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Assessing differences in inhaled corticosteroid response by self-reported race-ethnicity and genetic ancestry among asthmatic subjects

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Background: Inhaled corticosteroids (ICSs) are the preferred treatment for achieving asthma control. However, little is known regarding the factors contributing to treatment response and whether treatment response differs by population group.
Objective: We sought to assess behavioral, sociodemographic, and genetic factors related to ICS response among African American and European American subjects with asthma.
Methods: Study participants were part of the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE). The analytic sample included asthmatic subjects aged 12 to 56 years with greater than 12% bronchodilator reversibility and percent predicted FEV_1 of between 40% and 90%. Participants received 6 weeks of inhaled beclomethasone dipropionate. The primary measure of ICS response was a change in Asthma Control Test (ACT) score; the secondary measure was a change in prebronchodilator FEV_1. Adherence was measured with electronic monitors. Genetic ancestry was estimated for African American participants by using genome-wide genotype data.
Results: There were 339 study participants; 242 self-identified as African American and 97 as European American. Baseline ACT score, percent predicted FEV_1, degree of bronchodilator response, and ICS adherence were significantly associated with ICS response. A baseline ACT score of 19 or less was useful in identifying those who would respond, as evidenced by the significant dose-response relationship with ICS adherence. Neither self-reported race-ethnicity among all participants nor proportion of African ancestry among African American participants was associated with ICS responsiveness.
Conclusions: Our findings suggest that baseline lung function measures and self-reported asthma control predict ICS response, whereas self-reported race-ethnicity and genetic ancestry do not. (J Allergy Clin Immunol 2016;137:1364-9.)

Key words: *Inhaled corticosteroids, Adherence, medication, asthma, African Continental Ancestry Group, respiratory function tests*

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Repeated studies have demonstrated that long-term adherence to inhaled corticosteroid (ICS) medication among asthmatic subjects is poor.[1-3] The consequence of this nonadherence is an increased risk for severe asthma exacerbations, including the need for hospitalization.[4,5] Unaccounted for differences in medication adherence can also confound the relationship between treatment and response,[6] thereby obscuring the true effect of treatment. For example, previously described differences in ICS adherence between African American and European American subjects could result in inaccurate inferences regarding treatment effect.[7,8]

We have previously shown that after accounting for medication adherence, ICS response did not vary among African American subjects based on genetic ancestry (ie, the proportion of African ancestry vs European ancestry).[9] These findings implied that as a whole, a genetic contribution to treatment-related differences between African American and European American subjects with asthma is likely to be small.

In the current analysis we extended our earlier findings by expanding our study population of African American subjects and by including a group of European American subjects with asthma. This expanded study population allowed us to directly assess whether ICS treatment response differed by either self-reported race-ethnicity or genetic ancestry. All study subjects were part of the Study for Asthma Phenotypes and Pharmacogenomic Interactions

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Abbreviations used
ACT: Asthma Control Test
BMI: Body mass index
ICS: Inhaled corticosteroid
SAPPHIRE: Study for Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity

by Race-ethnicity (SAPPHIRE), had similar enrollment criteria, and received the same 6-week ICS treatment course.

METHODS

Study population

The study population was comprised of participants in the Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-ethnicity (SAPPHIRE), which was approved by the Institutional Review Board at Henry Ford Health System. Potentially eligible subjects were first identified through the medical record based on age (12-56 years), prior diagnosis of asthma, and lack of excluding diagnoses (ie, chronic obstructive pulmonary disease, congestive heart failure, or both). Subjects who met these criteria and who lived in southeast Michigan were invited for a clinical evaluation. Study participants (or their guardians in the case of minors) provided written consent before evaluation and study enrollment. Evaluation consisted of a staff-administered survey, vital sign and anthropomorphic measurements, and lung function tests. Race-ethnicity was based on subjects self-report at the initial study visit.

Lung function testing was performed with a Fleisch-type pneumotachometer in accordance with 2005 American Thoracic Society/European Respiratory Society guidelines for spirometry.[10] Bronchodilator response was defined as a greater than 12% improvement in FEV_1 after albuterol administration. Albuterol sulfate hydrofluoroalkane (360 μg, 4 puffs) was administered through a metered-dose inhaler by using a spacer device (AeroChamber Plus Flow-Vu; Monaghan Medical, Plattsburgh, NY), and lung function was measured 15 minutes later. Patients with 12% or less improvement in FEV_1 after the first albuterol dose received a second dose (360 μg for those ≥18 years and 180 μg for those <18 years), and lung function was remeasured after another 15-minute wait.

To receive 6 weeks of observed ICS treatment, study participants had to meet the following additional criteria: measured FEV_1 of between 40% and 90% of predicted value (based on age, sex, height, and race-ethnicity),[11] greater than 12% maximum bronchodilator reversibility, no smoking in the preceding year and less than 10 pack years of total smoking, no ICSs or systemic corticosteroids used in the preceding 4-week period, and not pregnant and not planning to become pregnant during the 6 weeks of ICS treatment. Patients in the SAPPHIRE cohort who both met these criteria and agreed to treatment received a 6-week course of beclomethasone dipropionate hydrofluoroalkane (320 μg/d administered as 2 puffs twice a day). Patients self-administered the ICS medication through a metered-dose inhaler and use of the previously described spacer device. At the end of the 6-week treatment period, patients returned to complete another staff-administered questionnaire and undergo lung function testing.

Assessment of exposure and outcomes

Patient medication adherence was assessed by using a DOSER-CT device (Meditrack, Easton, Mass). The DOSER-CT was attached to the metered-dose inhaler, and it counted each time that the inhaler was actuated. Adherence was calculated as the total number of recorded actuations divided by the product of the number of days between visits and 4 (the prescribed number of ICS puffs per day).

To assess changes in the level of asthma control, we measured differences in Asthma Control Test (ACT; QualityMetric, Lincoln, RI) responses before and after the 6-week course of ICS therapy. We also assessed changes in prebronchodilator FEV_1 between these time points.

Genome-wide genotype data were collected for the African American SAPPHIRE participants in the treatment trial by using commercial arrays (Affymetrix, Santa Clara, Calif). We have previously used these data to calculate the proportion of West African ancestry (heretofore called African ancestry) in these participants.[12] Briefly, the software program LAMP was used to estimate ancestry at each locus.[13,14] We then estimated each patient's global genetic ancestry (ie, proportion of African ancestry) as the proportion of African alleles among genotyped autosomal single nucleotide polymorphism locations.

Statistical analysis

The primary outcome of the study was ICS response, as measured by the change in ACT score between the initial visit and the 6-week follow-up visit after ICS treatment (ie, the composite $ACT_{[6\ weeks]} - ACT_{[initial]}$). The secondary outcome was the percentage change in prebronchodilator FEV_1 between these time points (ie, $FEV_{1[6\ weeks]} - FEV_{1[initial]}/FEV_{1[initial]}$). Linear regression was used to assess the relationship between both outcome variables and the following dependent variables: patient age, sex (coded male = 0, coded female = 1), self-reported race-ethnicity (coded European American = 0, coded African American = 1), body mass index (BMI), baseline percent predicted FEV_1, baseline ACT score, and ICS adherence. Both age and BMI were modeled for each unit increase (ie, years and kilograms per meters squared, respectively) but were aggregated into 10-unit increments for presentation in the tables. Based on the original validation of the ACT by Nathan et al,[15] we also dichotomized the composite ACT score at a cut point of 19 (ie, patients with scores ≤19 were considered to have "not controlled" or "uncontrolled" asthma and patients with scores ≥20 were considered to have "controlled" asthma). Similarly, we dichotomized lung function at 70% of predicted FEV_1 based on the midpoint for persistent moderate asthma in the current US asthma guidelines.[16] Therefore we stratified our models by both baseline ACT score (ie, ≤19 and ≥20) and baseline percent predicted FEV_1 (ie, <70% and 70% to 90% [90% was the upper limit in the treatment group]) to assess the relationship between exposure variables and outcomes within strata that are considered to separate clinically meaningful differences in asthma control and severity. Separate adjusted models limited to African American participants were used to assess the relationship between African ancestry and ICS response.

As a *post hoc* analysis, we assessed factors associated with achieving self-reported asthma control (ACT score ≥20) after 6 weeks of ICS treatment among all patients whose asthma was not controlled at baseline (ACT score ≤19). Logistic regression was used to assess the likelihood of achieving control as a function of the following variables: patient age, sex (coded male = 0, coded female = 1), self-reported race-ethnicity (coded European American = 0, coded African American = 1), BMI, baseline percent predicted FEV_1, and ICS adherence.

Analyses were performed with SAS statistical computing software (SAS Institute, Cary, NC).[17] A P value of less than .05 was considered statistically significant.

RESULTS

Three hundred thirty-nine participants in the SAPPHIRE cohort met the criteria and completed 6 weeks of observed ICS treatment; 242 enrollees identified themselves as African American, and 97 identified as European American. The characteristics of those subjects before and after stratification by race-ethnicity are shown in Table I. When compared with European American participants, African American study subjects were significantly younger (mean, 32.5 vs 36.8 years), had a higher BMI (mean, 32.8 vs 29.4 kg/m^2), and reported less well-controlled asthma (mean ACT score, 18.1 vs 20.0). African American subjects also had lower ICS adherence (mean, 0.76 vs 0.84), implying that on average, African American participants took 76% of their prescribed study dose compared with 84% in European American participants. The average estimated proportion of African ancestry in the African American participants was 79.9% ± 9.9% (SD), and the distribution is shown in Fig E1 in this article's Online Repository at www.jacionline.org.

TABLE I. Characteristics of SAPPHIRE study participants (n = 339)*

Variable	Overall (n = 339)	African American (n = 242)	European American (n = 97)	*P* value†
Age (y), mean ± SD	33.7 ± 13.8	32.5 ± 13.1	36.8 ± 14.9	<.01
Female sex, no. (%)	198 (58.4)	148 (61.2)	50 (51.6)	.11
Self-reported race-ethnicity, no. (%)				—
African American	242 (71.4)	242 (100.0)	—	—
European American	97 (28.6)	—	97 (100.0)	—
Proportion of African Ancestry	—	79.9 ± 9.9	—	—
BMI (kg/m^2), mean ± SD†	31.9 ± 9.5	32.8 ± 9.6	29.4 ± 8.8	<.01
ACT score at enrollment, mean ± SD‡	18.6 ± 5.1	18.1 ± 5.2	20.0 ± 4.5	<.01
Percent predicted FEV_1 at enrollment, mean ± SD	72.9 ± 12.7	73.5 ± 12.4	71.2 ± 13.2	.13
Bronchodilator response at enrollment, mean ± SD§	20.5 ± 15.3	20.4 ± 13.1	20.6 ± 19.8	.91
Change in ACT score, mean ± SD‖	3.1 ± 4.8	3.3 ± 4.9	2.4 ± 4.6	.11
Percentage change in prebronchodilator FEV_1, mean ± SD§	11.3 ± 18.1	10.6 ± 15.0	12.9 ± 24.2	.28
ICS adherence, mean ± SD; median; and interquartile range¶	0.79 ± 0.21; 0.84; 0.66-0.94	0.76 ± 0.22; 0.80; 0.61-0.93	0.84 ± 0.17; 0.89; 0.79-0.96	<.01

*Race-ethnicity was determined based on participant self-report.
†*P* value for comparison of African American and European American subjects.
‡ACT scores of 19 or less represent poor asthma control, whereas those of 20 or greater represent good control.
§Bronchodilator response is measured as the percentage change in FEV_1 after administration of inhaled albuterol.
‖Measured as the change between values measured at the time of enrollment and after 6 weeks of ICS treatment.
¶The mean, median, and interquartile range represent the proportion of the prescribed amount of ICS taken over 6 weeks of treatment.

Over the 6-week course of ICS treatment, the average improvement in ACT score and FEV_1 was similar among African American and European American participants. Improvements in ACT score were 3.3 and 2.4 points for African American and European American subjects, respectively ($P = .11$). Similarly, prebronchodilator FEV_1 improved by 10.6% and 12.9%, respectively ($P = .28$).

These above findings were supported in Table II, which examined the factors associated with change in ACT score and FEV_1 over the course of treatment. Self-identified race-ethnicity was not associated with change in ACT score or FEV_1, even after accounting for other variables, including ICS adherence. After adjusting for all of the variables shown, baseline ACT score (parameter estimate [β] = −0.71, $P < .01$), baseline percent predicted FEV_1 (β = 0.09, $P < .01$), degree of bronchodilator response (β = 0.05, $P < .01$), and ICS adherence (β = 2.38, $P < .01$) were significantly associated with the change in ACT score. In contrast, only degree of bronchodilator response was significantly associated with the change in FEV_1 with treatment in the multivariable model (β = 0.72, $P < .01$).

Because the effects of ICS adherence can differ with underlying asthma control or lung function, we stratified our analyses according to baseline ACT score (uncontrolled asthma = ACT score ≤19; controlled asthma = ACT score ≥20) and initial percent predicted FEV_1 (ie, <70% and ≥70%; Table III).[16] ICS adherence was found to be a significant predictor of ACT improvement among subjects with uncontrolled asthma at baseline (β = 3.95, $P = 0.04$). Although ICS adherence had a consistent and positive association with FEV_1 improvement in both lung function strata (percent predicted FEV_1 <70% and ≥70%), this association did not reach statistical significance in either group (β = 5.35, $P = .49$ and β = 4.19, $P = .22$, respectively). Both percent predicted FEV_1 at baseline (β = 0.11, $P < .01$) and degree of bronchodilator response (β = 0.09, $P < .01$) were significantly associated with a change in ACT score among those whose asthma was initially uncontrolled (ACT score ≤19). Bronchodilator response was associated with FEV_1 improvement among those in both lung function strata ($P < .01$ for those with an initial percent predicted FEV_1 <70% and ≥70%). In none of these stratified models was self-reported race-ethnicity significantly associated with change in ACT score or change in FEV_1.

We assessed whether African ancestry was a predictor of ICS responsiveness (Table IV).[16] Proportion of African ancestry was unrelated to ICS response, as measured by both the change in ACT score and the change in FEV_1. African ancestry was similarly not related to ICS response, even after stratifying by baseline level of asthma control and lung function.

As a *post hoc* analysis, we assessed factors associated with the likelihood of achieving self-reported asthma control (ACT score ≥20) after 6 weeks of ICS treatment among all subjects whose asthma was not controlled at baseline (initial ACT score ≤19). As shown in Table E1 in this article's Online Repository at www.jacionline.org, age, initial percent predicted FEV_1, and degree of bronchodilator response were associated with the likelihood of reporting controlled asthma at the 6-week treatment follow-up.

DISCUSSION

Few studies have described the relationship between ICS treatment and the change in longitudinal measures of lung function and asthma control among African American subjects when compared with European American subjects. Here we demonstrate that neither self-identified race-ethnicity nor genetic ancestry were associated with ICS treatment response, as defined by a change in either ACT score or FEV_1. This study builds on our earlier analysis in African American subjects alone, showing no relationship between African ancestry and change in FEV_1.[9]

TABLE II. Predictors of ICS response measured as change in ACT score and change in lung function over 6 weeks of treatment*

	Measure of ICS response							
	Change in ACT score*				Percentage change in FEV_1†			
	Univariable parameter estimate (β)	*P* value	Multivariable parameter estimate (β)‡	*P* value	Univariable parameter estimate (β)	*P* value	Multivariable parameter estimate (β)‡	*P* value
Age (y)§	−0.10 ± 0.19	.62	−0.19 ± 0.14	.17	−0.07 ± 0.72	.92	−0.68 ± 0.57	.24
Sex‖	0.43 ± 0.53	.42	0.18 ± 0.36	.62	1.09 ± 1.99	.59	1.21 ± 1.52	.43
Race-ethnicity¶	0.93 ± 0.58	.11	−0.57 ± 0.40	.16	−2.36 ± 2.17	.28	−2.52 ± 1.69	.14
BMI§	0.35 ± 0.28	.20	−0.01 ± 0.19	.96	0.40 ± 1.04	.70	0.45 ± 0.81	.58
ACT score at baseline	−0.68 ± 0.04	<.01	−0.71 ± 0.04	<.01	−1.02 ± 0.19	<.01	−0.24 ± 0.16	.12
Percent predicted FEV_1 at baseline	−0.03 ± 0.02	.21	0.09 ± 0.02	<.01	−0.65 ± 0.07	<.01	−0.13 ± 0.07	.07
Bronchodilator response at baseline	0.09 ± 0.02	<.01	0.05 ± 0.01	<.01	0.80 ± 0.05	<.01	0.71 ± 0.06	<.01
ICS adherence	2.23 ± 1.26	.08	2.38 ± 0.84	<.01	3.78 ± 4.75	.43	5.68 ± 3.55	.11

*ICS response was measured as the numeric change in composite ACT score from enrollment to follow-up after 6 weeks of ICS treatment.
†ICS response was measured as the percentage change in FEV_1 from enrollment to follow-up after 6 weeks of ICS treatment (ie, $FEV_{1[6\ weeks]} - FEV_{1[initial]}/FEV_{1[initial]}$).
‡Adjusted for all other variables listed.
§These variables were modeled for a single-unit increase (ie, years and kilograms per meters squared for age and BMI, respectively), but are aggregated here to show the effect of a 10-unit increase.
‖Referent is male (coded male = 0, coded female = 1).
¶Referent is European American (coded European American = 0, coded African American = 1).

TABLE III. Predictors of ICS response stratified by baseline ACT score and baseline FEV_1*

	Measure of ICS response							
	Change in ACT score*				Percentage change in FEV_1†			
	Initial ACT score ≤19		Initial ACT score ≥20		Initial percent predicted FEV_1 <70%		Initial percent predicted FEV_1 ≥70%	
	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value
Age (y)§	−0.35 ± 0.33	.29	0.06 ± 0.14	.70	−0.32 ± 1.35	.81	−0.61 ± 0.52	.24
Sex‖	0.28 ± 0.83	.73	0.33 ± 0.40	.40	1.64 ± 3.38	.63	1.01 ± 1.41	.48
Race-ethnicity¶	0.48 ± 1.00	.63	−0.17 ± 0.41	.69	−5.70 ± 3.76	.13	−0.84 ± 1.57	.59
BMI§	−0.07 ± 0.43	.88	0.13 ± 0.22	.55	−0.26 ± 1.58	.87	0.96 ± 0.84	.25
ACT score at baseline	—	—	—	—	−0.63 ± 0.32	.06	0.002 ± 0.16	.99
Percent predicted FEV_1 at baseline	0.11 ± 0.04	<.01	0.03 ± 0.02	.16	—	—	—	—
Bronchodilator response at baseline	0.09 ± 0.03	<.01	0.02 ± 0.03	.56	0.74 ± 0.08	<.01	0.63 ± 0.09	<.01
ICS adherence	3.95 ± 1.94	.04	1.41 ± 0.95	.14	5.35 ± 7.69	.49	4.19 ± 3.38	.22

*ICS response was measured as the numeric change in composite ACT score from enrollment to follow-up after 6 weeks of ICS treatment. The analysis was stratified by what was clinically considered to be uncontrolled asthma (ACT score ≤19) and controlled asthma (ACT score ≥20) at baseline.
†ICS response was measured as the percentage change in FEV_1 from enrollment to follow-up after 6 weeks of ICS treatment (ie, $FEV_{1[6\ weeks]} - FEV_{1[initial]}/FEV_{1[initial]}$). The analysis was stratified by percent predicted FEV_1 measured at baseline (ie, a cut point of 70% of predicted FEV_1, which is the midpoint for persistent moderate severity asthma in the current US asthma guidelines).[16]
‡Adjusted for all other variables listed.
§These variables were modeled for a single-unit increase (ie, years and kilograms per meters squared for age and BMI, respectively) but are aggregated here to show the effect of a 10-unit increase.
‖Referent is male (coded male = 0, coded female = 1).
¶Referent is European American (coded European American = 0, coded African American = 1).

The average improvement in FEV_1 was 11.3% in our overall study population. This is similar to our previous study, in which we observed an 11.6% improvement in FEV_1 after 6 weeks of ICS therapy.[9] This magnitude of FEV_1 improvement is similar to that described by some[18] but higher than seen by others.[19,20] Part of these differences might be due to the relatively high level of medication adherence in the current study. We observed an average adherence of 79%, which is higher than that usually seen in unselected populations of ICS-treated asthmatic patients.[3,4] This high level of adherence might be due to participants knowing that adherence was being monitored, as has been observed in other studies in which patients were conscious of adherence monitoring.[21-23]

Although we found that neither self-identified race-ethnicity nor ancestry was associated with ICS response, our earlier work showed African ancestry to be associated with asthma exacerbations,[24] nocturnal asthma,[12] and lung function.[25] Perhaps this indicates that although the genetic determinates of ICS controller response do not differ among African American and European American subjects, determinates of intrinsic disease severity do differ. The implication here would be that genetic ancestry has little independent contribution to drug response

TABLE IV. Assessment of genetic ancestry as a predictor of ICS response among African American subjects with asthma

	Measure of ICS response											
	Change in ACT score*						Percentage change in FEV_1†					
	All subjects		Initial ACT score ≤19		Initial ACT score ≥20		All subjects		Initial percent predicted FEV_1 <70%		Initial percent predicted FEV_1 ≥70%	
	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value	Parameter estimate (β)‡	*P* value
Age (y)§	−0.44 ± 0.19	.02	−0.85 ± 0.38	.03	0.04 ± 0.23	.86	−0.27 ± 0.72	.71	2.08 ± 1.77	.25	−0.67 ± 0.71	.35
Sex‖	0.54 ± 0.49	.27	0.57 ± 0.95	.55	0.88 ± 0.59	.14	1.73 ± 1.86	.35	3.07 ± 4.22	.47	1.04 ± 1.89	.58
Proportion of African Ancestry¶	1.63 ± 2.30	.48	1.37 ± 4.69	.77	0.67 ± 2.71	.81	2.96 ± 8.75	.74	4.80 ± 22.52	.83	2.45 ± 8.51	.77
BMI§	0.05 ± 0.26	.84	0.13 ± 0.49	.79	−0.01 ± 0.31	.98	−0.37 ± 0.97	.70	−1.38 ± 1.99	.49	−0.08 ± 1.06	.94
ACT score at baseline	−0.69 ± 0.05	<.01	—	—	—	—	−0.17 ± 0.18	.35	−0.71 ± 0.41	.09	0.15 ± 0.20	.44
Percent predicted FEV_1 at baseline	0.09 ± 0.03	<.01	0.06 ± 0.04	.19	0.06 ± 0.04	.14	−0.10 ± 0.10	.29	—	—	—	—
Bronchodilator response at baseline	0.07 ± 0.02	<.01	0.07 ± 0.04	.07	0.07 ± 0.04	.05	0.52 ± 0.09	<.01	0.52 ± 0.13	<.01	0.56 ± 0.12	<.01
ICS adherence	3.92 ± 1.12	<.01	7.84 ± 2.22	<.01	2.45 ± 1.37	.08	7.18 ± 4.28	.10	11.53 ± 9.08	.21	4.56 ± 4.64	.33

*ICS response was measured as the numeric change in the composite ACT score from enrollment to follow-up after 6 weeks of ICS treatment. The ACT is stratified by what is clinically considered to be uncontrolled asthma (ACT score ≤19) and controlled asthma (ACT score ≥20).

†ICS response was measured as the percentage change in FEV_1 from enrollment to follow-up after 6 weeks of ICS treatment (ie, $FEV_{1[6\ weeks]} - FEV_{1[initial]}/FEV_{1[initial]}$). The analysis was stratified by percent predicted FEV_1 measured at baseline (ie, a cut point of 70% of predicted FEV_1, which is the midpoint for persistent moderate severity asthma in the current US asthma guidelines).[16]

‡Adjusted for all other variables listed.

§These variables were modeled for a single-unit increase (ie, years and kilograms per meters squared for age and BMI, respectively) but are aggregated here to show the effect of a 10-unit increase.

‖Referent is male (coded male = 0, coded female = 1).

¶Modeled as effect of each percentage increase in the proportion of overall African ancestry, as measured by using genome-wide genotype data.

beyond that already captured through baseline measures of asthma severity, asthma control, and lung function. Another potentially important implication of our findings is that differences in corticosteroid response are unlikely to account for between-group differences in asthma control and complication rates observed for African American and European American subjects on a population level.[26,27]

It is important to note that the lack of association for overall African ancestry should not be interpreted as an absence of population-specific pharmacogenomics variants. Genetic variants that influence drug response can occur exclusively or at different frequencies between population groups.[28,29] However, in a recent review of the pharmacogenomics of the ICS response,[30] none of the existing genome-wide association studies included substantial numbers of African American subjects. Therefore it is not known whether the risk variants that have been identified to date are generalizable to multiple population groups. Our results do not address the generalizability of existing pharmacogenomic associations. Rather, our study implies that the sum effect of genetic variants influencing ICS response is likely to be similar among subjects of African and European descent.

Our study is not without other limitations. First, the subjects in our study were all members of a single large health system in southeast Michigan; therefore the findings from our study might not be generalizable to other patient populations within the United States. However, the proportion of West African ancestry estimated for the subjects in our study is similar to that reported for other African American groups throughout the United States.[31,32]

Second, because we did not have admixture estimates in our European American participants, we could not assess the effect of ancestry within this group. However, there is no *a priori* reason to suspect that the effect of genetic ancestry would have differed between groups, and the lower degree of continental ancestral variation in European American subjects would have required a much greater number of subjects to perform the same assessment.[33,34]

Third, although this study did include both African American and European American subjects, the latter comprised a much smaller number of patients. Consequently, additional replication is needed to bolster our findings.

In this burgeoning era of personalized genomics, there is an increased effort to target therapies to subjects most likely to respond to treatment. Differences in medication response and treatment-related side effects by race-ethnicity have now been noted for a number of medications.[35-37] Fortunately, African American subjects, who as a group disproportionately have asthma complications,[38,39] did not demonstrate response differences to ICS medication, the cornerstone treatment for persistent asthma. African American and European American subjects appeared to equally enjoy the benefits of ICS treatment for improving asthma control and lung function. In identifying subjects most likely to benefit from treatment, our study suggested that arguably more mundane factors, such as medication adherence, level of bronchodilator responsiveness, baseline lung function, and patient-reported asthma control, were consistently predictive of ICS response. Therefore although pharmacogenomics might eventually pave the way for more targeted asthma

treatment, fundamental characteristics of disease severity/control and management remain primary concerns for selecting and optimizing treatment.[16]

Key messages

- **Neither self-reported race-ethnicity nor African ancestry appears to be a major driver of ICS treatment response, strongly suggesting that this cornerstone therapy is equally beneficial in treating African American and European American subjects.**
- **Easily obtained measures of lung function and asthma control might be useful in assessing the likelihood of response.**

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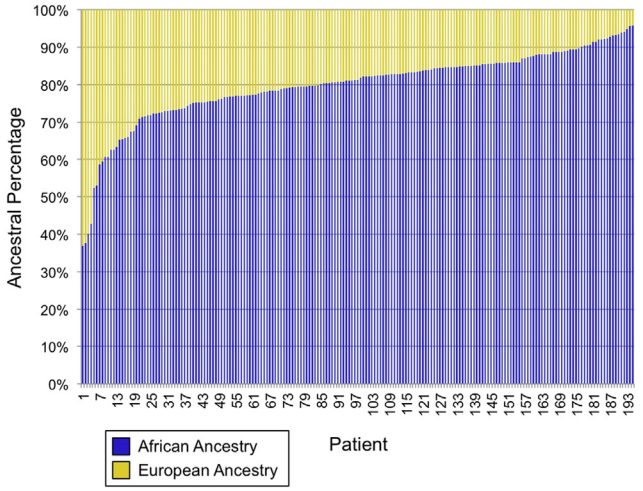

FIG E1. Distribution of genetic ancestry among African American study participants with genome-wide genotype data is shown (n = 195). Each column represents an individual study participant. The percentage of African ancestry is depicted in *blue,* and the percentage of European ancestry is depicted in *yellow*.

TABLE E1. Likelihood of achieving asthma control among subjects whose self-reported asthma was not controlled at baseline*

	aOR (95% CI)†	*P* value
Age (y)‡	0.71 (0.53-0.96)	.02
Sex§	1.62 (0.77-3.41)	.20
Race-ethnicity‖	0.60 (0.23-1.51)	.28
BMI‡	0.70 (0.48-1.03)	.07
Percent predicted FEV_1 at baseline	1.05 (1.01-1.08)	<.01
Bronchodilator response at baseline	1.03 (1.00-1.06)	.03
ICS adherence	1.01 (0.19-5.35)	.99

aOR, Adjusted odds ratio.
*Odds ratios represent the likelihood of achieving self-reported asthma control (composite ACT score ≥20) among patients whose baseline ACT score was 19 or less (ie, uncontrolled asthma).
†The odds ratio for each dependent variable is adjusted for all of the other variables shown.
‡These variables were modeled for a single-unit increase (ie, years and kilograms per meters squared for age and BMI, respectively) but are aggregated here to show the effect of a 10-unit increase.
§Referent is male (coded male = 0, coded female = 1).
‖Referent is European American (coded European American = 0, coded African American = 1).