to the use of genetic testing: a study of racial and ethnic disparities. Genet Med 2009;11:655-62.
37. Heimall JR, Hagin D, Hajjar J, Henrickson SE, Hernandez-Trujillo HS, Tan Y, et al. Use of genetic testing for primary immunodeficiency patients. J Clin Immunol 2018;38:320-9.
38. Chinen J, Lawrence M, Dorsey M, Kobrynski LJ. Practical approach to genetic testing for primary immunodeficiencies. Ann Allergy Asthma Immunol 2019; 123:433-9.
39. Tawfik SM, Elhosseiny AA, Galal AA, William MB, Qansuwa E, Elbaz RM, et al. Health inequity in genomic personalized medicine in underrepresented populations: a look at the current evidence. Funct Integr Genomics 2023;23:54.
40. Waltenburg R, Kobrynski L, Reyes M, Bowen S, Khoury MJ. Primary immunodeficiency diseases: practice among primary care providers and awareness among the general public, United States, 2008. Genet Med 2010;12:792-800.
41. Lawrence MG, Rider NL, Cunningham-Rundles C, Poli MC. Disparities in diagnosis, access to specialist care, and treatment for inborn errors of immunity. J Allergy Clin Immunol Pract 2024;12:282-7.
42. Pappalardo AA, Codispoti CD, Mahdavinia M. Health care access in allergy and immunology: problems and potential solutions. J Allergy Clin Immunol 2024;153:401-3.
43. Orange JS, Seeborg FO, Boyle M, Scalchunes C, Hernandez-Trujillo V. Family physician perspectives on primary immunodeficiency diseases. Front Med 2016;3:12.
44. Srinivasa BT, Alizadehfar R, Desrosiers M, Shuster J, Pai NP, Tsoukas CM. Adult primary immune deficiency: what are we missing? Am J Med 2012;125:779-86.
45. Abolhassani H, Rezaei N, Mohammadinejad P, Mirminachi B, Hammarstrom L, Aghamohammadi A. Important differences in the diagnostic spectrum of primary immunodeficiency in adults versus children. Expert Rev Clin Immunol 2015;11:289-302.
46. Rosenberg E, Dent PB, Denburg JA. Primary immune deficiencies in the adult: a previously underrecognized common condition. J Allergy Clin Immunol Pract 2016;4:1101-7.
47. Shovlin CL, Hughes JMB, Simmonds HA, Fairbanks L, Deacock S, Lechler R, et al. Adult presentation of adenosine deaminase deficiency. The Lancet 1993; 341(8858):1471.
48. Schäfer I, Hansen H, Schön G, Höfels S, Altiner A, Dahlhaus A, et al. The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the multicare cohort study. BMC Health Serv Res 2012;12:89.
49. Salive ME. Multimorbidity in older adults. Epidemiol Rev 2013;35:75-83.
50. Anderson JT, Cowan J, Condino-Neto A, Levy D, Prusty S. Health-related quality of life in primary immunodeficiencies: impact of delayed diagnosis and treatment burden. Clin Immunol 2022;236:108931.
51. Menzin J, Sussman M, Munsell M, Zbrozek A. Economic impact of infections among patients with primary immunodeficiency disease receiving IVIG therapy. Clin Outcomes Res 2014;297:297-302.
52. Björkander J, Bake B, Hanson LA. Primary hypogammaglobulinaemia: impaired lung function and body growth with delayed diagnosis and inadequate treatment. Eur J Respir Dis 1984;65:529-36.
53. Khan SS, McGowan C, Seegmiller LE, Kershaw KN. Associations between neighborhood-level racial residential segregation, socioeconomic factors, and life expectancy in the US. JAMA Health Forum 2023;4:e231805.
54. Brokamp C, Jones MN, Duan Q, Rasnick Manning E, Ray S, Corley AMS, et al. Causal mediation of neighborhood-level pediatric hospitalization inequities. Pediatrics 2024;153:e2023064432.
55. Hutchinson RN, Putt MA, Dean LT, Long JA, Montagnet CA, Armstrong K. Neighborhood racial composition, social capital and black all-cause mortality in Philadelphia. Soc Sci Med 1982 2009;68:1859-65.
56. Booth JM, Teixeira S, Zuberi A, Wallace JM. Barrios, ghettos, and residential racial composition: examining the racial makeup of neighborhood profiles and their relationship to self-rated health. Soc Sci Res 2018;69:19-33.
57. Kim EJ, Kim T, Conigliaro J, Liebschutz JM, Paasche-Orlow MK, Hanchate AD. Racial and ethnic disparities in diagnosis of chronic medical conditions in the USA. J Gen Intern Med 2018;33:1116-23.
58. Martin S, Ulrich C, Munsell M, Taylor S, Lange G, Bleyer A. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist 2007; 12:816-24.