ONE SIZE DOES NOT FIT ALL: ETHNIC-SPECIFIC DIFFERENCES IN DRUG RESPONSE AMONG LATINO CHILDREN WITH ASTHMA

Presented by:

Lesly-Anne Samedy-Bates, PharmD, PhD, MS

Disclosures

- No Financial Disclosures
- No Conflicts of Interest

Learning Objectives

- Describe the basic principles of genetic inheritance and variability in humans.
- Describe how human genetic variability as well as environmental and social factors impact drug action and response.
- Define the role of pharmacogenomics in patient care.
- Evaluate existing evidence and guidelines for use in clinical decision making.
- Explain the ethical, social and legal implications surrounding the clinical application of pharmacogenomic biomarkers

Outline

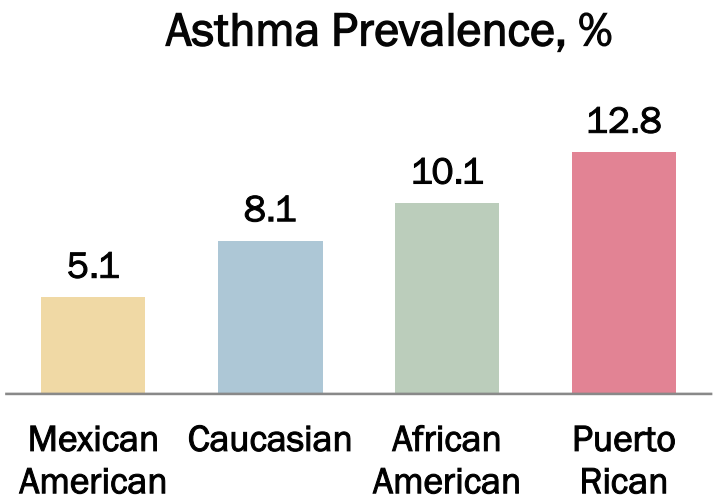
- What is the problem?
- What are the current standards?
- What is being done to address the problem?
- What is the future impact?

“Of all the forms of inequality, injustice in **health care** is the most shocking and inhuman.”

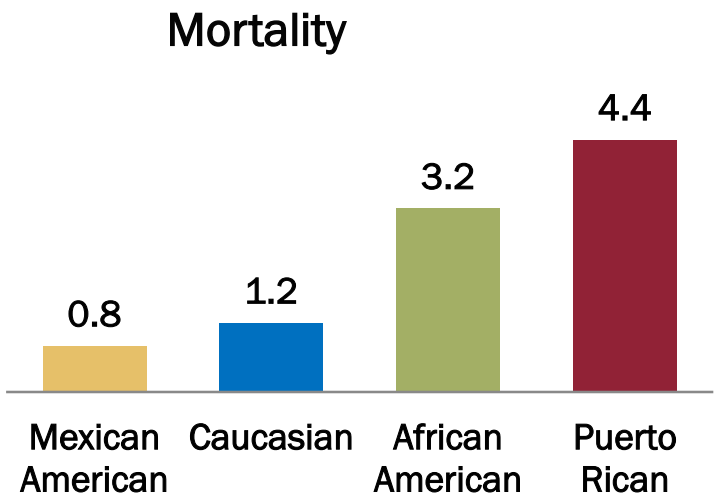
— **Dr. Martin Luther King, Jr.**
March 25, 1966, to the second convention of the Medical Committee for Human Rights

Asthma in the United States

- Asthma is the most common chronic disease among children.
- Asthma prevalence, morbidity and mortality are highest among minority children.
- Minorities also have the highest number of emergency room visits and hospital stays due to asthma
  - Top causes of missed school days, among children ages 5 to 17



CDC, 2017. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

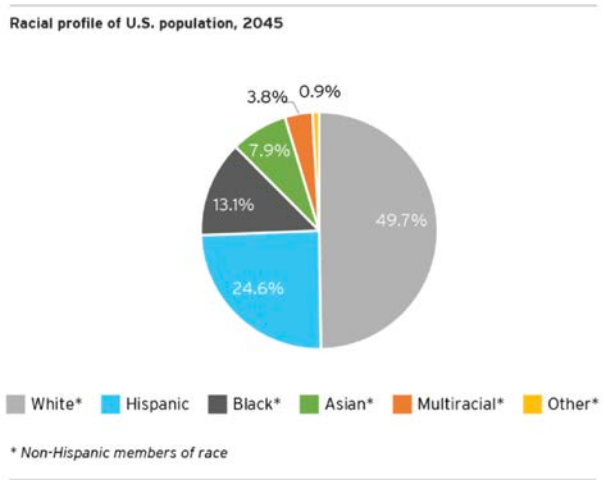


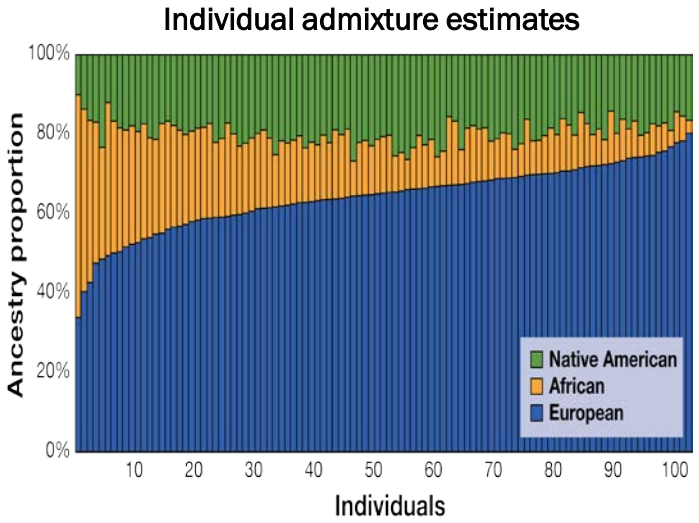
Akinbami L. CDC/NCHS (http://www.cdc.gov/nchs/data/hestat/asthma03-05/asthma03-05.htm)
Number of asthma dealths per 100,000 population

Akinbami, L. J., Simon, A. E., & Rossen, L. M. (2016). Changing trends in asthma prevalence among children. *Pediatrics*, *137*(1), e20152354.

Akinbami, L. J. (2006). The state of childhood asthma; United States, 1980-2005.

The Latino population in the United States is the nation's **largest** ethnic or racial minority.

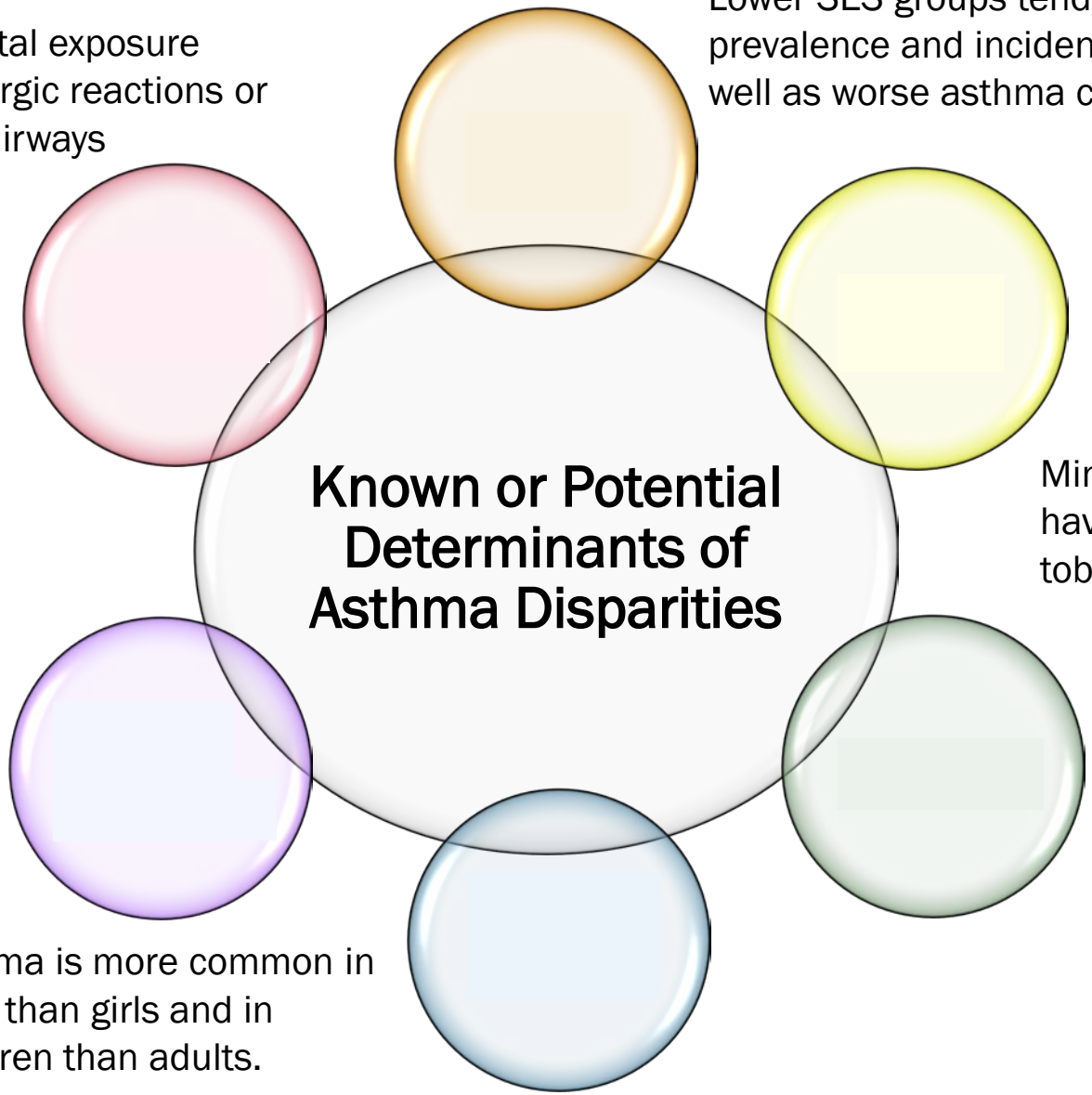




Source: William H Frey analysis of U.S. Census population projections released March 13, 2018 and revised September 6, 2018.

Environmental exposure provoke allergic reactions or irritate the airways

Lower SES groups tend to have a higher prevalence and incidence of asthma, as well as worse asthma control.



Minority children also have the highest tobacco exposure.

Asthma is more common in boys than girls and in children than adults.

ETS = *environmental tobacco smoke*
SES = *socioeconomic status*

Thakur, Neeta et al. "Socioeconomic status and childhood asthma in urban minority youths. The GALA II and SAGE II studies." *American journal of respiratory and critical care medicine* vol. 188,10 (2013): 1202-9. doi:10.1164/rccm.201306-10160C

Ellison-Loschmann, L., Sunyer, J., Plana, E., Pearce, N., Zock, J. P., Jarvis, D., ... & Kogevinas, M. (2007). Socioeconomic status, asthma and chronic bronchitis in a large community-based study. *European Respiratory Journal*, *29*(5), 897-905.

Pharmacogenomics

- ***Definition:*** *study of how genes affect a person's response to drugs*
- Differences in a person's genes have a big impact on a drug's safety or effectiveness

Genes-environments & Admixture in Latino Americans (GALA II)

- N = 5032
- 2006-2018
- Houston, Chicago, San Francisco Bay Area, New York City and Puerto Rico

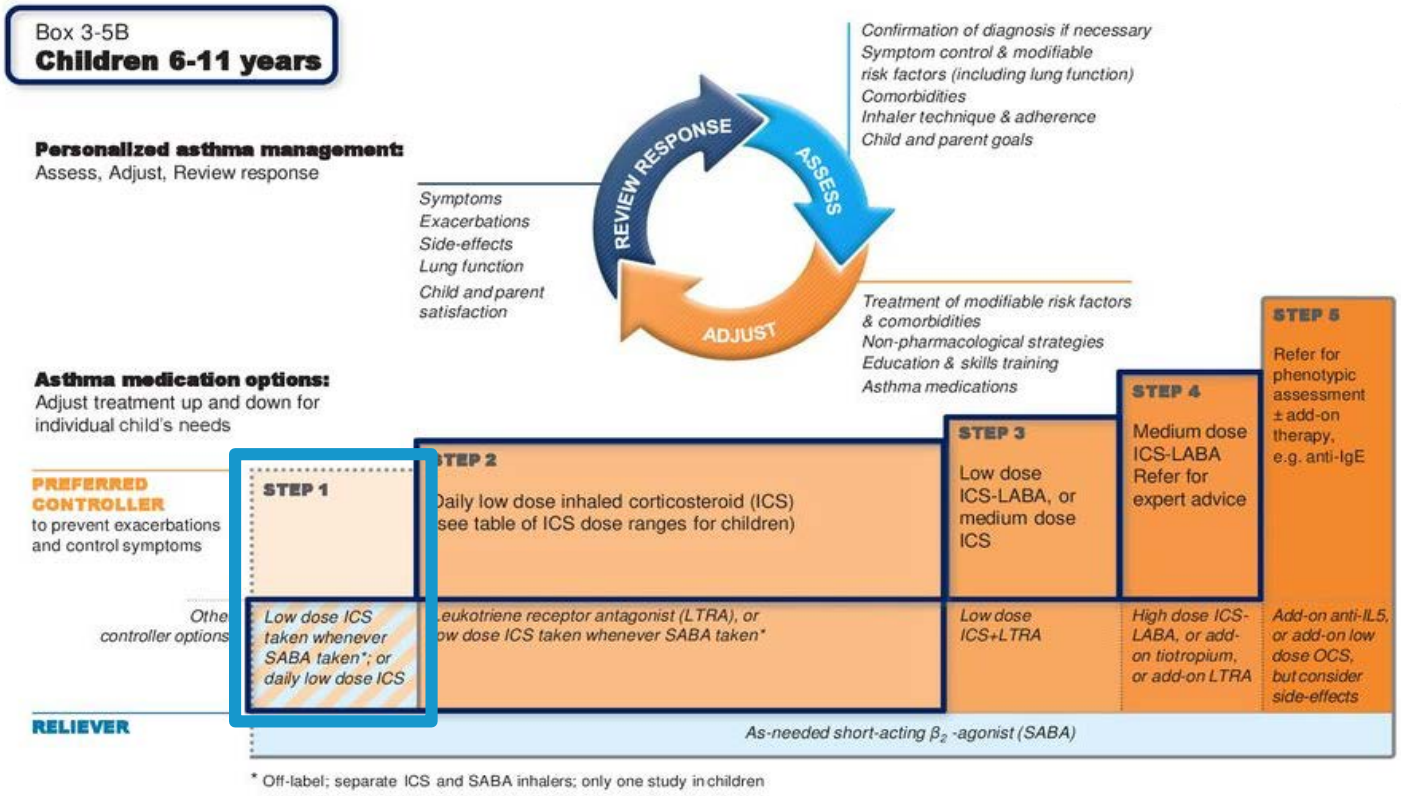
Inclusion criteria:

- Ages 8 to 21
- Physician-diagnosed asthma
- Experienced symptoms of coughing, wheezing, or shortness of breath for at least 2 years

** pregnancy or history of other lung/chronic diseases were excluded

Asthma Treatment

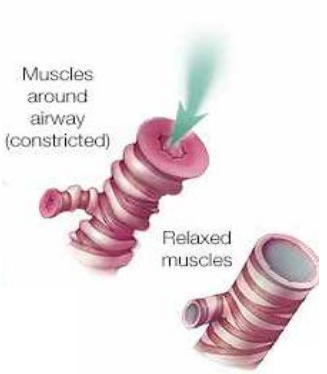
GINA guidelines 2019



Step 1: *As-needed short-acting β_2-agonist (SABA)*

Alternate Option: *Low dose ICS taken whenever SABA is taken*

Pharmacogenetics of Bronchodilator Drug Response



- Albuterol produces bronchodilation by causing rapid smooth muscle relaxation in the airways.
- Among low-income and minority populations, albuterol is often the only medication used for asthma.
    - *regardless of asthma severity*
- Puerto Rican and African American children have **significantly lower** BDR than white and Mexican American children

Objective: To identify genetic variants important for bronchodilator drug response (BDR) in racially diverse children.

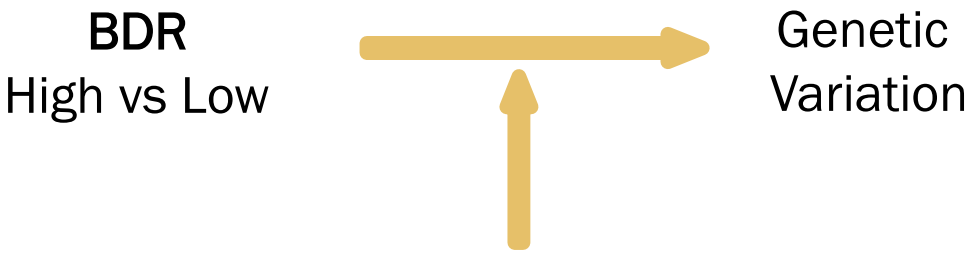
Burchard EG, Avila PC, Nazario S, Casal J, Torres A, Rodriguez-Santana JR, et al. Genetics of Asthma in Latino Americans (GALA) Study. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. *Am J Respir Crit Care Med*. 2004;169:386–392.

Naqvi M, Thyne S, Choudhry S, Tsai HJ, Navarro D, Castro RA, et al. Ethnic-specific differences in bronchodilator responsiveness among African Americans, Puerto Ricans, and Mexicans with asthma. *J Asthma*. 2007;44:639–648.

Pharmacogenetics of BDR in Diverse Populations

Examined high and low drug responders from three ethnic groups:

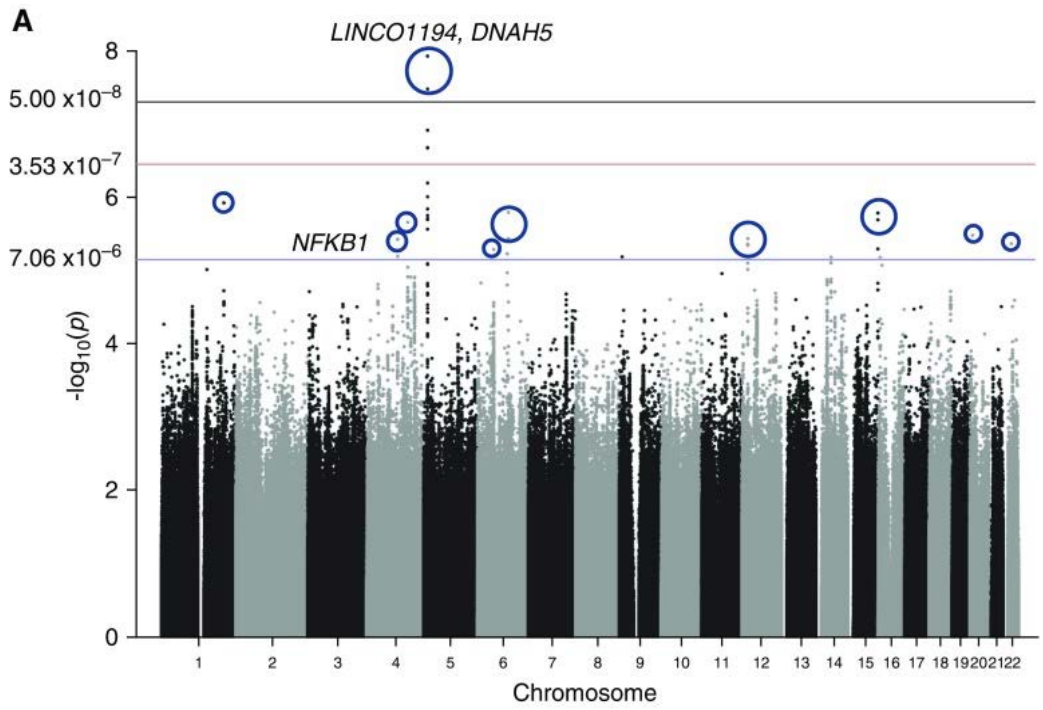
Puerto Ricans (n=483),
Mexicans (n=483), and
African Americans (n=475).



- Age
- Sex
- Body Mass Index (category)
- First 10 principal components

Mak ACY, White MJ, Eckalbar WL, et al. Whole-Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma. *Am J Respir Crit Care Med*. 2018;197(12):1552–1564. doi:10.1164/rccm.201712-2529OC

Pharmacogenetics of BDR in Diverse Populations



genome-wide threshold

universal significance

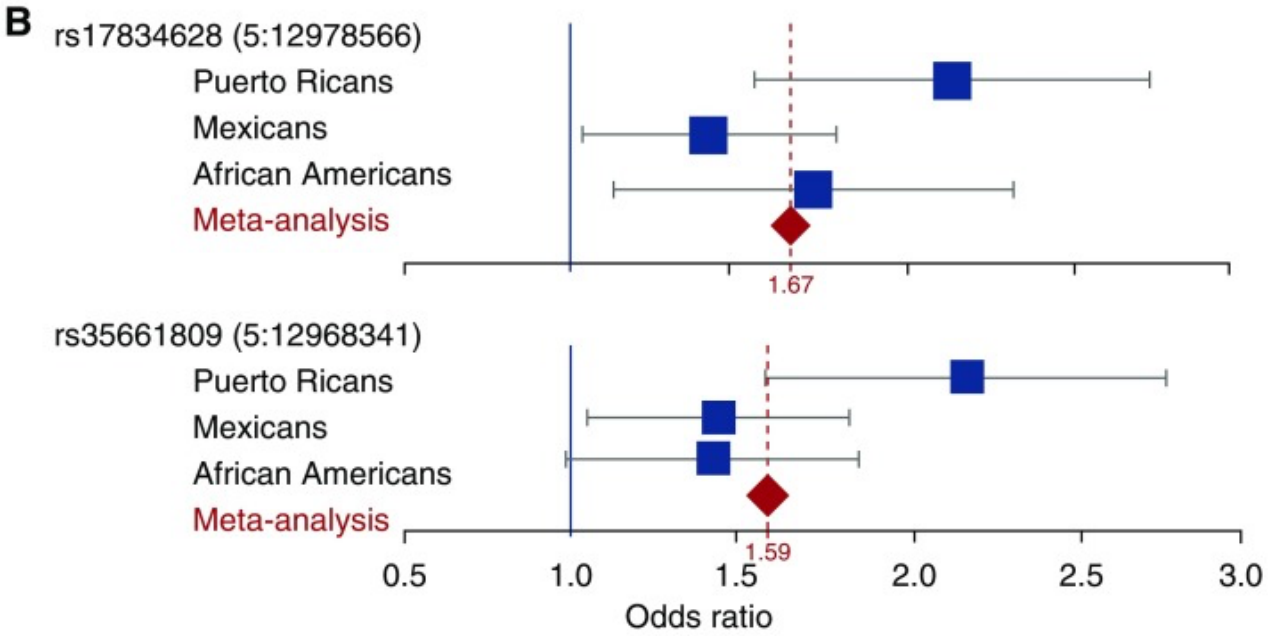
adjusted significance

suggestive significance

Identified 10 unique loci (represented by 27 SNPs) significantly or suggestively associated with BDR status

Mak ACY, White MJ, Eckalbar WL, et al. Whole-Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma. *Am J Respir Crit Care Med*. 2018;197(12):1552–1564. doi:10.1164/rccm.201712-2529OC

Pharmacogenetics of BDR in Diverse Populations



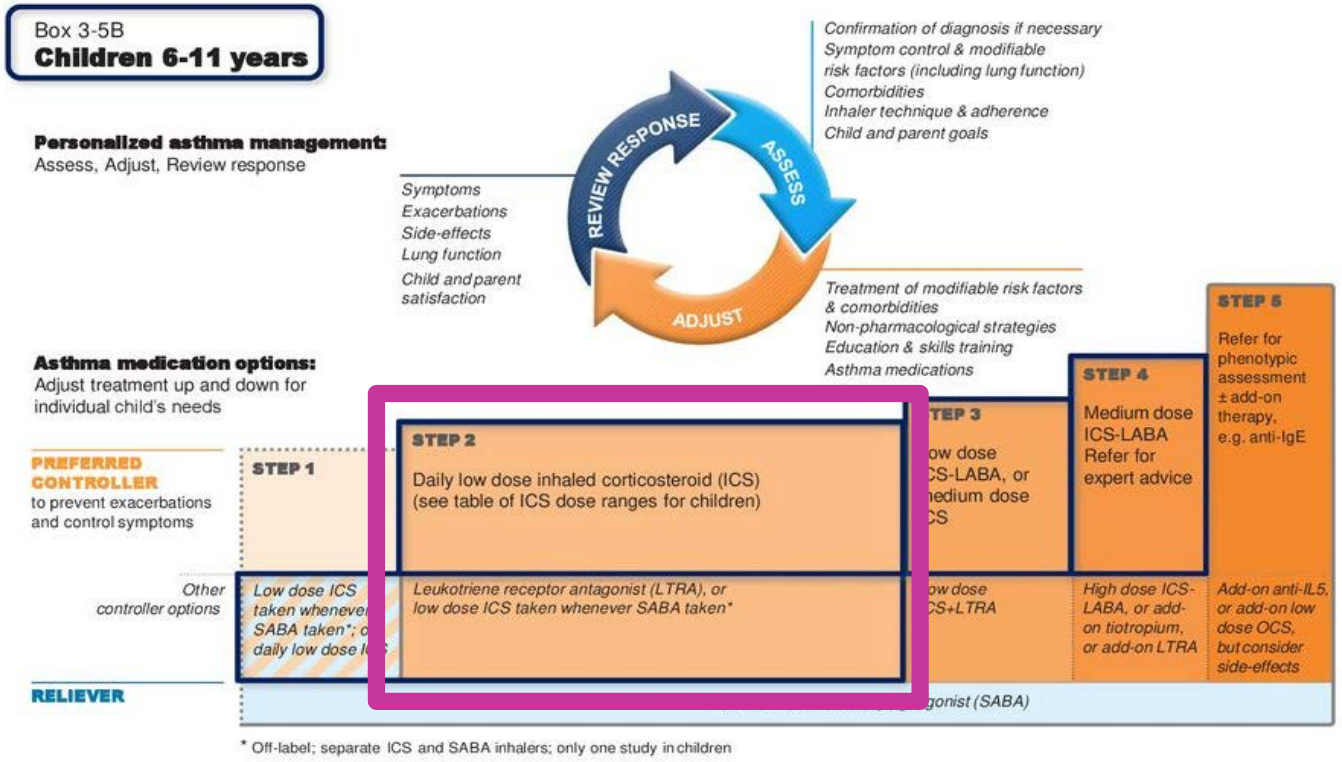
Two SNPs located on chromosome 5 (rs17834628 and rs35661809) were **significantly associated** with BDR.

($P = 1.18 \times 10^{-8}$ and 3.33×10^{-8})

Mak ACY, White MJ, Eckalbar WL, et al. Whole-Genome Sequencing of Pharmacogenetic Drug Response in Racially Diverse Children with Asthma. *Am J Respir Crit Care Med*. 2018;197(12):1552–1564. doi:10.1164/rccm.201712-2529OC

Asthma Treatment

GINA guidelines 2019

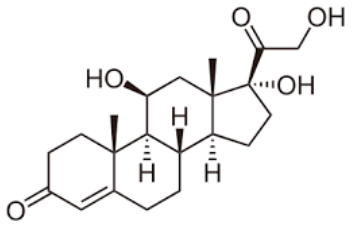


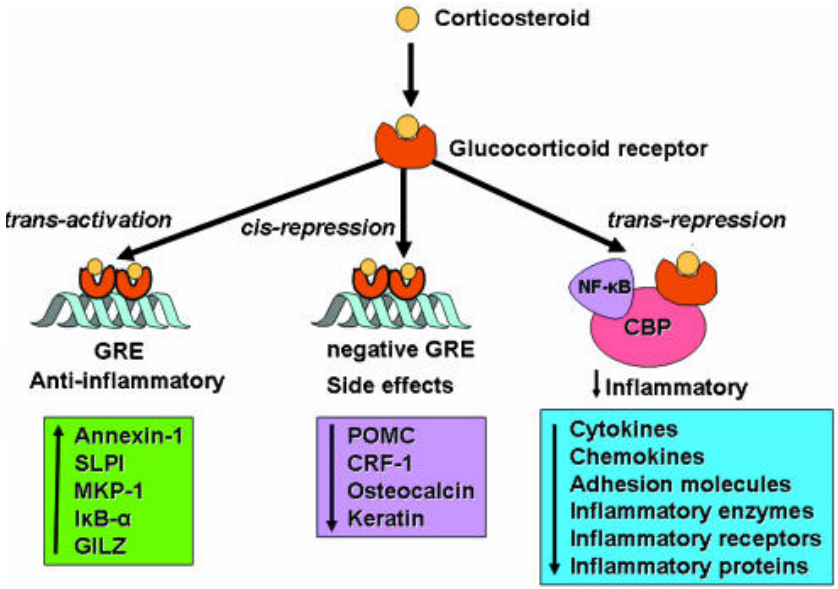
Step 2: Low dose inhaled corticosteroid (ICS) + *As-needed SABA*

Alternate Option: *Leukotriene receptor antagonists (LTRA) or Low dose ICS taken whenever SABA is taken*

Inhaled corticosteroids

- Inhaled corticosteroids (ICS) are the cornerstone for achieving control of asthma.

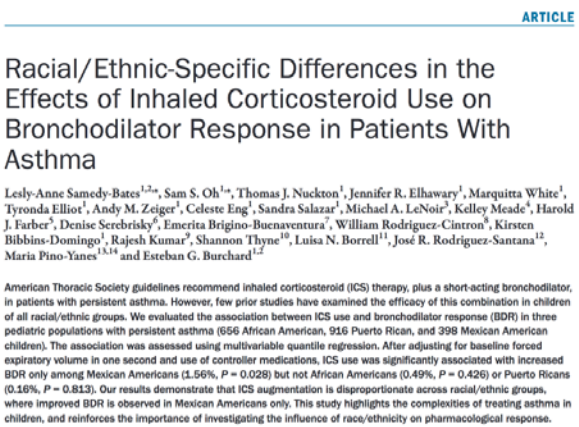




Barnes PJ. 2005. *Br J Pharmacol.* 2006;148(3):245–254

Effect of ICS Use on BDR

Objective: *To evaluate the effect of ICS on BDR in 3 ethnically diverse, large pediatric populations with persistent asthma.*



ARTICLE

Racial/Ethnic-Specific Differences in the Effects of Inhaled Corticosteroid Use on Bronchodilator Response in Patients With Asthma

Lesly-Anne Samedy-Bates[1,2,*], Sam S. Oh[1,*], Thomas J. Nuckton[1], Jennifer R. Elhawary[1], Marquitta White[1], Tyronda Elliot[1], Andy M. Zeiger[1], Celeste Eng[1], Sandra Salazar[1], Michael A. LeNoir[3], Kelley Meade[4], Harold J. Farber[5], Denise Serebrisky[6], Emerita Brigino-Buenaventura[7], William Rodriguez-Cintron[8], Kirsten Bibbins-Domingo[1], Rajesh Kumar[9], Shannon Thyne[10], Luisa N. Borrell[11], José R. Rodríguez-Santana[12], Maria Pino-Yanes[13,14] and Esteban G. Burchard[1,2]

American Thoracic Society guidelines recommend inhaled corticosteroid (ICS) therapy, plus a short-acting bronchodilator, in patients with persistent asthma. However, few prior studies have examined the efficacy of this combination in children of all racial/ethnic groups. We evaluated the association between ICS use and bronchodilator response (BDR) in three pediatric populations with persistent asthma (656 African American, 916 Puerto Rican, and 398 Mexican American children). The association was assessed using multivariable quantile regression. After adjusting for baseline forced expiratory volume in one second and use of controller medications, ICS use was significantly associated with increased BDR only among Mexican Americans (1.56%, $P = 0.028$) but not African Americans (0.49%, $P = 0.426$) or Puerto Ricans (0.16%, $P = 0.813$). Our results demonstrate that ICS augmentation is disproportionate across racial/ethnic groups, where improved BDR is observed in Mexican Americans only. This study highlights the complexities of treating asthma in children, and reinforces the importance of investigating the influence of race/ethnicity on pharmacological response.

	non-ICS (n=666)	ICS Use (n=648)
Self-reported Race/Ethnicity		
Puerto Rican, %	79.9	59.3
Mexican American, %	20.1	40.7

Effect of ICS Use on BDR

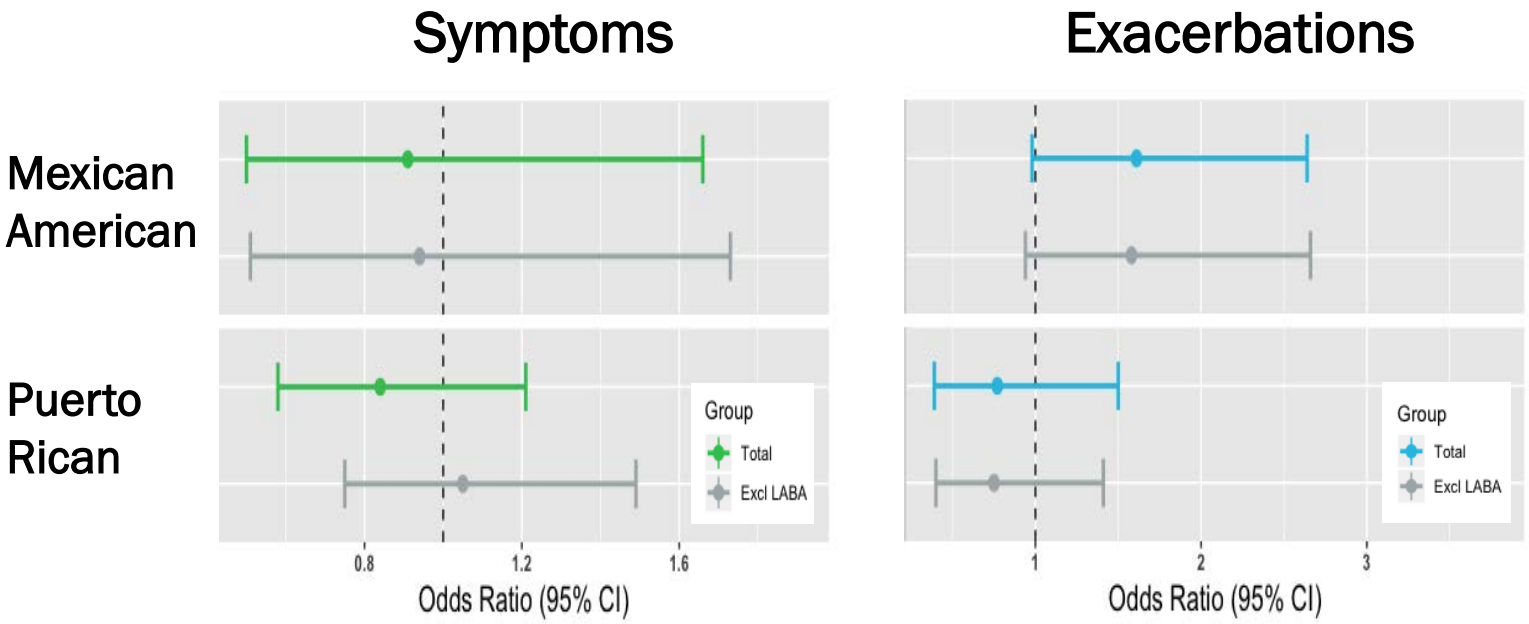
Regression Analysis: Association of inhaled corticosteroid (ICS) use with bronchodilator responsiveness, in GALA II study, 2006-2018.

Variable	Puerto Ricans (n= 916)		Mexican Americans (n = 398)	
	b	*p-value*	b	*p-value*
A. Bivariate Regression				
ICS use	0.20	0.669	1.47	0.035
B. Multivariable Quantile Regression				
ICS use	0.16	0.813	1.56	0.028
Covariates				
Baseline FEV_1	-1.85	<0.001	-2.30	<0.001
Controller medication	0.16	0.801	-0.94	0.269

Abbreviations: ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second
b coefficients represent percentage difference in FEV_1 between nonICS and ICS use groups

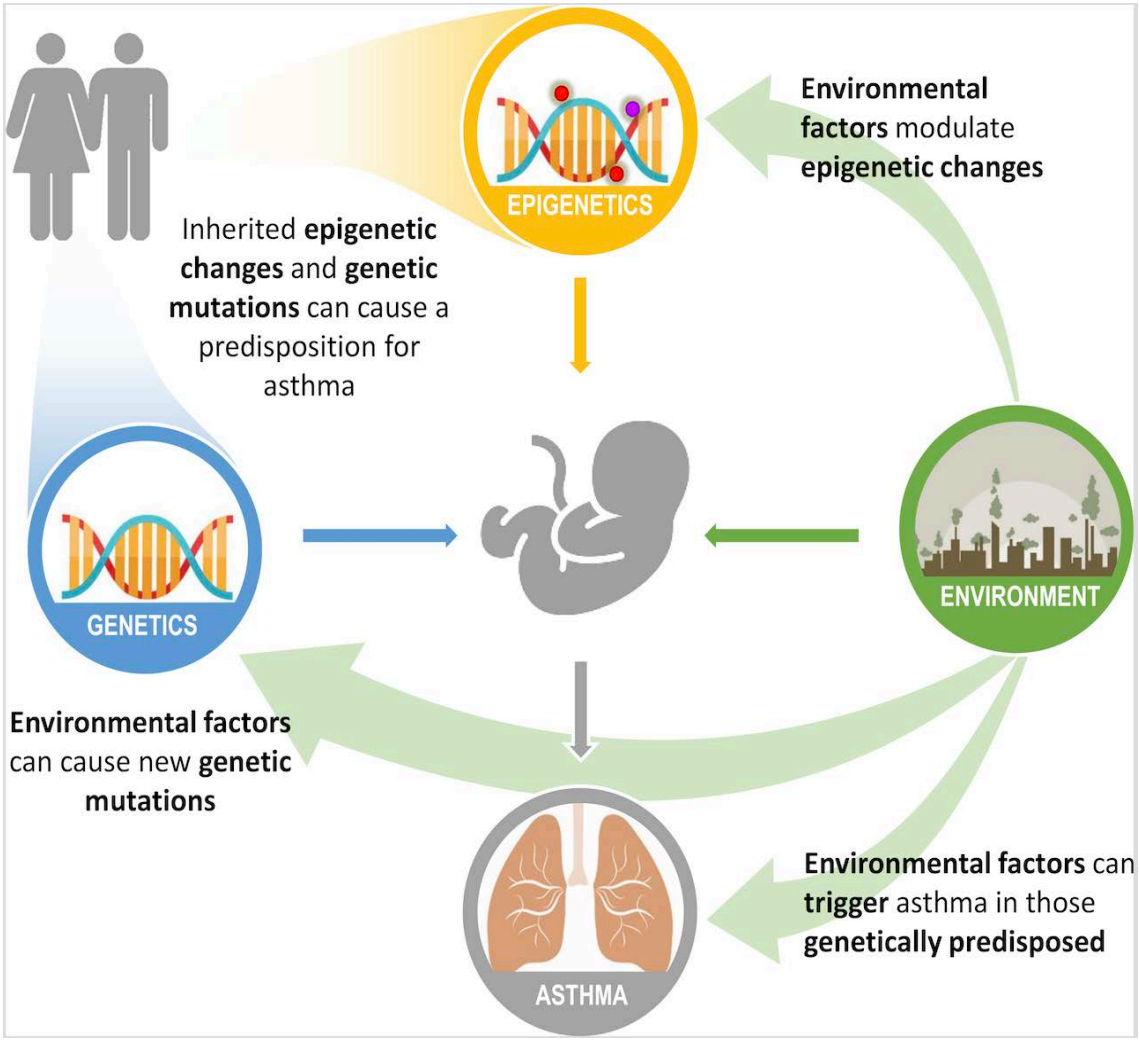
Significant association between ICS use and increased BDR in Mexican Americans, but Puerto Ricans.

Effect of ICS Use on BDR



Adjusted Odds Ratios for the Association between ICS Use and Asthma Symptoms/Exacerbations

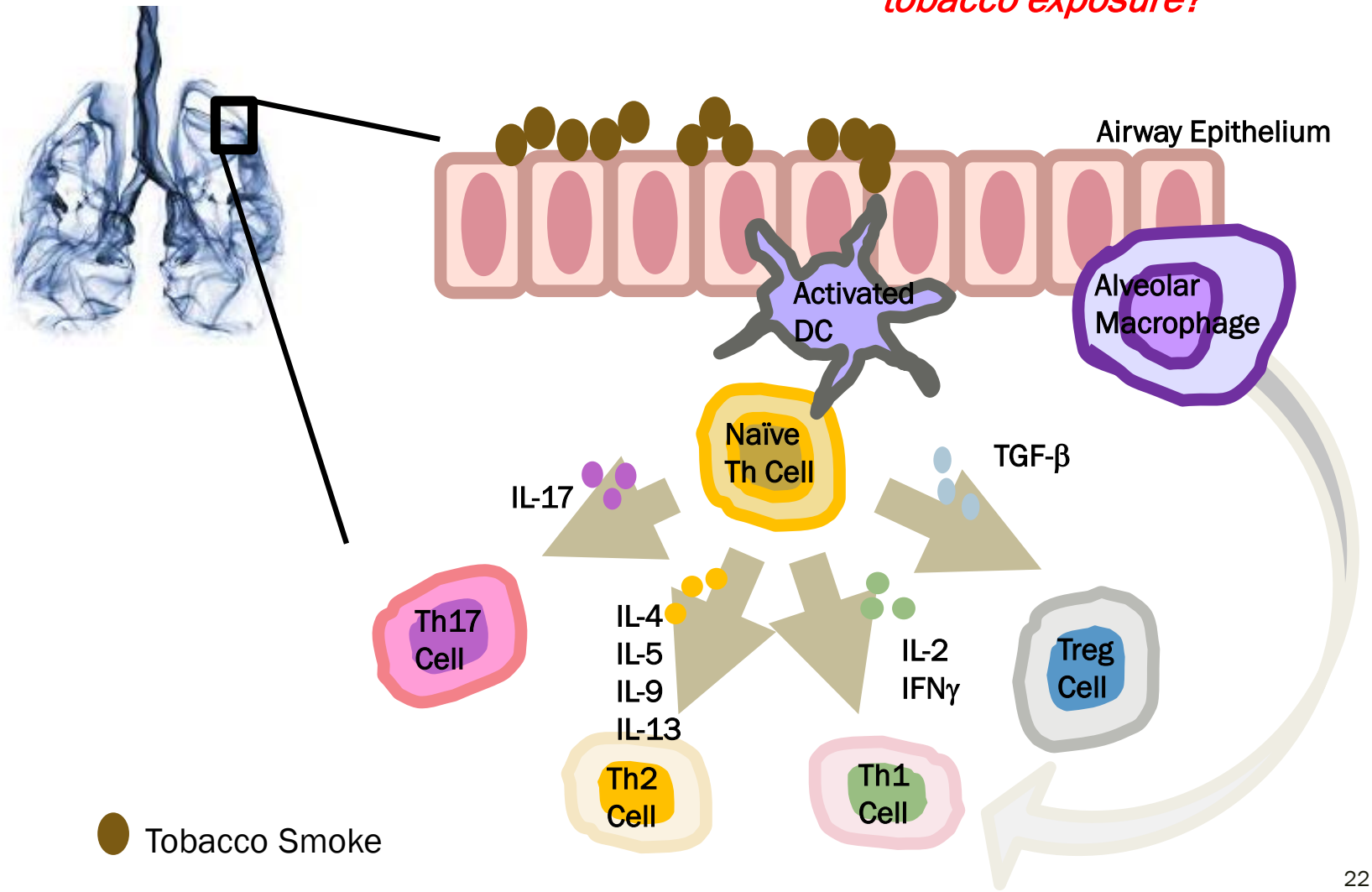
Adjusted for age, baseline FEV_1, and controller medication.



Genetic, environmental, and socioeconomic factors significantly impact the clinical presentation of asthma in children.

Tobacco Smoke Exposure

How is asthma drug response influenced by tobacco exposure?



"Your zip code shouldn't determine how long you live, but it does."

- Dr. Anthony Iton,
TCE's Senior Vice President
for Healthy Communities

Influence of Tobacco Smoke Exposure on of ICS Response

- Secondhand smoke (SHS) exposure is linked with asthma exacerbations, poor asthma control and increased asthma symptoms among children with asthma
- Disparities exist in the prevalence of SHS exposures based on race/ethnicity and socioeconomic status
- Prevalence of cigarette smoking among Hispanic/Latino sub-groups is highest in Puerto Rican
  - Puerto Rican women have the highest rates of smoking during pregnancy

Objective: *To investigate the contribution of current second-hand smoke exposure toward ICS response in Latino children with asthma*

Podlecka, D., Malewska-Kaczmarek, K., Jerzyńska, J., Stelmach, W., & Stelmach, I. (2018). Secondhand smoke exposure increased the need for inhaled corticosteroids in children with asthma. *Annals of Allergy, Asthma & Immunology*, *121*(1), 119-121.

Neophytou, Andreas M., et al. "Secondhand smoke exposure and asthma outcomes among African-American and Latino children with asthma." Thorax 73.11 (2018): 1041-1048.

Results

Table 3. Regression Analysis: *Association of inhaled corticosteroid (ICS) use with bronchodilator responsiveness, in SAGE study, 2006-2015 and GALA II study, 2006-2018, strafied by SHS exposure.*

Variable	African Americans (n = 656)				Puerto Ricans (n= 916)				Mexican Americans (n = 398)			
	non SHS		SHS		non SHS		SHS		non SHS		SHS	
	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
A. Bivariate Regression												
ICS use	0.50	0.643	0.64	0.608	1.03	0.159	-0.98	0.412	1.65	0.103	1.44	0.365
B. Multivariable Quantile Regression^												
ICS use	0.24	0.859	1.48	0.2	0.85	0.293	-1.44	0.234	1.46	0.055	2.59	0.194
Covariates												
Baseline FEV_1	-1.53	0.026	-2.92	<0.001	-1.93	<0.001	-3.41	<0.001	-1.85	<0.001	-4.01	0.014
Controller medication	-0.97	0.26	-1.58	0.286	0.12	0.886	1.34	0.267	-0.67	0.447	-1.30	0.479

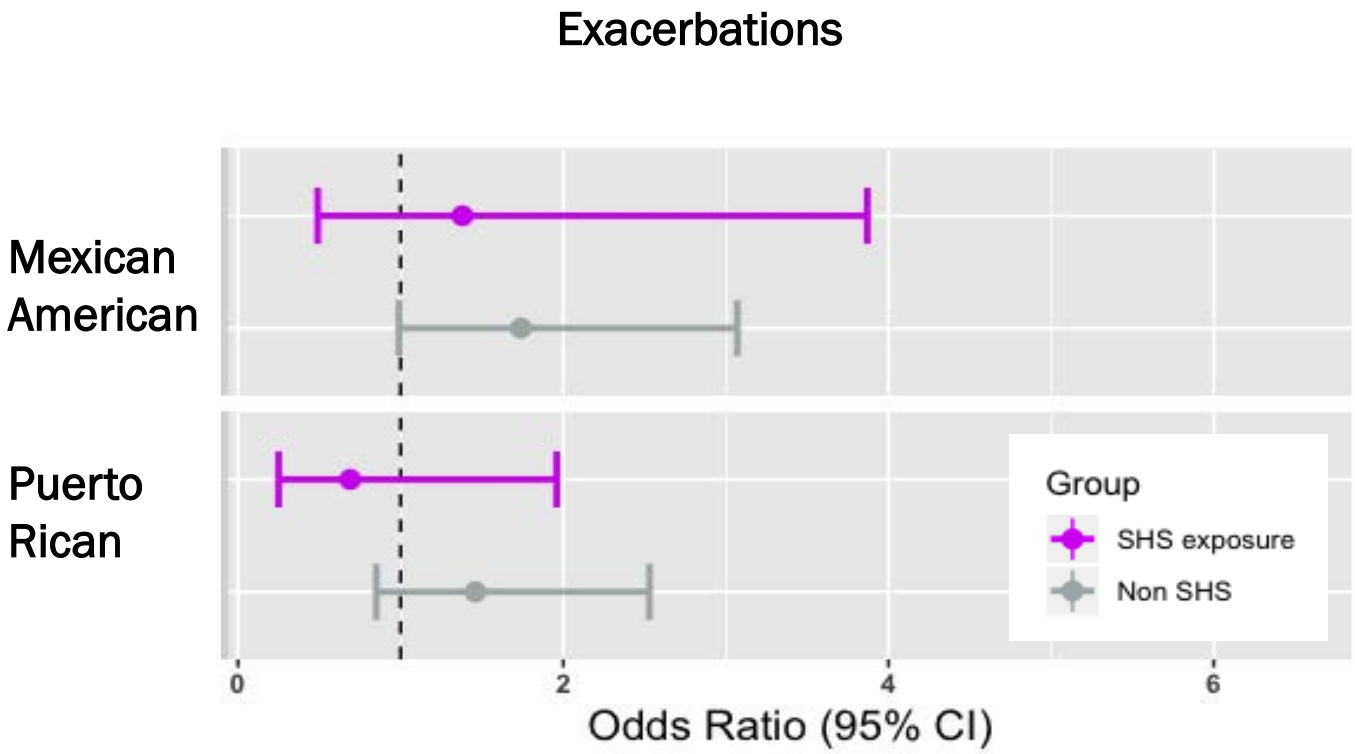
Abbreviations: ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second
β coefficients represent percentage difference in FEV_1 between nonICS and ICS use groups
^ Adjusted for baseline FEV1 and controller medications.

The presence of SHS exposure appears to be detrimental to ICS response.

ICS use appears to be ineffective in Puerto Ricans, despite exposure status.

In Mexican Americans, where we would typically expect to see an improvement with ICS use, no significant improvement is observed.

Results



Adjusted Odds Ratios for the Association between ICS Use and Asthma Symptoms/Exacerbations, stratified by SHS Exposure

Adjusted for baseline FEV_1, and controller medication.

Discussion

The worst form of inequality is to try to make unequal things equal.

- Aristotle

Public Health Response

- Racial/ethnic minorities make up more than half of all the children born in the United States, of which Latinos are the largest and fastest growing group.

- Generalizing results from research performed in one racial/ethnic group to another can work reasonably well, or it can have disastrous consequences.

- **How do we ensure equity?**
  - Research sample should reflect the diversity of the population
  - Increasing diversity in researchers

    "In order to increase diversity in participants, we need to increase diversity in those conducting the research"

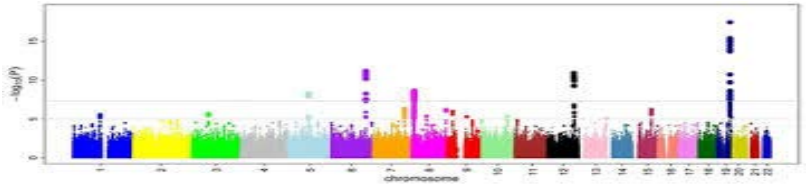
    - Maria Avila-Arcos, PhD
  - Consideration of ethnic constructs
    - Umbrella designations may disguise important differences within subgroups

Oh, S. S., White, M. J., Gignoux, C. R., & Burchard, E. G. (2016). Making precision medicine socially precise. Take a deep breath.

Future Plans

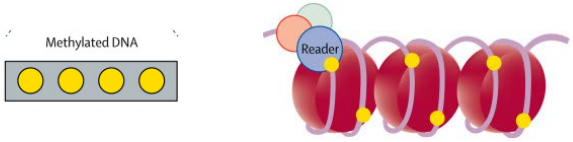
GWAS & GxE

- Characterization of predictive genetic biomarkers of in the therapeutic response to ICS, along with identifying predictive genetic-environmental biomarkers.



Epigenetic Regulation

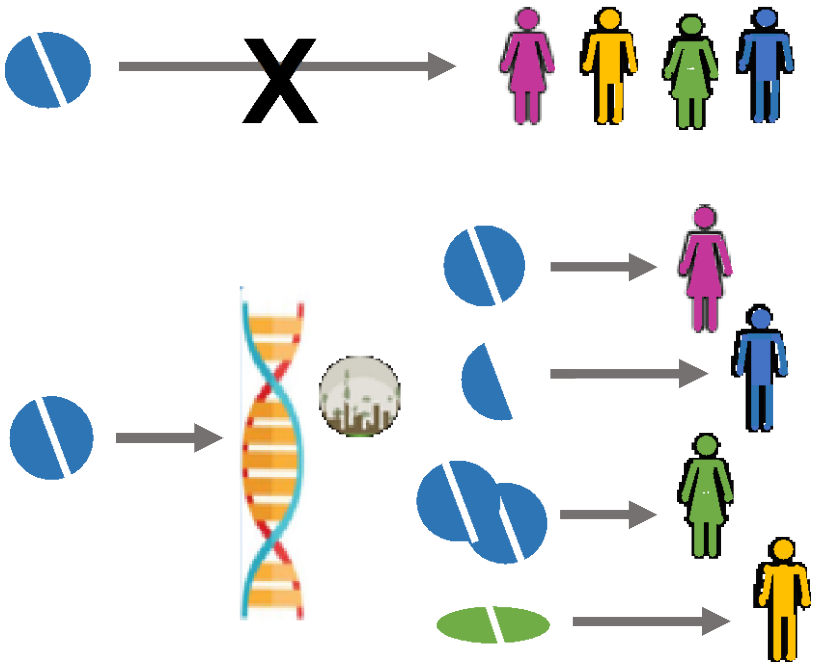
- Distinguishing differences in DNA methylation patterns in genes previously associated with SHS to better understand how tobacco leads to epigenetic changes



Impact

- Given the existing inequalities in asthma morbidity and mortality by race/ethnicity, it is important to elucidate the factors associated with response to asthma therapy Latino children with asthma.

- This knowledge may improve personalization of asthma therapy and reduce disparities in mortality/morbidity.



Conclusion

- Unraveling genetic mechanisms and environmental influences on therapeutic drug response in is necessary making precision medicine socially and scientifically precise.

- Studies, like these, help to lay the foundation of precision medicine for understudied and racially and ethnically diverse populations.

Oh SS, White MJ, Gignoux CR, Burchard EG. Making precision medicine socially precise: take a deep breath. *Am J Respir Crit Care Med*. 2016;193:348–350.

Acknowledgements

Esteban G. Burchard, MD, MPH

Sam Oh, PhD, MPH

Marquitta White, PhD

Angel Mak, PhD

UCSF Asthma Collaboratory

SAGE & GALA II collaborators

UCSF

UCSF
Asthma
Collaboratory

NIH National Heart, Lung, and Blood Institute

TOBACCO-RELATED DISEASE RESEARCH PROGRAM

TRDRP home

TRDRP Grant: 27IR-0030

References

1. Centers for Disease C, Prevention. Measuring childhood asthma prevalence before and after the 1997 redesign of the National Health Interview Survey--United States. MMWR Morb Mortal Wkly Rep. 2000;49(40):908-11.

2. Organization WH. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. 2007.

3. Barr RG, Aviles-Santa L, Davis SM, Aldrich TK, Gonzalez F, 2nd, Henderson AG, et al. Pulmonary Disease and Age at Immigration among Hispanics. Results from the Hispanic Community Health Study/Study of Latinos. Am J Respir Crit Care Med. 2016;193(4):386-95.

4. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. Natl Health Stat Report. 2011(32):1-14

5. Fedele DA, Tooley E, Busch A, McQuaid EL, Hammond SK, Borrelli B. Comparison of secondhand smoke exposure in minority and nonminority children with asthma. Health Psychol. 2016;35(2):115-22.

6. Marano C, Schober SE, Brody DJ, Zhang C. Secondhand tobacco smoke exposure among children and adolescents: United States, 2003-2006. Pediatrics. 2009;124(5):1299-305.

7. Martell BN, Garrett BE, Caraballo RS. Disparities in Adult Cigarette Smoking - United States, 2002-2005 and 2010-2013. MMWR Morb Mortal Wkly Rep. 2016;65(30):753-8.

8. Szefler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002;109(3):410-8.

Questions

Lesly-Anne Samedy-Bates, PharmD, PhD, MS
Lesly-anne.samedy@ucsf.edu