Finally, we must rise to the challenge of risk stratification. Not all children with asthma have attacks. In both the PROSE trial (9) and a previous omalizumab study (6), children with the highest levels of exhaled nitric oxide and peripheral blood eosinophils had the best response, and the peripheral blood eosinophil count is a promising marker in pediatrics (15). Personalizing treatment for asthma attacks must be the next goal, especially if omalizumab treatment is extended into the preschool years. ■

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References

- Sevelsted A, Phipper CB, Bisgaard H. Stable admission rate for acute asthma in Danish children since 1977. *Eur J Epidemiol* 2016;31:325–329.
- Murray CS, Poletti G, Kebabdzic T, Morris J, Woodcock A, Johnston SL, Custovic A. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax* 2006;61:376–382.
- Gielen V, Sykes A, Zhu J, Chan B, Macintyre J, Regamey N, Kieninger E, Gupta A, Shoemark A, Bossley C, *et al*. Increased nuclear suppressor of cytokine signaling 1 in asthmatic bronchial epithelium suppresses rhinovirus induction of innate interferons. *J Allergy Clin Immunol* 2015;136:177–188.e11.
- Djukanović R, Harrison T, Johnston SL, Gabbay F, Wark P, Thomson NC, Niven R, Singh D, Reddel HK, Davies DE, *et al*.; INTERCIA Study Group. The effect of inhaled IFN- β on worsening of asthma symptoms caused by viral infections. A randomized trial. *Am J Respir Crit Care Med* 2014;190:145–154.
- Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children. A randomized trial of mite-impermeable bedcovers. *Am J Respir Crit Care Med* 2017;196:150–158.
- Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, *et al*. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005–1015.
- Sears MR, Johnston NW. Understanding the September asthma epidemic. *J Allergy Clin Immunol* 2007;120:526–529.
- Almqvist C, Wickman M, Perfetti L, Berglind N, Renström A, Hedrén M, Larsson K, Hedlin G, Malmberg P. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. *Am J Respir Crit Care Med* 2001;163:694–698.
- Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes SJ Jr, Calatroni A, Wildfire JJ, Gergen PJ, Cohen RT, Pongracic JA, *et al*. Preseasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;136:1476–1485.
- Esquivel A, Busse WW, Calatroni A, Togias AG, Grindle KG, Bochkov YA, Gruchalla RS, Kattan M, Kerckmar CM, Khurana Hershey G, *et al*. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med* 2017;196:985–992.
- Bizzintino J, Lee WM, Laing IA, Vang F, Pappas T, Zhang G, Martin AC, Khoo SK, Cox DW, Geelhoed GC, *et al*. Association between human rhinovirus C and severity of acute asthma in children. *Eur Respir J* 2011;37:1037–1042.
- Ducharme FM, Zemek R, Chauhan BF, Gravel J, Chalut D, Poonai N, Guertin MC, Quach C, Blondeau L, Laberge S; DOORWAY Research Group of the Pediatric Emergency Research in Canada (PERC) Network. Factors associated with failure of emergency department management in children with acute moderate or severe asthma: a prospective, multicentre, cohort study. *Lancet Respir Med* 2016;4:990–998.
- Kloepfer KM, Lee WM, Pappas TE, Kang TJ, Vrtis RF, Evans MD, Gangnon RE, Bochkov YA, Jackson DJ, Lemanske RF Jr, *et al*. Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. *J Allergy Clin Immunol* 2014;133:1301–1307, 1307.e1–1307.e3.
- Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010;376:814–825.
- Lönnkvist K, Hellman C, Lundahl J, Halldén G, Hedlin G. Eosinophil markers in blood, serum, and urine for monitoring the clinical course in childhood asthma: impact of budesonide treatment and withdrawal. *J Allergy Clin Immunol* 2001;107:812–817.

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Bringing Lung Function Prediction Equations to Diverse Populations

Guidelines published in 2005 by the American Thoracic Society and European Respiratory Society (1) recommend using reference equations derived in populations that match the age and anthropometric, racial/ethnic, socioeconomic, and environmental characteristics of patients being tested in the pulmonary function laboratory. Although no specific reference equation is recommended, most pulmonary function laboratories in the United States default to equations derived by Hankinson and colleagues from three populations (whites, African Americans, and Mexican Americans) participating in NHANES III (the

third National Health and Nutrition Examination Survey) (2) for adults, whereas outside the United States the 2012 multiethnic Global Lung Initiative (GLI) equations are commonly used (3). Unfortunately, although these equations are reasonably well matched to the patient populations from which they are drawn, the equations from Hankinson and colleagues may be poorly predictive for racial/ethnic groups outside of the three used. Globally, the GLI equations included a paucity of participants from South Asia, the islands of the Pacific, Africa, and Latin America. This leaves clinicians evaluating patients inadequately matched to reference equations in a quandary. They can apply a race adjustment factor, if known, which is not as accurate as using ethnic-specific equations, or they can apply the reference equation of the

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population they believe is the closest match. Underlying this latter strategy is an assumption that similar racial/ethnic groups have similar normal lung volumes.

In this issue of the *Journal*, LaVange and colleagues (pp. 993–1003) leveraged a large, diverse sample of Latinos enrolled in HCHS/SOL (Hispanic Community Health Study/Study of Latinos) to identify between-group heterogeneity and develop subgroup-specific spirometry reference equations (4). Although all participants self-identified as ethnically “Hispanic or Latino,” a multitude of Latino subgroups were represented, including individuals of Cuban, Mexican, Puerto Rican, Dominican, Central American, and South American descent. Perhaps unsurprisingly, given the genetic (5–7) and environmental (8, 9) heterogeneity between them, the authors found that Puerto Rican and Dominican participants had, on average, lower values of FEV₁ and FVC than did other Latino ethnic subgroups or than the values predicted by Hankinson and coauthors (2) for Mexican Americans.

LaVange and colleagues then derived reference equations from 6,425 never-smoking participants in HCHS/SOL, which had the advantage of being a population-based probability-sampled study (10). By recruiting at four sites (Chicago, IL; Bronx, NY; Miami, FL; and San Diego, CA) the study was able to recruit a diverse population of Latinos. Although Mexicans composed the largest subpopulation studied (38%), the study also included at least 500 participants of Cuban, Dominican, Central American, Puerto Rican, and South American descent. This made it possible to derive spirometry reference equations that should match four of the five most common national origins, accounting for 78% of Latinos in the United States (11).

This article fulfills an important unmet need in the medical literature, as it provides reference equations for non-Mexican U.S. Latinos. Hitherto, clinicians seeking to compare observed results from an FVC maneuver to an expected normal value have had to extrapolate results derived in other populations. Crucial to this extrapolation is the now disproven assumption that all Latinos, regardless of heritage, have similar pulmonary function.

Given these findings, the new reference equations derived by LaVange and colleagues should become the standard of care for adult Latino patients, particularly those of Puerto Rican and Dominican descent for whom the equations derived by Hankinson and colleagues are particularly ill-suited, overestimating lung function (and thus exaggerating impairment) by between 5 and 10%. Given the higher prevalence of asthma and chronic obstructive pulmonary disease in these populations (12), the need for accurate reference equations is especially acute. Because HCHS/SOL did not recruit children, there remains a need for high-quality reference equations for Puerto Rican, Dominican, and other Latino children. In addition, because of lower sample size, all participants of South American descent were analyzed together, even though there is no reason to believe that South Americans are any more homogeneous than are participants of Caribbean descent, who were analyzed separately. Indeed, even within a particular subgroup of participants, there are likely to be large amounts of genetic (13–15) and socioeconomic heterogeneity and differences in environmental exposures.

Fortunately, the authors were also able to leverage genetic data to estimate ancestry for a subset of 4,037 participants with genetic data. Previous studies have shown that incorporating

African ancestry into lung function prediction equations could improve estimates for normal lung function in healthy African Americans (16), and that subcontinental ancestry was correlated with lung function in Mexicans (15). The authors were able to demonstrate that the proportion of African ancestry accounted for all of the differences in spirometry between ethnic subgroups in women and Dominican men. However, African ancestry was not able to fully explain differences in FEV₁ and FVC in Puerto Rican men. It is unclear whether the residual differences in lung function between Puerto Rican men and other Latino groups are due to the effect of non-African ancestry or are environmental, which may not correlate with ancestry. An earlier study in Brazilians with varying degrees of African ancestry (17) found that an inverse relationship between African ancestry and FEV₁ and FVC was attenuated when adjusting for environmental and socioeconomic variables, suggesting that genetic, epigenetic, social, and environmental variables all contribute to normal lung function (18). Future work should attempt to quantify the relative contributions and disentangle the effects of these factors on lung function in healthy Latinos. This is one of the advantages of working with diverse admixed populations, whose rich diversity in both ancestry and environmental exposures can provide a platform for separating these effects on biological processes (19). ■

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References

1. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, *et al*. Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26:948–968.
2. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
3. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, *et al*. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–1343.
4. LaVange L, Davis SM, Hankinson J, Enright P, Wilson R, Barr RG, Aldrich TK, Kalhan R, Lemus H, Ni A, *et al*. Spirometry reference equations from the HCHS/SOL (Hispanic Community Health Study/Study of Latinos). *Am J Respir Crit Care Med* 2017;196:993–1003.
5. Conomos MP, Laurie CA, Stilp AM, Gogarten SM, McHugh CP, Nelson SC, Sofer T, Fernández-Rhodes L, Justice AE, Graff M, *et al*. Genetic diversity and association studies in US Hispanic/Latino populations: applications in the Hispanic Community Health Study/Study of Latinos. *Am J Hum Genet* 2016;98:165–184.
6. Bryc K, Velez C, Karafet T, Moreno-Estrada A, Reynolds A, Auton A, Hammer M, Bustamante CD, Ostrer H. Colloquium paper: genome-wide patterns of population structure and admixture among Hispanic/Latino populations. *Proc Natl Acad Sci USA* 2010;107(Suppl 2):8954–8961.
7. Galanter JM, Fernández-López JC, Gignoux CR, Barnholtz-Sloan J, Fernandez-Rozadilla C, Hidalgo-Miranda A, Contreras AV, Figueroa LU, Raska P, Jimenez-Sanchez G, *et al*. LACE Consortium.

- Development of a panel of genome-wide ancestry informative markers to study admixture throughout the Americas. *PLoS Genet* 2012; 8:e1002554.
8. Daviglus ML, Talavera GA, Avilés-Santa ML, Allison M, Cai J, Criqui MH, Gellman M, Giachello AL, Gouskova N, Kaplan RC, *et al.* Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. *JAMA* 2012;308:1775–1784.
 9. Sanchez-Johnsen L, Craven M, Nava M, Alonso A, Dykema-Engblade A, Rademaker A, Xie H. Cultural variables underlying obesity in Latino men: design, rationale and participant characteristics from the Latino Men's Health Initiative. *J Community Health* 2017;311:806–813.
 10. Sorlie PD, Avilés-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, Schneiderman N, Raj L, Talavera G, Allison M, *et al.* Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol* 2010;20: 629–641.
 11. Ennis SR, Ríos-Vargas M, Albert NG. 2010 Census Briefs: The Hispanic population: 2010. 2011 May [accessed 2017 May 30]. Available from <https://www.census.gov/prod/cen2010/briefs/c2010br-04.pdf>
 12. Barr RG, Avilés-Santa L, Davis SM, Aldrich TK, Gonzalez F II, Henderson AG, Kaplan RC, LaVange L, Liu K, Loredó JS, *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;193:386–395.
 13. Via M, Gignoux CR, Roth LA, Fejerman L, Galanter J, Choudhry S, Toro-Labrador G, Viera-Vera J, Oleksyk TK, Beckman K, *et al.* History shaped the geographic distribution of genomic admixture on the island of Puerto Rico. *PLoS One* 2011;6:e16513.
 14. Avena S, Via M, Ziv E, Pérez-Stable EJ, Gignoux CR, Dejean C, Huntsman S, Torres-Mejía G, Dutil J, Matta JL, *et al.* Heterogeneity in genetic admixture across different regions of Argentina. *PLoS One* 2012;7:e34695.
 15. Moreno-Estrada A, Gignoux CR, Fernández-López JC, Zakharia F, Sikora M, Contreras AV, Acuña-Alonzo V, Sandoval K, Eng C, Romero-Hidalgo S, *et al.* Human genetics: the genetics of Mexico recapitulates Native American substructure and affects biomedical traits. *Science* 2014;344:1280–1285.
 16. Kumar R, Seibold MA, Aldrich MC, Williams LK, Reiner AP, Colangelo L, Galanter J, Gignoux C, Hu D, Sen S, *et al.* Genetic ancestry in lung-function predictions. *N Engl J Med* 2010;363:321–330.
 17. Menezes AMB, Wehrmeister FC, Hartwig FP, Perez-Padilla R, Gigante DP, Barros FC, Oliveira IO, Ferreira GD, Horta BL. African ancestry, lung function and the effect of genetics. *Eur Respir J* 2015;45: 1582–1589.
 18. Quanjer PH. Lung function, genetics and socioeconomic conditions. *Eur Respir J* 2015;45:1529–1533.
 19. Galanter JM, Gignoux CR, Oh SS, Torgerson D, Pino-Yanes M, Thakur N, Eng C, Hu D, Huntsman S, Farber HJ, *et al.* Differential methylation between ethnic sub-groups reflects the effect of genetic ancestry and environmental exposures. *eLife* 2017; 6:1655.

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Biomarkers in Critical Illness: New Insights and Challenges for the Future

Biomarkers are used in a variety of clinical settings and have transformed diagnosis and treatment of common diseases such as myocardial infarction, heart failure, and cancer. However, biomarkers have been slow to gain traction in critical illness, perhaps because the most common causes of critical illness, such as sepsis and acute respiratory distress syndrome (ARDS), are heterogeneous clinical syndromes rather than homogeneous disease states with well-defined pathogenesis. There are also current practical limitations to real-time measurement of biomarkers in the emergency department or the intensive care unit (ICU).

Prior studies of biomarkers in critical illness generally fall into three categories. The majority of studies are focused on identifying pathogenic mediators, an important endeavor to understand mechanisms of organ injury in patients and to avoid excessive dependence on animal models. This type of study has identified potential new therapeutic targets such as proinflammatory pathways in sepsis (1) and in ARDS (2) and immunomodulation in the later stages of sepsis (3). Other studies have identified biomarkers that can supplement current clinical definitions for diagnosis of clinical syndromes such as sepsis or ARDS (4). A third group of studies aims to identify biomarkers for prognostication. In this issue of the *Journal*, Mikacenic and colleagues (pp. 1004–1011) present a prognostic biomarker study involving the derivation and validation of a

two-biomarker panel for predicting mortality in critically ill patients, the majority of whom had sepsis (5). First, they tested the value of a panel of biomarkers of pathways known to be involved in inflammation, microvascular injury, and apoptosis, along with a panel of clinical predictors. In an unbiased least absolute shrinkage and selection operator evaluation of the clinical and biomarker variables, the biomarkers were much stronger predictors of 28-day inpatient mortality than the clinical predictors, suggesting that biomarkers add important prognostic information to clinical predictors of outcome in critical illness. A two-biomarker panel that included plasma IL-8 and soluble tumor necrosis factor receptor-1 provided optimal prognostication without overfitting and was roughly equivalent to Acute Physiology and Chronic Health Evaluation (APACHE) III for prognostication. This panel was subsequently validated in an internal validation dataset from the same cohort and an independent dataset from another academic institution.

The study by Mikacenic and colleagues (5) has several strengths. The inclusion of a large number of heterogeneous critically ill patients from different cohorts and institutions in a stepwise derivation and validation process enhances the reliability and generalizability of the findings. The initial analytic approach using the least absolute shrinkage and selection operator method minimizes overfitting, contributing to the robust performance of the model in the validation cohorts. Comparison of the biomarker model performance to the APACHE III and Sequential Organ Failure Assessment score allows the reader to assess the value of

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