

Race Adjustment of Pulmonary Function Tests in the Diagnosis and Management of COPD: A Scoping Review

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Aim: Increasing evidence suggests that the inclusion of self-identified race in clinical decision algorithms may perpetuate long-standing inequities. Until recently, most pulmonary function tests utilized separate reference equations that are race/ethnicity based.

Purpose: We assess the magnitude and scope of the available literature on the negative impact of race-based pulmonary function prediction equations on relevant outcomes in African Americans with COPD.

Methods: We performed a scoping review utilizing an English language search on PubMed/Medline, Embase, Scopus, and Web of Science in September 2022 and updated it in December 2023. We searched for publications regarding the effect of race-specific vs race-neutral, race-free, or race-reversed lung function testing algorithms on the diagnosis of COPD and COPD-related physiologic and functional measures. Joanna Briggs Institute (JBI) guidelines were utilized for this scoping review. Eligibility criteria: The search was restricted to adults with COPD. We excluded publications on other lung disorders, non-English language publications, or studies that did not include African Americans. The search identified publications. Ultimately, six peer-reviewed publications and four conference abstracts were selected for this review.

Results: Removal of race from lung function prediction equations often had opposite effects in African Americans and Whites, specifically regarding the severity of lung function impairment. Symptoms and objective findings were better aligned when race-specific reference values were not used. Race-neutral prediction algorithms uniformly resulted in reclassifying severity in the African Americans studied.

Conclusion: The limited literature does not support the use of race-based lung function prediction equations. However, this assertion does not provide guidance for every specific clinical situation. For African Americans with COPD, the use of race-based prediction equations appears to fall short in enhancing diagnostic accuracy, classifying severity of impairment, or predicting subsequent clinical events. We do not have information comparing race-neutral vs race-based algorithms on prediction of progression of COPD. We conclude that the elimination of race-based reference values potentially reduces underestimation of disease severity in African Americans with COPD.

Keywords: lung function tests, lung function prediction equations, African Americans

Introduction

Globally, nearly 600 million individuals aged ≥ 25 years are projected to have chronic obstructive pulmonary disease (COPD) by the year 2050, an increase of 23%.¹ COPD, one of the top three leading causes of death worldwide, is commonly manifested by a triad of persistent respiratory symptoms: dyspnea, cough/wheeze, and sputum production.² African American adults are known to develop COPD at younger ages, with less intensive smoking histories, have

a higher risk for severe exacerbations, and a reduced quality of life.^{3,4} The excess morbidity and mortality experienced by African Americans with COPD may result from reduced lung growth from early life factors, the high prevalence of asthma, nutritional factors, environmental and other exposures resulting from structural racism.⁴⁻⁶

Race-based algorithms may have been altruistically designed to enhance fairness to specific groups, but race is a social construct that is not a proxy for genetics, may be fluid and context dependent, and may reflect social and environmental conditions rather than true causality.⁷ Despite high risk for poor outcomes, several race-based clinical treatment algorithms have failed to help racial and ethnic minorities who are often disproportionately affected by certain diseases, leading to lower organ transplant rates, higher rates of invasive procedures, or lower referral rates for specialty care.⁸ Others have expressed concern with the lingering effect of the historical legacy of spirometry that was used to justify subordinate status, the ethical impact of the continued use of race in reference lung function prediction equations, and the ambiguity of inclusion or non-inclusion.⁹⁻¹¹ Prior to the adoption of reference standards from the Global Lung Initiative in the US, lung function prediction equations were based on NHANES III data.^{12,13} Without consideration of the influence of socioeconomic status on lung function, Hankinson et al found that the forced expiratory volume in 1 s (FEV₁) and the forced vital capacity (FVC) was 12–15% lower in African Americans compared to Caucasians.¹² Potentially, symptomatic African Americans could still be labeled as having normal lung function. In the past, a correction factor (also known as race adjustment or race norming) was applied to the values derived from Caucasians for use in minority populations, but this is no longer practiced.

Previously, major professional societies supported race-based testing and arguments exist on both sides of the issue.¹⁴⁻¹⁶ It has been stated that this too represents a form of race norming.¹¹ Associated with historic injustices, race is a socio-political construct. The continued inclusion of race in clinical calculators may not allow disentanglement from the effects of historic racism or address the inherent contribution of social determinants of health. Because of these issues, the American Thoracic Society issued an official statement recommending replacing race and ethnicity-specific equations with race-neutral average reference equations.¹⁷ This statement also recommended exhaustively re-evaluating the impact of this change along with more research and education. Additionally, a multi-society expert panel reviewing the evidence supporting the use of race- and ethnicity-based reference equations, the implications of their use or non-use, and the identification of research gaps and questions also supports this conclusion.¹⁸ In the past, race-specific algorithms were presumed to enhance accuracy, but recent research has challenged this perception.

Materials and Methods

The aim of this review was to assess the existing literature and identify areas for further research regarding the clinical use of race-adjustment in lung function testing, primarily for the diagnosis and treatment of chronic obstructive pulmonary disease (COPD) and COPD-related phenotypes in adults. Our research inquiry focused on the potential negative consequences for African American patients with COPD when race is incorporated into pulmonary function prediction equations. Additionally, we investigated whether race adjustment has an impact on relevant clinical outcomes and whether it contributes to underdiagnosis or misclassification. This review was performed using the Joanna Briggs Institute Method for Scoping Reviews.¹⁹

Inclusion Criteria

This review primarily focused on relevant studies involving Black or African American adults who have COPD or related phenotypes. We used the age criterion for adulthood, beginning at age 18, for screening purposes only. Patients with COPD or COPD-related phenotypes in our scoping review were \geq age 40. The age ranges were broader in participants in the Global Lung Initiative, where new and existing reference equations were calculated in adults and children. We specifically looked for published analyses that clearly outlined the reference equations used in pulmonary function tests and specified how COPD was defined using spirometric criteria. We also examined how race adjustment in lung function testing for the diagnosis and management of COPD could affect clinically relevant outcomes, such as mortality and severity. All types of interventions and study designs were considered, including gray literature, conference abstracts, review studies, and opinion pieces. The analysis included published and unpublished studies conducted in the United States and written in English, with no time limit.

Search Strategy and Study Selection

A structured literature search was implemented in PubMed/MEDLINE, Elsevier EMBASE, SCOPUS, and Clarivate Web of Science Core Collection, from the inception of each database through December 2023 ([Appendix A](#)). The search was executed using standardized indexing terms and keywords: chronic obstructive pulmonary disease, Forced Expiratory Volume, Respiratory Function Tests, Vital Capacity, Blacks, Black or African American, Race, and admixture. All results were exported to End-Note. The medical librarian used the duplicate finder in EndNote. After conducting the search, all identified records were gathered and uploaded to Covidence, and re-reviewed for duplicates. Two independent reviewers (MK and MF) screened the titles and abstracts of the identified records based on the inclusion criteria to select studies for a more thorough review. Full-text articles were carefully evaluated against the inclusion criteria. In cases where the two reviewers could not agree on the inclusion of a study, a discussion was held with a third reviewer (GW). The grey literature studies that were identified were screened using similar criteria, and duplicates were removed to ensure no overlap with the databases. Reference lists from retrieved articles were also reviewed.

Data Extraction and Analysis

Two independent reviewers (SD and MP) extracted data from the articles included in the scoping review using the data extraction tool/charting form developed specifically for this study by the research team ([Appendix B](#)). The extracted data consisted of general information such as study titles, contact details of lead authors, and the country where the study was conducted. It also included characteristics of the studies, such as their aims, study design, population description (eg, inclusion/exclusion criteria and smoking history), and participant characteristics (eg, age, percentage of African American participants, and percentage of female participants). Outcomes such as diagnosis, mortality, and exacerbations were recorded. Additionally, the reference standard used for race correction was extracted.

Data extracted by both reviewers were compared, and any discrepancies were resolved through discussion with a third reviewer (MF) until a consensus was reached. Extracted data were categorized and summarized based on key themes and similarities within each category. All authors participated in the interpretation and synthesis of the data.

Our process of search and study selection through review and inclusion in the review is presented in a PRISMA diagram ([Figure 1](#)), and qualitative themes are presented as summaries. As the aim of our scoping review is to provide a high-level descriptive overview, we elected not to conduct a critical appraisal of included sources of evidence.

Results

[Figure 1](#) presents a flow chart of study selection and a checklist has been submitted in [Appendix C](#) of 868 identified articles, 13 duplicate articles were removed. Of 855 articles screened, 818 were removed as they were not pertinent to the focus of our study. We then assessed 37 full-text articles for eligibility. Thirty-one articles were excluded as they did not specifically evaluate race-correction of PFTs on the diagnosis of COPD, COPD-related functional outcomes, or radiographic phenotypes. In the December 2023 update, we retrieved 188 articles from which 2 additional duplicates were identified. Ultimately, 17 studies were imported for full-text review. These 17 publications were further culled as 3 were previously included; 4 were editorials, opinion pieces, or replies; 4 were COPD-related but did not fit our inclusion criteria; 1 was a review of a previously included study; and 1 additional duplicate was identified. Combining the searches, the final data extraction involved 10 publications in the United States between 2016 and 2023. Seven of the 10 studies involved prospective cohorts and three studies involved convenience samples derived from electronic medical records. Of the final 10 studies, 4 were conference abstracts and the remaining 6 were peer-reviewed. A summary of the studies may be found in [Table 1](#).

Regan et al analyzed a group of self-identified non-Hispanic White and non-Hispanic African American ever-smokers ($n = 2246$) from the COPD Gene Study, matched by age ± 3 years and smoking status.²⁸ The authors analyzed individuals with normal, race-specific spirometry ($FEV_1/FVC > 0.7$ and $FEV_{1\%}$ predicted $> 80\%$) and compared spirometry measurements using the lower limit of normal (LLN) and % predicted to actual measured volume. They considered social deprivation to be a factor affecting spirometry and therefore estimated mean (SD) FEV_1 and FVC for participants above and below the midpoint for the Area Deprivation Index (ADI). The ADI ranges from 0 to 100 with higher scores

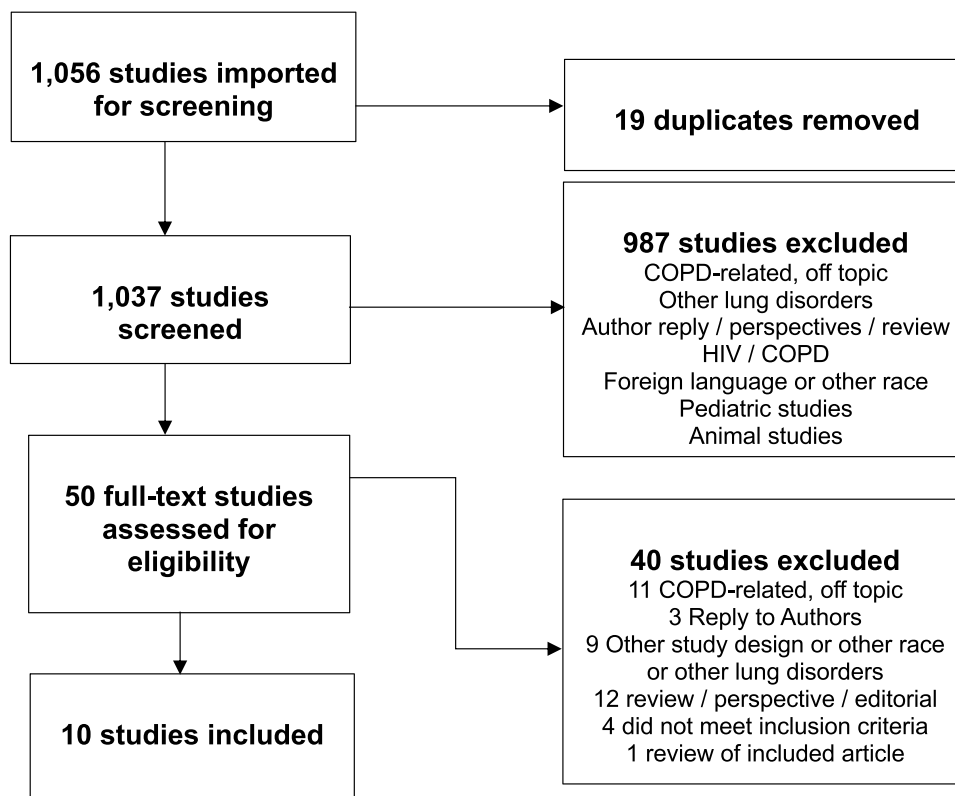


Figure 1 Flowchart of Study Selection.

reflecting worse deprivation.³⁷ Additionally, they also categorized participants using the 2019 COPDGene criteria utilizing exposure, symptoms, spirometry, and quantitative CT measures to ultimately classify individuals as having no COPD, possible, probable, or definite COPD.²⁹ In this conference abstract report, African Americans were more likely to report dyspnea (MMRC > 2, 35% vs 21%, $p < 0.0001$), have reduced 6-min walk distances (1356 vs 1551 ft., $p < 0.0001$), use respiratory medications (18% vs 14%), and report severe exacerbations (7% vs 5%). Spirometric measurements were lower in African Americans, by LLN or actual values, but higher when race-specific %predicted values were used. African Americans had lower socioeconomic status measured by ADI, income, or education. However, regardless of race, worse ADI is associated with lower FEV₁ [2.79 (0.68) vs 2.88 (0.67)] and FVC [3.54 (0.87) vs 3.70 (0.89)]. Using the 2019 COPDGene classification, fewer African Americans were reclassified as having no evidence of COPD and more African Americans were re-classified as possible or probable COPD.

Brems et al compared race-specific to multi-racial/universal spirometric approaches to assess differences in COPD severity or diagnosis.²⁷ An observational cohort composed of individuals \geq age 30 years, $n = 15,412$ [69% White and 31% Black], was developed from electronic medical records and spirometry from the Johns Hopkins COPD Precision Medicine Center of Excellence. In this abstract, the authors calculated pre-bronchodilator LLN and %predicted values for FEV₁, FVC, and FEV₁/FVC using race-specific Global Lung Initiative (GLI) and multi-racial/universal GLI-Other reference equations, with spirometry categorized as mild, moderate, severe, or very severe. Compared to the race-specific GLI approach, universal equations resulted in a mean FEV₁% predicted decrease (4.97 ± 1.84) in White patients vs an increase (5.41 ± 1.93) in Black patients. Race-specific equations were associated with obstruction in 40% vs 37% compared to 46% vs 43% of White to Black patients consecutively using universal equations. With universal equations, 12% of White patients were classified as less severe than when using race-specific equations, while 17% of Black patients increased in severity.

Chronic lower respiratory disease (CLRD), asthma, COPD, chronic bronchitis, and emphysema hospitalizations or deaths were analyzed by Elmalech-Sachs et al.²² These authors analyzed data from longitudinal follow-up of 3344 adults

Table 1 Study Characteristics

First Author	Type	Study Type	Participants	Sample Size	COPD Definition	Outcome
Checkley ²⁰ 2016	Peer-reviewed	Cohort	COPDGene Study ²¹	n=3772 White 67% AA 33%	Post-bronchodilator FEV ₁ /FVC < GLI race-specific LLN FEV ₁ / FVC < 0.7	Use of race-free absolute post-bronchodilator FEV ₁ or FEV ₁ /height ² performed as well as GOLD criterion or GLI Z-scores on COPD-related physiologic outcomes. Race-specific spirometry reference equations did not improve prediction of longitudinal COPD events and all-cause mortality.
Elmaleh-Sachs ²² 2021	Peer-reviewed	Cohort	MESA Lung Study ²³	n=3344 White 35% Black 25% Hispanic 23% Asian 17%		
Baugh ²⁴ 2022	Peer-reviewed	Cohort	Current and former smokers from the SPIROMICS Study ²⁵	n=2652 White 80% AA 20%	This study analyzed COPD-related outcomes.	Race-specific equations underestimated metrics of COPD severity (CAT, SGRQ, and airway wall thickness in African Americans.
Liu ²⁶ 2022	Peer-reviewed	Cohort	Cardia Study Participants	n=2674 White 53% Black 47%	This study analyzed individuals deemed to have normal spirometry.	Radiographic emphysema was often present before spirometry was abnormal, especially in Black men.
Brems ²⁷ 2022	Conference abstract	Cohort	Black and White individuals ≥ 30 years of age with pre-bronchodilator spirometry	n=15,412 White 69% Black 31%	FEV ₁ /FVC < LLN	The use of universal equations, compared to race-specific equations, resulted in shifts in disease classification, especially disease severity.
Regan ²⁸ 2022	Conference abstract	Matched case-control	Age and smoking history matched group from the COPDGene Study	n=2246 White 50% Black 50%	COPDGene 2019 Criteria ²⁹	Despite normal race-based spirometry, African Americans were more likely to have dyspnea, shorter 6MWD, use respiratory medicines, and have exacerbations.
Brems ³⁰ 2023	Conference abstract	Cohort	EMR study of COPD exacerbations	n=15,192 White 69% Black 31%	COPD Exacerbations	Compared Race-specific GLI vs GLI Other. Race-specific predictions associated Black race with COPD exacerbations.
Lowe ³¹ 2023	Conference abstract	Cohort	EMR study of transplant	n=30,885 White 85% Black 15%	FEV ₁ % predicted at different spirometric severity levels (20%, 30%, 50%, 80% predicted) GOLD 0–4 ⁵⁰	NHANES III NHB and NHW reference equations were used to determine re-classification of NHB patients at different severity thresholds, pulmonary referrals, and transplant referral orders
Non ³² 2023	Peer-reviewed	Cohort	NHANES (2007–2012) and COPDGene Study participants	Non-smoking subjects NHANES (n=3700) COPDGene (n=419) Smoking subjects NHANES (n=785) COPDGene (n=9419)		Race-specific reference equations were not superior to race-neutral race-free equations in predicting CT phenotypes or dyspnea. Race-neutral equations re-classified 19% of Black participants into more severe GOLD classes.
Regan ³³ 2023	Peer-reviewed	Cohort	COPDGene Study	n=10,132 White 67% Black 33%	FEV ₁ /FVC < 0.7 ³⁴ GOLD 0 (FEV ₁ /FVC < 0.7 and FEV ₁ %predicted ≥ 80%) PRISm ^{35,36}	Despite exacerbations, symptoms, and worse quality of life, race-specific equations classified Black participants as less impaired compared to race-reversed equations or multiethnic (GLI-Global and GLI-Other) equations

in MESA Lung, a multi-racial population-based cohort derived from the MESA Study.³⁸ Though this study was not restricted to COPD, the authors determined that using pre-bronchodilator spirometry and excluding individuals with prior chronic lower respiratory disease by physician diagnosis or hospitalizations, race/ethnic-based approaches (GLI-race) were not superior to race/ethnic-neutral (GLI-Other) approaches in terms of predicting CLRD events and mortality.

A statistical comparison of race-specific vs universal modeling approaches for FEV₁, FVC, and other COPD outcomes [COPD Assessment Test (CAT), St. George's Respiratory Quotient (SGRQ), CT % emphysema, airway wall thickness, and 6-min walk distance] was performed by Baugh and colleagues using GLI-Other vs race-specific NHANES non-Hispanic White reference values.²⁴ The authors also analyzed which factors contributed to absolute FEV₁ including covariates that reflect socioeconomic status and childhood exposures. With race-specific equations, African Americans had better lung function compared to non-Hispanic Whites (FEV₁ 76.8% vs 71.8% predicted, $p = 0.02$). Using universally applied equations, African Americans had worse lung function. Using Hankinson's NHANES III non-Hispanic White equation, FEV₁ was 64.7% vs 71.8%, $p < 0.001$. Using GLI-Other, FEV₁ was 70% vs 77.9%, $p < 0.001$. Prediction errors were lower with universally applied equations compared to race-specific equations for FEV₁%predicted, CAT, SGRQ, and airway wall thickness, $p < 0.001$ consecutively. Like Regan et al, African American participants had more adversity. However, this study found that less adversity was only associated with better FEV₁ in non-Hispanic White participants, p for interaction = 0.041.

Liu et al performed a secondary data analysis of the Coronary Artery Risk in Young Adults (CARDIA) Lung Study ($n = 2674$).²⁶ This cohort was derived from the CARDIA Study that was initiated in 1985–1986.³⁹ These authors analyzed spirometry obtained in 2015–2016 and chest CT scans performed in 2010–2011 in a biracial cohort of adults (aged 50–59 years) with a goal of determining the prevalence of visual emphysema in individuals with normal spirometry and whether this differed by race. Normal spirometry was defined as FEV₁/FVC > 0.7 or > LLN and an FEV₁ between 80–99%predicted or between 100–120%predicted. Race-specific GLI and GLI-Other equations were utilized. Visual emphysema (centrilobular, paraseptal, or both) was utilized rather than quantitative emphysema, as this was felt to be consistent with current clinical practice. CT images were evaluated by three expert readers. Visual emphysema was present in 4% of participants with race-specific FEV₁ between 100–120%predicted. This finding was especially true for Black men compared to White men, 13% vs 2.2% [6.4 (CI 2.2–18.7)].

Checkley et al compared absolute post-bronchodilator FEV₁ and FEV₁/height², measures that do not require reference equations, to GLI race-adjusted equations, Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion, and GLI Z-scores of post-bronchodilator FEV₁ to predict 6MWD, SGRQ, the 36-item Short-Form Health survey (SF-36) physical health component score, and the MMRC Dyspnea Score in 3772 participants with COPD from the COPD Gene Study.^{20,21} Absolute FEV₁ and FEV₁/height² had similar prediction errors for 6MWD, SGRQ, SF-36, and MMRC compared to GOLD criterion. Similar prediction errors were found for absolute post-bronchodilator FEV₁ and FEV₁/height² compared to GOLD criterion, with similar predictive accuracy when compared to Z-scores except for 6MWD where absolute FEV₁ performed better. These two measures were considered easy, accessible, and available in situations where prediction equations do not exist.

Brems et al extended their work with an analysis of the impact of lung function measured by race-specific (GLI) vs race-neutral (GLI-Other) reference equations on the prospective development of COPD exacerbations.^{27,30} In this analysis of electronic medical records from a single center, COPD exacerbations were serious, defined by ICD-10 codes of emergency room visits or hospitalizations in individuals \geq age 30 years where spirometry had been performed within a year of resource utilization. Multivariable logistic regression models were used to estimate the probability of >1 exacerbation. These models were controlled for age, race, sex, body mass index (BMI), FEV₁%predicted, and controller medications. Smoking status and social determinants of health were not reported in this conference abstract. Though the mean number of exacerbations per person-year (0.06 vs 0.07, $p = 0.15$) was similar in both races. The use of race-specific GLI reference equations resulted in an association of Black race with exacerbations (OR 1.31, 95% CI 1.08–1.59) where the use of GLI-Other reference equations did not (OR 0.99, 95% CI 0.82–1.20). The authors felt that the race-neutral approach, where outcomes did not differ between the races analyzed, supported the race-neutral approach.

Listing for lung transplantation for patients with COPD is recommended for FEV₁ < 20% predicted and referral for evaluation when the FEV₁ is < 25% predicted.⁴⁰ Lowe et al evaluated Cleveland Clinic medical records to assess whether

Black patients at different spirometric severity levels would be reclassified using NHANES III NHB and NHW reference equations.³¹ Additionally, they analyzed rates of referral for pulmonary consultation and transplant referral orders. They used thresholds of FEV₁ at 20%, 30%, 50%, and 80% predicted to determine the proportion of NHB patients who were above the threshold using NHB reference values and below the same threshold when calculations were performed with NHW values. The authors found that when using the NHW prediction equations on NHB COPD patients, the potential for reclassification was higher with higher FEV₁ values. They found no difference in pulmonary referral rates or lung transplantation referral rates regardless of re-classification. They acknowledged that reliance on a single measure might not accurately reflect an individual's true lung function (Table 2).

Absent race, Non et al generated a new race-free reference equation for FEV₁ and FVC using data from non-smokers, the COPDGene Study (n = 419) and the NHANES III cohort (n = 3700). These authors also developed race-specific reference equations from the same cohorts. The new equations and the race-specific NHANES III reference values,¹² GLI race-specific equations and GLI-Other (considered race-neutral using a universal race-correction),⁴¹ and GLI-Global reference equations (employing inverse probability weighting for each racial group)⁴² were applied to former smokers from the NHANES III cohort and in current and former smokers from the COPDGene Study. Specifically, the authors analyzed how the FEV₁% predicted derived from these approaches contrastingly affected GOLD severity⁴³ in both smoking groups and analyzed quantitative chest CT phenotypes (emphysema, air trapping, and airway wall thickness) and dyspnea in the COPDGene Study participants. Using a variety of statistical approaches, they found that race-specific equations resulted in higher FEV₁% predicted values in Black participants by 7–11% compared to White participants.⁴⁴ They found that race-specific equations did not offer a substantial clinical advantage to the prediction of self-reported breathlessness or prediction of the presence of quantitative CT phenotypes. Additionally, these authors found that removing race/ethnicity from the prediction equations mainly reclassified individuals with less severe impairment, potentially enhancing earlier detection.

Compared to non-Hispanic White participants, Black participants in the COPDGene Study report more exacerbations, more dyspnea, and worse quality of life.³³ Race-specific prediction equations classified these Black participants as less impaired with lower GOLD stages, but average raw spirometry values were lower in each GOLD stage. The use of race-reversed (race-specific White) equations re-classified smoking-exposed Blacks who did not meet the GOLD criteria for COPD, from normal to PRISm,^{35,36} a category considered to be a precursor condition for some individuals.³⁴

Inclusion of African Americans

Even though the aim of the study was to evaluate race adjustment of lung function testing, the study with the highest percentage of African Americans involved in each patient population was Regan et al's matched study with 1123/2246 (50%).²⁸ The lowest percentage of African Americans was reported in Baugh's study (20% vs 80%).²⁴

Race Correction Reference Standards

The Global Lung Function Initiative reference equations were initially published in 2012 and have evolved as a resource for standardized lung function reference values for spirometry.⁴¹ GLI race-specific reference equations exist for Caucasian (White European), African American, South East Asian, and North East Asian ancestries. Collaborative professional society interpretive strategies using GLI have been published.¹⁴ The GLI-Other (2022) equation averages reference values from several racial groups. These reference values are the result of international collaboration between medical providers, researchers, and other stakeholders. The most recent update occurred in 2017 where reference equations for diffusing capacity (also known as transfer factor) for carbon monoxide, derived in White participants, were published.⁴⁵ Bowerman et al reported that the most recent iteration, GLI-Global “reflects the wide range of lung function observed within and between populations”.⁴² These authors used inverse-probability weighting to offset the potential bias that could result from over-representation of any racial group. Additionally, NHANES III data were re-analyzed with sitting height and the Cormic Index (sitting height/height) to determine if body proportions predicted lung function better than race and ethnicity. Sitting height was highest in Whites, but the Cormic index was similar across ethnic groups. Previously, differences in lung function in African Americans were attributed to trunk-to-leg ratios, but this study found that sitting height did not explain the differences in spirometry between the NHANES III racial groups. GLI-Global (2022) equations, considered race-neutral, had similar model fit to GLI-Other (2012) equations but with

Table 2 Race-Based Spirometry and Lung Transplant Eligibility

COPD Severity Classes	Total by Racial Group		N (% Racial Group)	Pulmonary Referral %	Transplant Referral %
Mild COPD FEV ₁ > 80% predicted	NHB = 1588 NHW = 7465	NHB unchanged	718 (45.2%)	413 (58%)	4 (0.6%)
		NHB < 80% predicted using NHW equations	870 (54.8%)	528 (61%)	8 (0.9%)
Moderate COPD FEV ₁ > 50% predicted and < 80% predicted	NHB = 2040 NHW = 11,432	NHB unchanged	1463 (71.7%)	882 (60%)	30 (2.1%)
		NHB < 50% predicted using NHW equations	577 (28.3%)	378 (66%)	7 (1.2%)
Severe COPD FEV ₁ < 50% predicted and > 30% predicted	NHB = 858 NHW = 5222	NHB unchanged	698 (81.4%)	420 (60%)	17 (2.4%)
		NHB < 30% predicted using NHW equations	160 (18.6%)	101 (63%)	5 (3.1%)
Very Severe COPD FEV ₁ < 30% predicted and > 20% predicted	NHB = 203 NHW = 1393	NHB unchanged	155 (76.4%)	95 (61%)	3 (1.9%)
		NHB < 20% predicted using NHW equations	48 (23.6%)	23 (48%)	1 (2.1%)
Severe and Transplant Eligible FEV ₁ < 20% predicted	NHB = 62 NHW = 622	NHB unchanged	62	24 (39%)	4 (6.5%)
		NHW	622	142 (23%)	19 (3.1%)

Notes: This table was modified from Lowe, K. E. et al. *J Heart Lung Transplant* 2023;42:45.³¹

Abbreviations: 6MWD, six-minute walk distance; CAT, COPD Assessment Test; COPDGene, Genetic Epidemiology of COPD: COPDGene®, AA, African Americans; MESA, The Multi-Ethnic Study of Atherosclerosis; FEV₁, forced expiratory volume in one second; GLI, Global Lung Initiative; GLI-Global, Global Lung Initiative – Global; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NHANES III, National Health and Nutrition Examination Survey III (1988–1994); SGRQ, St. George's Respiratory Questionnaire; SPIROMICS, Subpopulations and Intermediate Outcome Measures in COPD Study; EMR, electronic medical record; NHB, non-Hispanic Black; NHW, non-Hispanic White.

wider limits of normal. Although GLI-Global equations provide a single benchmark to standardize lung function measurements against sex, standing height, and age, the wider limits of normal were acknowledged to reflect greater uncertainty and that pathological reductions in lung function could still be labelled as healthy.

How Race-Specific Values Vs Raw Values Affect Outcomes

None of the final 10 studies included race-neutral reference equations alone. Rather, 8 of the 10 studies analyzed race-specific and race-neutral prediction equations,^{20,22,24,26,27,30,33,42} whereas two studies analyzed race-adjusted data only.^{28,31} These studies evaluated a variety of physiological, functional, and clinically important metrics for disease classification such as FEV₁, imaging characteristics,^{24,26,28,32,33} 6-min walk distance (6MWD),^{20,24,28,33} quality of life scores,^{20,24,33} MMRC dyspnea score,^{20,28,32} and chronic lower respiratory disease (CLRD) hospitalizations, exacerbations, or death.^{22,30,33} Diffusing capacity (DLCO), an indirect measure of lung tissue available for gas exchange and an important component of emphysema diagnosis, is not race-adjusted in the US. As such, this parameter was not evaluated in this scoping review. Most of the studies found that race-adjustment reduced the sensitivity for COPD diagnoses and morbidity for African American patients. Baugh et al found that removal of race from lung function equations resulted in a reduction in FEV₁%predicted in African Americans.²⁴ Using race-adjusted prediction algorithms, Regan et al reported that FEV₁ and FVC were higher for African-Americans, lacking consistency with reports of increased dyspnea, less exercise tolerance, and more severe exacerbations.²⁸ Brems et al observed that the use of different prediction equations changed COPD severity classifications.²⁷ Finally, Elmalech-Sachs et al found that race/ethnic-based approaches were not superior to race/ethnic-neutral approaches in terms of predicting chronic lower respiratory disease events and mortality.²² In summary, the use of race-specific equations in African American patients with COPD leads to inadequate characterization and misclassification of severity.

Discussion

The consensus from this scoping review is that race-correction may have negative consequences for the diagnosis of COPD or severity assessments in African American patients. Our scoping review shows that race-specific equations failed to sufficiently reflect symptomatology, resource utilization, and objective impairment, leading to misclassification of severity of COPD with the potential of delaying early diagnosis and appropriate treatment.

Adoption of new pulmonary function reference equations requires in-depth analysis of the implications of such changes. For instance, we reviewed studies that evaluated statistical considerations like model fit, changes in diagnostic or severity classifications for COPD, or prediction of important COPD-related outcomes like symptoms, imaging, and mortality. The removal of race had a variable effect on diagnostic and severity classifications with discordance by race. For African Americans, the elimination of race-adjustment improved correlation with respiratory symptoms and physiologic impairment that preceded thresholds for impairment based on race-specific algorithms. The need to eliminate race-specific reference equations is obvious, but the impact of race-neutral reference equations varies by race. This uncertainty is a considerable limitation as fairness may improve with one group but has the opposite effect on another.

Globally and from a precision medicine viewpoint, the GLI lacks data from several of the world's other diverse populations.⁴² The reference values in race-neutral equations also do not represent the pulmonary function of the ideal adult. Compared to the GLI-Global equations where care was taken not to overrepresent any racial group, lung volumes and DLCO cannot be integrated into race-neutral equations, as most of the existing data were derived from White patients. PFT manufacturers need to educate relevant stakeholders, like providers and patients, on these limitations.

We agree that there are knowledge and practice gaps on both sides of this issue. For African Americans, the current recommendation to adopt agnostic reference equations may have unknown downstream consequences including, but not limited to, surgical eligibility for lung resection and transplantation, prediction of post-operative lung function, employability in specific occupations, insurability, or potential exacerbation of existing disparities.^{46–48} Bhakta et al outlined several existing areas for future research, as follows: 1) research to ascertain the determinants of pulmonary function in the absence of early-life risk factors and social deprivation; 2) are White-specific reference values of value as an unadjusted benchmark for individuals existing ideally without the unmeasured effects of racism; 3) what test or anatomic measurement better approximates lung size; 4) the mechanism(s) underlying epigenetic modifications due to environmental influences on gene expression.¹⁷

Comparing pulmonary function tests obtained with race-specific to race-neutral algorithms, Moffett et al analyzed a cross-sectional cohort of 8431 Black (33%) and White (67%) individuals from a single academic center.⁴⁹ Race-neutral equations resulted in an approximately 10% increase in Blacks diagnosed with restrictive impairment and an absolute 3.3% increase in the diagnosis of nonspecific ventilatory impairment. The results were the opposite in Whites. The authors identified that race-neutral equations increased the number of respiratory diagnoses in Blacks along with a concurrent increase in disease severity, but the downstream, real-world impact on referral patterns, treatment, and diagnosis remain to be determined. The latter study was not focused on obstructive lung impairment but demonstrates the uncertainty surrounding this paradigm change and the need to determine the clinical significance of these changes.

We acknowledge that scoping reviews are not as comprehensive as systematic reviews, may not be generalizable, do not assess the quality of the included studies, and may reflect the biases of the authors.⁵⁰ Additionally, the size of the research team has also been found to affect the conduct of the review process.

Conclusion

The consensus of this scoping review is that race-adjusted prediction equations often lead to misclassification of COPD in African Americans, impacting outcomes and clinical decision-making. This review provides support that race-specific reference values do not enhance the prediction of relevant COPD outcomes like health status, exercise capacity, COPD events, or quantitative imaging metrics of COPD in this population.⁴⁴

Our intention in performing this scoping review was to assess the extent of the literature, identify knowledge gaps, and ascertain areas for potential research. This review determined that several areas of future research should be pursued. There is a need to explore new predictive strategies incorporating a combination of parameters like biomarkers and lung

imaging or whether the inclusion of better anthropometric measurements enhances prediction of lung function. Additionally, the optimal reference equation has not been determined. More context from diverse patient populations needs to be considered when designing race-neutral equations in the future and the impact of race-specific equations on diagnoses of other chronic respiratory diseases should be explored. Clinical decision tools based on empirical data derived from well-designed studies with adequate representation of relevant participants may not be applicable to all global populations. We recognize that a one-size-fits-all approach may not be optimal. At the individual patient level, the accuracy of a diagnosis may be nuanced and involve factors in addition to whether one is above or below a certain threshold. This reinforces the need for intentionality around enhancing diversity in clinical studies, which is a moral imperative.

Data Sharing Statement

Data reported in this scoping review is available upon request to Dr. Marilyn G. Foreman.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work

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