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# Pharmacogenetics of Bronchodilator Response: Future Directions

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## Abstract

**Purpose of Review—**Several genome-wide association studies (GWASs) of bronchodilator response (BDR) to albuterol have been published over the past decade. This review describes current knowledge gaps, including pharmacogenetic studies of albuterol response in minority populations, effect modification of pharmacogenetic associations by age, and relevance of BDR phenotype characterization to pharmacogenetic findings. New approaches, such as leveraging additional "omics" data to focus pharmacogenetic interrogation, as well as developing polygenic risk scores in asthma treatment responses, are also discussed.

**Recent Findings—**Recent pharmacogenetic studies of albuterol response in minority populations have identified genetic polymorphisms in loci (*DNAH5*, *NFKB1*, *PLCB1*, *ADAMTS3*, *COX18*, and *PRKG1*), that are associated with BDR. Additional studies are needed to replicate these findings. Modification of the pharmacogenetic associations for *SPATS2L* and *ASB3* polymorphisms by age has also been published. Evidence from metabolomic and epigenomic studies of BDR may point to new pharmacogenetic targets. Lastly, a polygenic risk score for response to albuterol has been developed but requires validation in additional cohorts.

**Summary—**In order to expand our knowledge of pharmacogenetics of BDR, additional studies in minority populations are needed. Consideration of effect modification by age and leverage of other "omics" data beyond genomics may also help uncover novel pharmacogenetic loci for use in precision medicine for asthma treatment.

### Keywords

Bronchodilator response; Pharmacogenetics; β2-agonist; Polygenic risk score; Effect modification by age

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## Introduction

Asthma affects over 300 million people worldwide [1] and is characterized by wheeze, chronic airway inflammation, and reversible airflow obstruction. Asthma is also the most common chronic disease in children globally [2]. Individuals with asthma often require pharmacological treatment throughout the course of their illness. Short-acting beta-agonists (SABAs) are prescribed as a rescue medication for asthma, to be utilized as a bronchodilator to treat acute bronchospasm. SABAs, such as albuterol, act on beta-2 adrenergic receptors to relax bronchial smooth muscle [3]. However, like many of the pharmacotherapeutic options for asthma, SABA medications are not universally effective for all patients [4•], and some individuals are unable to derive much benefit from these treatments.

Part of an individual's response to albuterol is determined by genetics. Bronchodilator response (BDR) measures the change in bronchoconstriction before and after the administration of a short-acting $\beta_2$-agonist, such as albuterol, which reduces airway constriction by stimulating the $\beta_2$-adrenergic receptors ($\beta_2$ARs) on airway smooth muscle. In fact, it is estimated that 31–92% of BDR is heritable [5-8]. This review article will equate BDR with response to albuterol.

Genome-wide association studies (GWASs) and candidate gene studies have identified genetic polymorphisms associated with BDR. These findings have been reviewed recently elsewhere [9-13] and include genetic associations within the *ADRB2*, *ARG1*, *ARG2*, *THRB*, *SPATS2L*, *ASB3*, *SOCS*, *ADCY9*, *CRHR2*, *COL22A1*, and *CLOCK* genes. *ADRB2* and *ARG1* are two of the most studied genes for BDR [12]. *ADRB2* is a gene that encodes for the $\beta_2$ adrenergic receptor, which is involved in bronchodilator response and is the target of $\beta_2$ adrenergic agonists. Polymorphisms in *ADRB2* have been extensively studied in multiple populations, although findings have been variable (some cohorts detect no associations with BDR, while others report associations with BDR and/or asthma exacerbations) [12]. *ARG1* polymorphisms have been linked to lower BDR in several studies [12]. Overall, the total variability in BDR accounted for by all genetic polymorphisms across all associated loci is quite low. A further limitation of these genetic association studies is that they are mainly conducted in Caucasian populations, which means the findings may not be applicable across multiple racial/ethnic populations.

### Pharmacogenetics of BDR in Minority Populations

Minority populations, in particular Blacks and Puerto Ricans, have the highest asthma morbidity as well as the lowest BDR [14, 15]. Genetic associations in minority populations often do not replicate in Caucasian populations, suggesting that genetic determinants of albuterol response may be partly population-specific [16•, 17, 18•] As reviewed by Jerome et al. in 2021 [19•], there have been few studies of BDR among Black cohorts. In a GWAS performed by Spear and colleagues, an intergenic SNP on chromosome 9q21 was associated with BDR among Black participants [16•]. After meta-analyzing data from both their Black and Latino cohorts, Spear and colleagues identified three polymorphisms in the intronic region of *PRKG1* that were associated with BDR. However, these findings failed to replicate in additional Black and Latino populations. In a multi-ethnic meta-analysis by Finkelstein et al. in 2009, the beneficial effects of rs1042713 (A > G) in the *ADRB2* gene

on BDR were most pronounced in Black participants (as compared to whites) [17]. In 2018, Mak et al. conducted a whole-genome sequencing study in Black participants from the SAGE II cohort [18•]. While no genome-wide significant associations were observed within Black participants alone, a trans-ethnic meta-analysis of Black, Puerto Rican, and Mexican American participants (from SAGE II and GALA II cohorts) did identify 27 SNPs in 10 loci associated with BDR. Polymorphisms in these genetic loci explained 23%, 16%, and 18% of the variation in bronchodilator responder status in Puerto Rican, Mexican American, and Black participants, respectively [18•], In contrast to some of the genetic loci identified in Caucasian participants, these loci were within genes associated with lung capacity (*DNAH5*) immunity (*NFKB1* and *PLCB1*). Similar to some of the findings in Caucasians, two of the loci identified in the Mak et al. multi-ethnic meta-analysis were in the β-adrenergic signaling pathway (*ADAMTS3* and *COX18*). It is important to note that the investigators were not able to replicate these associations, a limitation which may stem from a lack of available minority populations with a sufficient sample size for validation.

## Impact of Bronchodilator Response Phenotype Classification

In addition to racial differences across cohorts, another critical aspect to consider when examining genetic associations for response to albuterol is the distribution and classification of the BDR outcome variable. The majority of GWAS studies of BDR have modeled percent change in $FEV_1$ following administration of albuterol as a continuous outcome. However, some have utilized extremes of the BDR distribution in their study to classify “responders” and “non-responders” to albuterol. Differences in genetic association findings arise when different decisions are made about how to model the outcome variable. One such example is the twin set of BDR studies conducted in the same group of cohorts (GALA and SAGE) by Spear et al. [16•] and Mak et al. [18•]. In Spear et al., BDR was modeled as a continuous outcome variable, while in Mak et al., the extremes of the BDR distribution were used to classify “responders” and “non-responders” to albuterol. While the former study identified variants in *PRKG1* as top hits, the latter study, based instead on a binary rather than a continuous outcome measure, identified a distinct set of SNPs as potential BDR response candidates. Both studies provide useful information about potential predictors of BDR. However, it may be difficult to translate the results of such findings to the commonly accepted “clinical threshold” of BDR, where response to albuterol is defined not as a continuous outcome or an extreme phenotype, but as whether an individual responds at or above a threshold of a 12% difference in $FEV_1$ after administration of albuterol [20-22].

Furthermore, there may even be subtleties in characterization of the continuous BDR phenotype when researchers consider changes in $FEV_1$ post albuterol as change in the % initial value vs. % of the predicted value [23]. BDR expressed as a change in percent predicted $FEV_1$ is adjusted for age and height, so that comparisons across individuals of various ages and sizes can easily be made. However, the % initial value may be most practical in countries where the lack of spirometric norms and inaccessibility of prediction software make calculation of age, sex, and height-adjusted percent predicted values difficult. Of course, an important caveat is that the easier to compute % initial has issues with bias with respect to sex and size [24].

These issues in BDR phenotype characterization should all be considered when comparing findings from across pharmacogenomic studies of response to albuterol. If possible, sensitivity analyses with multiple phenotypes should be explored to determine if associations are robust to choice of phenotype variable, or specific to a particular derivation of BDR phenotype.

## Effect Modification of Pharmacogenetic Responses by Age

Variability in treatment response in children is an understudied area, and elucidating age-dependent treatment effects is important. Childhood is a unique time period with rapid growth and hormonal development. Extrapolating adult asthma pharmacogenetic studies to children does not adequately address the unique needs of child asthma sufferers. Statistical models of pharmacogenetic responses typically include the main effects of genotypes, with standard adjustment for covariates. Some genetic epidemiology studies of asthma stratify populations by age group prior to analysis. For example, in GWASs of asthma, populations are often stratified by childhood onset vs. adult onset asthma [25•]. In pharmacogenetic research, age is rarely considered an effect modifier of genetic responses [26]. Aging is correlated with changes in immune, hormonal and inflammatory responses [27, 28], which may alter the influence of genetic polymorphisms on response to asthma medications. As one example, *ARG1* is a gene known to be associated with BDR in children and adults, but the effect is greater in adults than in children [29]. Furthermore, *ADRB2*, which works through β-adrenergic pathway, is one of the most studied genes for BDR and has more pronounced effects for children with asthma than for adults [30-33].

Our group has conducted several studies of age-related modifications of pharmacogenetics of asthma treatment responses [34-36], including studies of age by genotype interactions on BDR [37, 38]. In our analysis of repeated continuous BDR outcome measures in the CAMP clinical trial, we observed that polymorphisms in *SPATS2L* and *ASB3* were most predictive of BDR in children prior to adolescence [38]. These same polymorphisms were no longer predictive of BDR after age 15 years. In another multi-cohort study, we observed effect modification by age for genetic polymorphisms in the genes *PRAG1* and *ADRB2* [37]. Both of these studies suggest that age should be considered an effect modifier in pharmacogenetic research, to enhance our understanding of how genetic effects vary with age, and also to aid in discovery of genetic variants that would not be identified without explicitly accounting for age-related heterogeneity. It should be noted, that Vin order for effective medication to be studied adequately, even larger sample sizes are needed, as an interaction effect is now the primary measure of interest. Therefore, either increase in the sample size of multiple cohorts throughout various important age ranges is necessary before significant scientific understanding in this area will occur.

## Leveraging “Omics” Data to Identify Pharmacogenetic Targets

Results from traditional GWAS approaches in pharmacogenetics, where millions of individual polymorphisms are considered “agnostically” without regard to functional importance, may be insufficient to predict an individual’s BDR. While larger GWAS studies based on whole-genome sequencing data may enhance our knowledge of pharmacogenetic responses somewhat, they are unlikely to completely capture the full spectrum of genetic

effects. A “bottom-up” approach that leverages associations of BDR with other “omics” data may help focus pharmacogenetic studies on the most relevant genetic predictors. Metabolomics and epigenomics are two types of “omics” data that can be leveraged in this context. Modifications of the metabolome and epigenome are more proximal physiologically to asthma medication response and, as intermediary biomarkers, may highlight the most relevant pathways for consideration in pharmacogenetic testing.

Metabolomics studies of albuterol response have been conducted in airway and serum samples. In a study by Gaugg et al., metabolomics analysis of exhaled breath condensate (EBC) collected 10–30 min after albuterol administration revealed 131 mass spectral features that were altered as compared to placebo [39]. The changes in these features were strongly correlated within a given chemical class, suggesting that changes in biochemical processes in response to albuterol can be monitored using EBC. Fatty acids associated with lipolysis (acetic, propionic, and butyric acid) were increased following albuterol administration. Similarly, serum metabolomic profiling has also shown alterations in fatty acid levels directly following albuterol administration [40]. Metabolomic profiles may be influenced by administration of a drug, but that does not necessarily mean that the altered metabolic pathways play a role in the drug’s effectiveness. Future studies that examine whether metabolomics varies by BDR profile may help pinpoint specific metabolic pathways (and the genes that encode for them) for consideration in pharmacogenetics studies. We conducted one such study in the Childhood Asthma Management Program (CAMP) and Genetics of Asthma in Costa Rica Study (GACRS) populations [35]. Findings from our group show that response to albuterol is associated with a butyrate metabolite (2-hydroxyglutarate) in these two independent cohorts, further supporting the role of fatty acid metabolism as a potential pathway to consider for potential genetic influences of BDR using a pharmacogenetic framework.

Epigenomics is another type of “omics” that may prove useful for pharmacogenetic prediction [41]. The idea of epigenomics for precision medicine has been hypothesized previously [42]. Epigenetic signals, particularly those in airway cells, may highlight the most relevant genes involved in asthma treatment response for pharmacogenetic studies, or may in and of themselves serve as a predictive biomarker of drug response. The nasal methylome demonstrates a distinct DNA methylation pattern for BDR that is entirely independent of the altered DNA methylation signals observed for allergy, fraction exhaled nitric oxide (FeNO), or asthma status. In our 2019 Nature Communications study [43], we observed differential DNA methylation of 130 CpG sites in a cohort of over 500 adolescents with BDR data. Some of the top differentially methylated CpGs were in *LGALS8* (gene for an integrin-like protein involved in cell–cell adhesion and apoptosis), *STIM1* (a mediator of Ca + 2 influx channels), *ACTR3* (actin-related protein 3), and *KCNJ4* (a potassium ion conductance gene). Nasal samples were collected prior to assessing BDR. Therefore, these DNA methylation marks are predictive of response to albuterol, as opposed to being affected by administration of the drug. Additional studies are needed to determine whether airway epigenomics will be valuable as a tool for guiding our interrogation of the genome, or whether some combination of genetic polymorphisms and epigenetic marks may contribute to precision medicine for BDR in asthma.

### Polygenic Risk Scores in Pharmacogenetics

Polygenic risk scores (PRSs) provide the opportunity to combine small effects of individual genetic polymorphisms into an overall genetic risk score for prediction of a phenotype. The ability to predict individual responses to asthma medications through PRSs has great potential to guide treatment and may also provide information for sub-phenotyping of asthma. PRSs have been used successfully to predict respiratory disease phenotypes, including COPD [44]. This same concept can be applied to pharmacogenetic responses as well. Pharmacogenetic polygenic risk scores have been developed for drug responses in diabetes and cardiovascular disease [45-47]. Our group recently published a proof of concept study for a pharmacogenetic PRS for BDR [48] that prioritized GWAS variants with high combined annotation dependent depletion (CADD) scores for functional relevance. For PRS computation, we used results from a GWAS of BDR and ranked the top GWAS polymorphisms by CADD scores. CADD scores integrate multiple annotations into one score, in a way that prioritizes functional, deleterious, and disease causal variants across a wide range of functional categories. We observed a 0.63% decrease in BDR in response to albuterol for a standard deviation increase in the PRS. Additional studies in larger and more diverse populations are required to validate this PRS for BDR and to further develop a PRS with higher accuracy, so that it may be used clinically for albuterol response prediction.

## Conclusion

In order to expand our knowledge of BDR pharmacogenetics, larger studies with higher proportions of minority participants are needed to identify population-specific as well as transethnic loci. Replication of initial findings in minority populations has been challenging, due to the limited number of pharmacogenetics studies in these populations. Sensitivity analyses by BDR phenotype characterization may also be helpful, to determine whether genotypes are linked to incremental changes in BDR along with a continuous distribution and/or whether they are predictive of BDR above a certain threshold. Pharmacogenetic studies that incorporate effect modification by age, as well as those that leverage additional “omics” data types to identify the most relevant genetic pathways, may also help uncover novel pharmacogenetic loci for use in precision medicine. Developing pharmacogenetic PRSs also may have significant clinical value.

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## References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive

pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med. 2017.

2. Martinez FD, Vercelli D. Asthma Lancet. 2013;382(9901):1360–72. [PubMed: 24041942]
3. Billington CK, Penn RB, Hall IP. β2 Agonists. Handb Exp Pharmacol. 2017;237:23–40. [PubMed: 27878470]
4 •. Beasley R, Braithwaite I, Semprini A, Kearns C, Weatherall M, Pavord ID. Optimal asthma control: time for a new target. Am J Respir Crit Care Med. 2020;201(12):1480–7. [PubMed: 31905013] This review discusses the current limitations of pharmacological treatment of adult asthma, and proposes the development of practical methods to identify treatable traits contributing to respiratory symptoms in asthma.
5. McGeachie MJ, Stahl EA, Himes BE, Pendergrass SA, Lima JJ, Irvin CG, et al. Polygenic heritability estimates in pharmacogenetics: focus on asthma and related phenotypes. Pharmacogenet Genomics. 2013;23(6):324–8. [PubMed: 23532052]
6. Nieminen MM, Kaprio J, Koskenvuo M. A population-based study of bronchial asthma in adult twin pairs. Chest. 1991;100(1):70–5. [PubMed: 2060393]
7. Fagnani C, Annesi-Maesano I, Brescianini S, D'Ippolito C, Medda E, Nisticò L, et al. Heritability and shared genetic effects of asthma and hay fever: an Italian study of young twins. Twin Res Hum Genet. 2008;11(2):121–31. [PubMed: 18361712]
8. Wu AC, Tantisira K, Li L, Schuemann B, Weiss S. Childhood asthma management program research group. Repeatability of response to asthma medications. J Allergy Clin Immunol. 2009;123(2):385–90. [PubMed: 19064281]
9. Daya M, Ortega VE. Asthma genomics and pharmacogenomics. Curr Opin Immunol. 2020;66:136–42. [PubMed: 33171417]
10. Figueiredo RG, Costa RS, Figueiredo CA, Cruz AA. Genetic determinants of poor response to treatment in severe asthma. Int J Mol Sci. 2021;22(8):4251. [PubMed: 33923891]
11. Vijverberg SJH, Farzan N, Slob EMA, Neerincx AH and Maitlandvan der Zee AH. Treatment response heterogeneity in asthma: the role of genetic variation. EXPERT REVIEW OF RESPIRATORY MEDICINE, 2018; 12(1) 55–65 [PubMed: 29115880]
12. García-Menaya JM, Cordobés-Durán C, García-Martín E, Agündez JAG. Pharmacogenetic factors affecting asthma treatment response, potential implications for drug therapy. Front Pharmacol. 2019;10:520. [PubMed: 31178722]
13. Perez-Garcia J, Espuela-Ortiz A, Lorenzo-Diaz F, Pino-Yanes M. Pharmacogenetics of pediatric asthma: current perspectives. Pharmgenomics Pers Med. 2020;13:89–103. [PubMed: 32256100]
14. Naqvi M, Thyne S, Choudhry S, Tsai H, 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(8):639–48. [PubMed: 17943575]
15. Burchard EG, Avila PC, Nazario S, Casal J, Torres A, Rodriguez-Santana JR, et al. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. Am J Respir Crit Care Med. 2004;169(3):386–92. [PubMed: 14617512]
16 •. Spear ML, Hu D, Pino-Yanes M, Huntsman S, Eng C, Levin AM, et al. A genome-wide association and admixture mapping study of bronchodilator drug response in African Americans with asthma. Pharmacogenomics J. 2019;19(3):249–59. [PubMed: 30206298] GWAS study of bronchodilator response in minority populations (Latinos and African Americans) indicates that both population-specific and shared genetic variation contribute to differences in BDR phenotypes.
17. Finkelstein Y, Bournissen FG, Hutson JR, Shannon M. Polymorphism of the ADRB2 gene and response to inhaled beta-agonists in children with asthma: a meta-analysis. J Asthma. 2009;46(9):900–5. [PubMed: 19905915]
18•. Mak ACY, White MJ, Eckalbar WL, Szpiech ZA, Oh SS, Pino-Yanes M, et al. Whole-genome sequencing of pharmacogenetic drug response in racially diverse children with asthma. Am J Respir Crit Care Med. 2018 15;197(12):1552–64. [PubMed: 29509491] The first whole-genome sequencing pharmacogenetics study of children with asthma. The study focused on racially diverse children and used "responder" and "non-responder" status from the tails of the bronchodilator response distribution as the phenotype of interest.

19 •. Jerome RN, Pulley JM, Sathe NA, Krishnaswami S, Dickerson AB, Worley KJ, et al. Uncovering Outcome Disparities of β2 Adrenergic Agonists in Blacks: A Systematic Review. J Natl Med Assoc. 2021; 113(l):8–29. [PubMed: 32732018] Systematic review of studies on β2 agonist response among Blacks, including pharmacogenetics studies.

20. Global Strategy for Asthma Management and Prevention. 2019. Date last accessed: 2 August 2021.

21. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948–68. [PubMed: 16264058]

22. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138. [PubMed: 17983880]

23. Guezguez F, Ben SH. What constitutes a "clinically significant" bronchodilator response in children? Eur Respir J. 2020;55(5):2000207. [PubMed: 32381631]

24. Waalkens HJ, Merkus PJ, van Essen-Zandvliet EE, Brand PL, Gerritsen J, Duiverman EJ, et al. Assessment of bronchodilator response in children with asthma. Dutch CNSLD Study Group. Eur Resp J. 1993;6(5):645–51.

25 •. Ferreira MA, Mathur R, Vonk JM, Szwajda A, Brumpton B, Granell R, et al. Genetic architectures of childhood-and adult-onset asthma are partly distinct. The Am J Hum Genet. 2019;104(4):665–84. [PubMed: 30929738] This study examined the extent to which genetic risk factors are shared between childhood-onset (COA) and adult-onset (AOA) asthma. Distinct loci for COA vs. AOA may be useful for differentiating patho-physiology and enhancing precision in treatments for asthma by age of onset.

26. Dunn RM, Lehman E, Chinchilli VM, Martin RJ, Boushey HA, Israel E, et al. Impact of age and sex on response to asthma therapy. Am J Respir Crit Care Med. 2015;192(5):551–8. [PubMed: 26068329]

27. Gubbels Bupp MR, Potluri T, Fink AL, Klein SL. The confluence of sex hormones and aging on immunity. Front Immunol. 2018;9:1269. [PubMed: 29915601]

28. van den Beld AW, Kaufman J-M, Zillikens MC, Lamberts SWJ, Egan JM, van der Lely AJ. The physiology of endo-crine systems with ageing. Lancet Diabetes Endocrinol. 2018;6(8):647–58. [PubMed: 30017799]

29. Litonjua AA, Lasky-Su J, Schneiter K, Tantisira KG, Lazarus R, Klanderman B, et al. ARG1 is a novel bronchodilator response gene: screening and replication in four asthma cohorts. Am J Respir Crit Care Med. 2008;178(7):688–94. [PubMed: 18617639]

30. Lipworth BJ, Basu K, Donald HP, Tavendale R, Macgregor DF, Ogston SA, et al. Tailored second-line therapy in asthmatic children with the Arg(16) genotype. Clin Sci (Lond). 2013;124(8):521–8. [PubMed: 23126384]

31. Palmer LJ, Celedón JC, Chapman HA, Speizer FE, Weiss ST, Silverman EK. Genome-wide linkage analysis of bronchodilator responsiveness and post-bronchodilator spirometric phenotypes in chronic obstructive pulmonary disease. Hum Mol Genet. 2003;12(10):1199–210. [PubMed: 12719384]

32. Zuurhout MJL, Vijverberg SJH, Raaijmakers JAM, Koenderman L, Postma DS, Koppelman GH, et al. Argl6 ADRB2 genotype increases the risk of asthma exacerbation in children with a reported use of long-acting β2-agonists: results of the PACMAN cohort. Pharmacogenomics. 2013;14(16):1965–71. [PubMed: 24279851]

33. Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calhoun WJ, et al. Effect of beta2-adrenergic receptor polymorphism on response to long-acting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet. 2009;374(9703):1754–64. [PubMed: 19932356]

34. Dahlin A, Sordillo JE, McGeachie M, Kelly RS, Tantisira KG, Lutz SM, et al. Genome-wide interaction study reveals age-dependent determinants of responsiveness to inhaled corticosteroids in individuals with asthma. PLoS One. 2020;15(3):e0229241. [PubMed: 32119686]

35. Kelly RS, Sordillo JE, Lutz SM, Avila L, Soto-Quiros M, Celedón JC, et al. Pharmacometabolomics of bronchodilator response in asthma and the role of age-metabolite interactions. Metabolites. 2019;9(9):E179. [PubMed: 31500319]

36. Sordillo JE, Lutz SM, Kelly RS, McGeachie MJ, Dahlin A, Tantisira K, et al. Plasmalogens mediate the effect of age on bronchodilator response in individuals with asthma. Front Med (Lausanne). 2020;7:38. [PubMed: 32118022]
37. Voorhies K, Sordillo JE, McGeachie M, Ampleford E, Wang AL, Lasky-Su J, et al. Age by single nucleotide polymorphism interactions on bronchodilator response in asthmatics. J Pers Med. 2021;11(1):59. [PubMed: 33477890]
38. Sordillo JE, McGeachie M, Lutz SM, Lasky-Su J, Tantisira K, Tsai CH, et al. Longitudinal analysis of bronchodilator response in asthmatics and effect modification of age-related trends by genotype. Pediatr Pulmonol. 2019;54(2):158–64. [PubMed: 30585438]
39. Gaugg MT, Engler A, Nussbaumer-Ochsner Y, Bregy L, Stöberl AS, Gaisl T, et al. Metabolic effects of inhaled salbutamol determined by exhaled breath analysis. J Breath Res. 2017;11(4):046004. [PubMed: 28901297]
40. Nowadly CD, Liao S-Y, Rose JS. Effects of continuous albuterol inhalation on serum metabolome in healthy subjects: more than just lactic acid. J Clin Pharmacol. 2021;61(5):649–55. [PubMed: 33128239]
41. Cascorbi I, Schwab M. Epigenetics in drug response. Clin Pharmacol Ther. 2016;99(5):468–70. [PubMed: 27061003]
42. Olivier M, Asmis R, Hawkins GA, Howard TD, Cox LA. The need for multi-omics biomarker signatures in precision medicine. Int J Mol Sci. 2019;20(19):E4781. [PubMed: 31561483]
43. Cardenas A, Sordillo JE, Rifas-Shiman SL, Chung W, Liang L, Coull BA, et al. The nasal methylome as a biomarker of asthma and airway inflammation in children. Nat Commun. 2019 12;10(1):3095. [PubMed: 31300640]
44. Moll M, Sakornsakolpat P, Shrine N, Hobbs BD, DeMeo DL, John C, et al. Chronic obstructive pulmonary disease and related phenotypes: polygenic risk scores in population-based and case-control cohorts. Lancet Respir Med. 2020;8(7):696–708. [PubMed: 32649918]
45. Li JH, Szczerbinski L, Dawed AY, Kaur V, Todd JN, Pearson ER, et al. A polygenic score for type 2 diabetes risk is associated with both the acute and sustained response to sulfonylureas. Diabetes. 2021;70(1):293–300. [PubMed: 33106254]
46. Lewis JP, Backman JD, Reny J-L, Bergmeijer TO, Mitchell BD, Ritchie MD, et al. Pharmacogenomic polygenic response score predicts ischaemic events and cardiovascular mortality in clopidogrel-treated patients. Eur Heart J Cardiovasc Pharmacother. 2020;6(4):203–10. [PubMed: 31504375]
47. Chasman DI, Giulianini F, Demler OV, Udler MS. Pleiotropy-based decomposition of genetic risk scores: association and interaction analysis for type 2 diabetes and CAD. Am J Hum Genet. 2020;106(5):646–58. [PubMed: 32302534]
48. Sordillo JE, Lutz SM, McGeachie MJ, Lasky-Su J, Weiss ST, Celedón JC, et al. Pharmacogenetic polygenic risk score for bronchodilator response in children and adolescents with asthma: proof-of-concept. J Pers Med. 2021;11(4):319. [PubMed: 33923870]