EXPERT OPINION



# Influence of ethnicity on response to asthma drugs

Mario Cazzola[†], Paola Rogliani, Alessandro Sanduzzi & Maria Gabriella Matera

[†]*University of Rome Tor Vergata, Department of Systems Medicine, Respiratory Clinical Pharmacology Unit, Rome, Italy*

***Introduction:*** Understanding variability in the response to asthma medications is essential to ensure appropriate prescribing. Given that there are increased asthma treatment failures observed in ethnic minorities receiving asthma therapeutics, it is fundamental to understand the factors related to ethnicity that can modify the response to asthma therapy.

***Areas covered:*** Race/ethnicity is an important determinant of drug response and therefore contributes to interindividual variability. It is generally recognized that its effects on drug response are determined by both genetic and environmental factors to a varying extent, depending on the ethnic groups and probe drugs studied. Also, adherence to therapy can influence pharmacological response to asthma therapeutics.

***Expert opinion:*** Health-care professionals might never use the treatment in their patients irrespective of their ethnicity and thus inadvertently increase ethnic health inequality. However, our understanding of whether and/or how ethnicity influences pharmacological response to asthma therapeutics is still very scarce. A holistic, integrative systems biology approach that combines large-scale molecular profiling traits (e.g., transcriptomic, proteomic, metabolomic traits) and genetic variants could help to personalize the treatment of asthmatic patients regardless of race/ethnicity.

**Keywords:** asthma, asthma therapeutics, environmental factors, ethnicity, genetic factors, health care, race

*Expert Opin. Drug Metab. Toxicol. [Early Online]*

## 1. Introduction

Race distinguishes major groups of people according to their ancestry and a more or less distinctive combination of physical characteristics. On the contrary, according to the Oxford Dictionaries, ethnicity is the fact or state of belonging to a social group that has a common national or cultural tradition [1]. This means that culture, religion, ancestry and language should be incorporated in the concept of ethnicity. Consequently, ethnicity not only includes what is usually called race, but also refers to characteristics that are of social, psychological, cultural and political nature [2].

Ethnic disparities in health and health care recently have received considerable attention. The quality of health care received by ethnic minority groups has overall been shown to be poorer than that received by the majority population and this is likely to contribute to their poorer health outcomes [3]. There are multiple factors associated with ethnic disparities in health and health care. These factors include structural barriers (e.g., ability to access the health-care system), process-of-care barriers (e.g., ability to navigate the health-care system), and process-of-care barriers at the interpersonal level (e.g., ability to work effectively with a health-care provider) for equitable, quality care [4].

However, several key issues were identified as likely to be ethnic-specific rather than a reflection of minority status: impact of parental and professional knowledge

10.1517/17425255.2015.1047341 © 2015 Informa UK, Ltd. ISSN 1742-5255, e-ISSN 1744-7607

**Article highlights.**

- A possible explanation for the increased asthma treatment failures observed in ethnic minorities receiving asthma therapeutics is that some minorities might have a pharmacogenomic predisposition to either nonresponse or to adverse response with this class of therapy.
- The effects of ethnicity on pharmacological response to asthma therapeutics are also determined by environmental factors to a varying extent, depending on the ethnic groups.
- Differences in adherence to therapy by race-ethnicity are well described. Adherence to therapy can influence pharmacological response to asthma therapeutics.
- The published evidence clearly shows that our understanding of whether and/or how ethnicity influences pharmacological response to asthma therapeutics is still very scarce and almost all the information available to us have been produced in the United States.
- Minority ethnic people are markedly under-represented in research.
- Studying response to specific therapies using race as a phenotype is a too simplistic approach and could lead to erroneous conclusions because it does not reflect the complexity of asthma.
- A personalized approach based on individual characteristics such as age, body mass index, race, and local environment, with incorporation of predictive biomarkers including genetic profiles or scores that combine several risk-associated genetic variants is needed.

This box summarizes key points contained in the article.

and beliefs, health service utilization pattern explanations and the impact of prejudice and stigmatization [5].

As elegantly highlighted by Davidson *et al.* [3], ethnic minority asthma sufferers are less well managed by specialist and preventative care, less likely to be prescribed guidance-based treatments, and are more likely to leave consultations without care plans or appropriate prescription. All this in itself makes the quality of asthma treatment poor. However, an analysis that compared African Americans and whites who participated in clinical trials, and thus had equal access to asthma caregivers and asthma medications, documented that African Americans experienced a higher rate of asthma treatment failures than whites [6]. The increased rate of treatment failures seemed to occur in African Americans being treated with long-acting $\beta_2$-agonists (LABAs), without a protective effect by the concomitant use of either inhaled corticosteroids (ICSs) or leukotriene receptor antagonists (LTRAs). Moreover, a Danish study that analyzed data obtained from the Danish Civil Registration System, the Central Taxpayers' Register and the Danish National Prescription Register documented that in Denmark ethnic differences in the use of anti-asthmatic medication are present to a higher degree for preventive rather than relief medication and this can induce a higher risk of under-medication and suboptimal disease control [7]. These differences cannot be explained by socioeconomic characteristics because they have been recorded within a Nordic welfare context where access to health-care services is free with no payment, and with outpatient prescription drug use being highly reimbursed for chronic conditions.

Since, a possible explanation for the increased asthma treatment failures observed in ethnic minorities receiving asthma therapeutics is that some minorities might have a pharmacogenomic predisposition to either nonresponse or to adverse response with this class of therapy [8], it is fundamental to understand, when possible, the factors related to ethnicity that can modify the response to asthma therapy. In assessing the role of ethnicity on response to asthma therapeutics both genetic and environmental factors must be considered.

Epidemiologic trends suggest that asthma may provide an excellent paradigm for understanding the role of ethnicity on health disparities. Ethnicity is an important determinant of drug response and therefore contributes to interindividual variability. It is generally recognized that the effects of ethnicity on drug response are determined by both genetic and environmental factors to a varying extent, depending on the ethnic groups and probe drugs studied [9]. Also adherence to therapy can influence pharmacological response to asthma therapeutics.

Since understanding variability in the response to asthma medications is essential in order to ensure appropriate prescribing, in this review we will describe the influence of ethnicity on pharmacological response to asthma therapeutics.

## 2. Genetic factors

Several genetic factors that affect the pharmacotherapeutic responses to asthma medications have now been recognized.

### 2.1 β2-agonists

Pharmacogenetic studies in multiethnic populations have focused on the gene encoding for the $\beta_2$-adrenoceptor (*ADRB2*), which is located on chromosome 5q31 – 33. So far, nearly 49 validated genetic polymorphisms in the *ADRB2* gene have been described, with the greatest attention devoted to the single-nucleotide polymorphisms (SNPs) causing amino acid substitutions at positions 16 and 27. Several SNPs have been identified in the coding region of the *ADRB2* gene [10]. The most common SNPs result from three missense mutations in the coding region of *ADRB2*. The first SNP (A>G), at nucleotide 46, causes the substitution of glycine (Gly) for arginine (Arg) at codon 16, while the second one (C>G), at nucleotide 79, results in the substitution of glutamic (Glu) acid for glutamine (Gln) at codon 27 and the third one the substitution of isoleucine (Ile) for threonine (Thr) at codon 164 [10]. Replacement of the base may not only alter the gene expression and function of the $\beta_2$-adrenoceptor, it may also alter the response to $\beta_2$-agonist therapies.

The Arg16Gly and Gln27Glu polymorphisms result in differential agonist-stimulated $\beta_2$-adrenoceptor downregulation in transfected cell systems, including human airway smooth muscle cells [11]. Significantly greater isoprenaline-induced $\beta_2$-adrenoceptor downregulation was demonstrated in receptors with the Gly16 compared with the Arg16 genotype [11]. Conversely, the Glu27 allele is relatively resistant to downregulation of $\beta_2$-adrenoceptor during exposure to $\beta_2$-agonists in comparison with receptors with the Gln27 genotype [11]. When Glu27 is co-inherited with Gly16, phenotypic responses favor the Gly16 genotype [11]. Gln27 influences the behavior of cells with the Gly16Gln27 haplotype, which exhibits less acute and long-term desensitization as measured by cAMP levels [11]. The Thr164Ile polymorphism has been associated with impaired receptor ligand binding and coupling to $G_s$ protein in response to different short-acting $\beta_2$-agonists (SABAs) such as isoproterenol and salbutamol resulting in a significant reduction in basal $\beta_2$-adrenoceptor activity and agonist-stimulated activation, at least *in vitro* [11].

In initial clinical studies that examined the influence of $\beta_2$-adrenoceptor genotype on the response to long-term and repeated dosages of SABAs, the Arg16 genotype was more closely associated with reduced responses with enhanced agonist-mediated desensitization than Gly16 genotype [10], but subsequent studies found opposite results or no association [12]. Also the evidence regarding the association between *ADRB2* polymorphism and altered response to LABAs is rather inconsistent [10,11]. Two prospective genotype-stratified trials, the Asthma Clinical Research Network Long-Acting Beta Agonist Response by Genotype (LARGE) Trial [13] and a trial by Bleecker *et al.* [14] failed to show differences in peak expiratory flow rate (PEFR) responses between Gly16Arg genotypes during LABA treatment, independent of whether LABA was administered as a monotherapy or in combination with ICS therapy. However, in the LARGE trial [13], African–American subjects harboring the Arg/Arg polymorphism demonstrated no incremental benefit of LABAs with respect to lung function compared with placebo, whereas Gly/Gly African Americans did improve with LABAs.

Genetic variation in *ADRB2* differs significantly between ethnic groups [15]. The allelic frequency of Arg16 is lower in white Americans (39.3%) than in African Americans (49.2%), and thus African Americans are more likely to be homozygous for Arg16 (i.e., to have the Arg/Arg genotype) [16]. Despite having more severe asthma, Puerto Ricans, who are an admixed population of African, European, and Native American ancestries, have lower bronchodilator response compared with African Americans or Mexicans [17,18], and African Americans have lower bronchodilator response compared with patients of European ancestry [17,18]. Genetic variations may help to explain the lower response to salbutamol in Puerto Ricans than other Hispanic subgroups [19].

However, we have already mentioned that the Arg/Arg polymorphism at position 16 of the β-adrenoreceptor is also present in African Americans and whites (allele frequency 0.5 in African Americans [20], 0.37 in a white Scottish population [21]) and also in Han Chinese, Japanese and Mexican Americans (allele frequency 0.58, 0.44 and 0.48, respectively [22]). Therefore, it likely does not explain the whole story regarding adverse effects of LABAs, and, in any case, it is unlikely that these genetic variations account for the rare, life-threatening events seen with LABA use [23]. Lastly, it has been suggested that the rare *ADRB2* variant Ile164 in non-Hispanic white patients and an insertion–deletion polymorphism within the regulatory region (–376 In-Del) in African Americans are associated with adverse events during LABA therapy [24].

The results of a genome-wide association study suggested that other rare variations contribute to individual differences in response to salbutamol, notably in solute carrier genes that include membrane transport proteins involved in the transport of endogenous metabolites and xenobiotics [25]. It is intriguing that a recent genome-wide association study of bronchodilator response in patients of European ancestry identified spermatogenesis associated, serine-rich 2-like (*SPATS2L*) as a novel candidate gene for being an important regulator of $\beta_2$-adreneceptor downregulation [26]. The minor allele of rs295137 in *SPATS2L* is associated with a greater acute SABA bronchodilator response and is more common in an African population compared with populations of European descent [26] and is less frequent in Han Chinese and Japanese [22].

β-Agonists bind to $\beta_2$-adreneceptor to activate a G-protein-coupled receptor pathway via adenylyl cyclase type 9. An SNP (Ile772Met) adjacent to adenylyl cyclase type 9 gene (*ADCY9*) has been associated with salbutamol bronchodilator response in Puerto Rican and Mexican asthmatics from the Genetics in Latino Americans (GALA) study cohort [25]. *ADCY9* has also been associated with bronchodilator response to LABA in an ICS-treated Korean asthma cohort [27]. These findings suggest that G-protein-coupled receptor pathway-related gene variation might determine responsiveness to β-agonists. The variable allele frequency between different ancestral populations for *ADCY9* is 0.36 in Americans with European ancestry, 0.12 in Yorubans from Nigeria, 0.12 in African Americans, 0.22 in Mexican Americans, 0.4 in Han Chinese and 0.36 in Japanese [22]. The corticotrophin-releasing hormone receptor-2 is a G-protein-coupled receptor that regulates airway smooth muscle relaxation via adenylyl cyclase activation Also an SNP adjacent to corticotrophin-releasing hormone receptor-2 gene (*CRHR2*) has been associated with salbutamol bronchodilator response in Puerto Rican and Mexican asthmatics [25].

### 2.2 Inhaled corticosteroids

Genetic variation could also contribute to significant between-person variability in response to ICSs, although the genetic predictors of a poor long-term response to ICS differ markedly depending on the definition of response (exacerbation versus improved lung function) [28]. Chan *et al.* found

that African Americans had a 38% prevalence of steroid-resistant asthma compared with 12% in white patients [29]. An *in vitro,* study has suggested that steroid responsiveness might differ between African American and white patients, as evidenced by between-group differences in the ability of dexamethasone to suppress T-cell proliferative responses [30]. Interethnic differences in steroid sensitivity reflect variation in transcriptional response at many genes, including regulators with large effects (e.g., *NFKB1*, a gene found to predict lymphocyte steroid sensitivity within populations) and numerous other genes with smaller effects [31]. Lower steroid sensitivity in individuals of African ancestry reveals weaker transcriptional response at a large number of genes [31]. Rosenwasser *et al.* [32] found an association between the IL-4 C-589→T sequence variant in the *IL4* gene promoter polymorphism, which is linked with increased *IL4* gene transcription, and steroid-resistant asthma. Interestingly, the frequency of this IL-4 C-589→T sequence variant is significantly greater among African–American asthmatic patients than among white asthmatic patients [33]. In any case, the results of a study that sought to determine the degree to which African–American patients respond to ICS medication and whether the level of response is influenced by other factors, including genetic ancestry suggested that genetic ancestry might not contribute to differences in ICS controller response among African–American patients with asthma [34].

Intriguingly, it has reported that in patients on ICS those with the Arg16Arg genotype had a significantly lower methacholine $PC_{20}$ than those with the Gly16Gly genotype, but there was no interaction between ICS use and race (African Americans and Whites with asthma) [35]. However, the clinical response to an LABA did not differ among *ADRB2* Arg16Gly SNPs during chronic dosing in the presence of an ICS in Chinese Han asthmatic patients [36].

The minor allele of rs37972 in the glucocorticoid-induced transcript gene *GLCCI1* is associated with a diminished response to ICSs and is less common in populations of African descent compared with a European population [37].

### 2.3 Leukotriene modifiers

Cysteinyl leukotrienes (cysLTs) are synthesized from arachidonic acid located in membrane-phospholipids by cytosolic phospholipase $A_2$ in response to stimulation [38,39]. Arachidonic acid is converted to 5-hydroperoxyeicosatetraenoic acid and leukotriene $A_4$ ($LTA_4$) by membrane-bound 5-lipoxygenase (ALOX5) and 5-lipoxygenase activating protein (ALOX5AP). In human mast cells, basophils, eosinophils and macrophages, $LTA_4$ is converted to $LTB_4$ by $LTA_4$ hydrolase ($LTA_4H$), or is conjugated with reduced glutathione by $LTC_4$ synthase to form $LTC_4$. $LTC_4$ is transported to the extracellular space mainly by the multidrug resistance protein 1 (MRP1). $LTC_4$ is converted to $LTD_4$ and $LTE_4$ by γ-glutamyltransferase and dipeptidase that promoter polymorphisms in the *ALOX5* and the $LTC_4$ synthase (*LTC4S*) genes contribute to variability in response to LT modifiers and LT-selective antagonists. The complexity of the LT pathway explains why there are multiple pharmacogenetic loci in modulating the therapeutic response to leukotriene modifiers [39].

Variants in the *ALOX5AP* and *LTA4H* genes would modify both the effects of leukotriene modifiers at the cysLT receptor and the effects of $LTB_4$ at its receptor, thereby affecting these medications' ability to augment bronchodilator responsiveness [40]. *LTA4H* and *ALOX5AP* polymorphisms are associated with augmentation of bronchodilator responsiveness by leukotriene modifiers in Puerto Ricans, but not Mexicans [40].

The frequency of both *LTA4H* and *ALOX5AP* by racial group is higher in Mexicans, Chinese and Japanese than in African Americans, Africans living in Nigeria and European white descents with ancestry from northern and Western Europe [7].

Carrying two copies of a minor variant *ALOX5* promoter SP1 tandem repeat allele contributes to a trend toward worse asthma control, likely because of an increased 5-lipoxygenase activity [41]. Variant alleles for this tandem repeat polymorphism occur at a much higher frequency in African–American children than in those of white European descent [41].

### 2.4 Theophylline

Theophylline is metabolized to 1,3-dimethyl uric acid through 8-hydroxylation by CYP1A2, a subtype of CYP, and partly by *CYP2E1*, as well as by *CYP1A2*, to 1-methylxanthine through 3-demethylation or to 3-methylxanthine through 1-demethylation [42]. Genetics appear to be responsible for ~ 35% of variability in CYP1A2 activity. The frequency of poor metabolizer-phenotype status varies in different racial/ethnic groups [43]. Examples of poor metabolizer frequency in different populations are Australians (5%), Chinese (5%) and Japanese (14%). Overall, Asian and African populations have lower CYP1A2 activity compared to Caucasians [44].

## 3. Exogenous or environmental factors

Environmental exposure to both allergens and air pollutants exposures can influence not only the pathogenesis and severity of asthma but also the response to therapy. Also obesity increases susceptibility to asthma and can modify the response to therapy.

### 3.1 Smoke

In subjects with mild asthma who smoke, the response to ICSs is attenuated, suggesting that adjustments to standard therapy may be required to attain asthma control [45]. Also secondhand smoke induces a reduced response to corticosteroids [46].

There are several proposed mechanisms of corticosteroid resistance in asthmatic smokers [47]. Cigarette smoking and oxidative stress impair HDAC2 function [48]. HDAC activity is necessary for corticosteroids to fully suppress cytokine production. In fact, corticosteroids suppress multiple inflammatory genes that are activated in chronic inflammatory

diseases by reversing histone acetylation of activated inflammatory genes through binding of liganded glucocorticoid receptors to coactivator molecules and recruitment of HDAC2 to the activated transcription complex. Moreover, airway mucosal permeability is increased in smokers with normal lung function and in asthmatic patients who do not smoke [47]. Another proposed mechanism of corticosteroid resistance is the downregulation of $\beta_2$-adrenoceptors in lymphocytes that is caused by cigarette smoking [47]. An increase in the number of neutrophils found in the airway in heavy smokers who have asthma has also been associated with poor corticosteroid response [49].

A recent study that used the Centers for Disease Control and Prevention's 2009–2010 Behavioral Risk Factor Surveillance System documented that both current and former smokers had a significantly higher asthma prevalence than nonsmokers among whites, blacks, Hispanics and American Indians or Alaska Natives (current smokers only) but not among Asian/Pacific Islanders and those in the other race category [50]. Smoking behavior among adults varies with ethnicity and secondhand smoke, with members of certain ethnic groups (e.g., Puerto Ricans) smoking more often and/or more heavily than members of other groups (e.g., Mexicans). Interestingly, in a retrospective study, Chan *et al*. found that patients with corticosteroid-insensitive asthma were more likely to be African American [51]. Moreover, in a study that showed that ICS use may be associated with augmented bronchodilator responsiveness to salbutamol in Mexican Americans and Puerto Ricans, but not in African Americans, with persistent asthma, African–American asthmatic patients had a higher prevalence of tobacco use than Mexican Americans but not Puerto Ricans [52].

It must be mentioned that it has been reported the joint effects of functional variants in *ADRB2* and personal history of smoking on asthma [53].

### 3.2 Obesity

Obesity is strongly associated with asthma [54]. This association is stronger among women than men [55]. However, its presence in black and Hispanic men supports the concept that the male finding, while weaker, is indeed present among some men [56] and ethnicity may play a role.

In effect, among asthmatics in the Childhood Asthma Management Program (CAMP), the proportion of overweight was higher in blacks and Hispanics than in whites and in members of other races [57]. In the United States, 21.2% in Mexican Americans, 24.3% in non-Hispanic blacks, and 14% in non-Hispanic whites are obese [58]. Interestingly, worse asthma control is uniformly associated with increased body mass index in boys. Among girls, the direction of this association varied with race/ethnicity [59]. Obese Mexican American girls had greater odds of worse asthma control compared with their normal-weight counterparts. In contrast, obese African–American girls (overweight or obese) had greater odds of having better asthma control compared with their normal-weight counterparts [59].

Obese patients are less likely than the nonobese to achieve asthma control with an ICS or an ICS combined with an LABA [60]. ICSs might be less effective in overweight and obese asthmatic subjects because in these patients inflammatory state might have a systemic component rather than being confined to the airways [61].

### 3.3 Environmental factors

It is widely accepted that exposure to ambient concentrations of air pollutants can cause short-term exacerbations in those who already have asthma [62]. Air pollution may contribute to the higher prevalence of asthma, especially in some minority children exposed to higher levels of air pollution [63]. Obviously, effects of ethnicity might be confounded with those effects associated with low socioeconomic status. Lower-income, minority communities have higher exposures to environmental pollutants because of the disproportionately higher numbers of toxic waste dumps, major highways, bus terminals, industry, and so forth located nearby [58]. In USA, being a member of a racial/ethnic minority group (non-Hispanic black 4.4%, Hispanic 5%, non-Hispanic white 3.1%), being foreign born (5.1 vs 3.5% native born), and speaking a language other than English at home (Spanish 5.1% vs English 3.3%) increases the probability of living close to a major highway [64]. In a population of predominantly African–American and Latino children living in the economically stressed city of Detroit, current levels of ambient air pollution adversely affected children with asthma who were corticosteroid dependent, a marker of the disease severity [65].

Recent exposure to $NO_2$ and possibly $O_3$ may reduce the response to SABAs in producing bronchodilation in Mexican children with asthma who were residing in a highly polluted environment [66]. In any case, patients with severe asthma might be the most likely to have respiratory symptoms with exposure to air pollutants, despite treatment with steroids [67].

## 4. Adherence to therapy

Most obviously, if a person does not adhere to treatment, symptoms may not be relieved or the disorder may not be cured. Differences in adherence to therapy by race-ethnicity are well described. External factors such as income, possession of commercial health insurance, psychosocial stressors (e.g., residential crime rates) and characteristics of the facility where care is provided can all affect the level of medication adherence [68]. Internal factors, such as patients' beliefs, mainly belief in God's control of health, knowledge and motivation, may also influence adherence to asthma therapy [68].

It is likely that misunderstanding of the role of inhaled anti-inflammatory medication is the main factor associated with reduced adherence to its daily use [69]. However, patient-dependent factors, such as cultural attitudes toward treatments, disease treatment expectations and effects on the

quality of life, are also likely to play a significant role in shaping patients' approach to asthma management and their acceptance of asthma and its impact.

A study carried out in Detroit, USA identified poorer ICS adherence in African–American patients compared with white patients even after adjusting for multiple socioeconomic variables [70]. In any case, African–American patients also had a lower median household income and a higher index crime rate in their area of residence and were more likely to live in an inner-city location. In the Pharmacogenetics of Asthma Medication in Children: Medication with Anti-inflammatory Effects (PACMAN) cohort study, Dutch ethnicity was associated with higher ICS adherence rates [71]. Non-Dutch parents had more often high concerns about their child's medication use, and were more often low educated.

## 5. Conclusion

Compared to their white counterparts, African–Americans and Hispanics/Latinos suffering from asthma seem to be less responsive to ICSs and LABAs when prescribed as part of the general asthma guidelines. A variety of factors including race/ethnicity, genetics, culture and environment give reason for the lack of treatment efficacy in these groups.

## 6. Expert opinion

The published evidence clearly shows that our understanding of whether and/or how ethnicity influences pharmacological response to asthma therapeutics is still very scarce and almost all the information available to us have been produced in USA. Unfortunately, minority ethnic people are markedly under-represented in research [72] and in any case, comparative USA–European data reveal that minority ethnic people are significantly more likely to be recruited into asthma trials in the USA than in Europe [73] likely because the US National Institute of Health's (NIH) Revitalization Act 1993 dictates that all NIH-funded clinical research must include people from ethnic minority groups [74], whereas there is no similar mandatory policy in the European Union.

This is a critical issue because an asthma treatment that works well in a trial where all the participants are white Europeans might not be suitable for other ethnic groups [72]. Therefore, health-care professionals might never use an asthma treatment in all their patients irrespective of their ethnicity and thus inadvertently increase ethnic health inequality [72].

On the other hand, we must honestly admit that the response to drug treatment in asthma is a complex trait and is markedly variable even in patients with apparently similar clinical features and, in any case, advances in defining responders and nonresponders have not progressed significantly since the sequencing of the human genome. Moreover, asthma is regarded as a heterogeneous disorder with distinct phenotypes and specific treatments for asthma are unlikely to benefit all patients with asthma, but more likely target specific phenotypes [75].

It is obvious that better phenotyping of patients and larger sample sizes are absolutely required. Wechsler *et al.* [76] stressed the importance of studying response to specific therapies using race as a phenotype. We believe that this approach is too simplistic and could lead to erroneous conclusions. For example, in a study that replicated the Severe Asthma Research Program (SARP) pediatric asthma clusters by using a separate, large clinical trials network, early-onset/severe-lung function and early-onset/comorbidity clusters were associated with differential and limited response to therapy, respectively, but there was no difference in race among clusters [77].

Rather than consider race, we should think about the genetic profile of the patient that we must treat. For instance, there is much debate on the reduced response to LABAs in African–American subjects harboring the Arg/Arg polymorphism at position 16 of the β-adrenoreceptor [22]. However, we have already mentioned that this polymorphism is also present in whites as well as in Chinese and Japanese and, accordingly, it cannot be considered to be a peculiarity of a specific race/ethnicity. In any case, the pharmacogenetic effect of any individual variant is likely to be small [78]. Therefore, given that multiple genes influence the bronchodilation induced by $\beta_2$-agonists, investigating the effects and potential interaction of multiple genes is necessary. Each of these genes may have a small but significant effect; thus, synergism may exist between different genetic variants [78]. This makes the possibility of a specific effect of race/ethnicity even weaker.

We completely agree with Ortega that, as our understanding of the pharmacogenetics of asthma improves, it will then be possible to create biomarkers panels designed for personalized, precision approaches in asthma based on an individual's genetic profile [22]. In order to do so, it is time to move to a more holistic integrative systems biology approach that combines large-scale molecular profiling traits (e.g., transcriptomic, proteomic, metabolomic traits) and genetic variants [78].

The goal of all health-care professionals is to prescribe the right drug for the right patient. Therefore, therapeutic options must be tailored for each individual patient. This means that clinicians must personalize the prescribed therapy. Personalized medicine is based on individual characteristics such as age, body mass index, race and local environment, with incorporation of predictive biomarkers including genetic profiles or scores that combine several risk-associated genetic variants [79]. Obviously, the influence of ethnicity on pharmacological response to asthma therapeutics is something that must be considered. However, the mere focus on race/ethnicity runs the risk of losing sight of the complexity of asthma and, consequently, increasing ethnic health inequality in a true unreasonable manner.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.



## Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Oxford Dictionaries. Oxford University Press. Retrieved 28 December 2014
2. Abramson HJ. Ethnic diversity in catholic America. Wiley; New York, NY: 1973
3. Davidson E, Liu JJ, Sheikh A. The impact of ethnicity on asthma care. Prim Care Respir J 2010;19:202–8

• **An interesting review that examined the impact of ethnicity on asthma, with a focus on the literature from the UK and the USA.**

4. Cabana MD, Lara M, Shannon J. Racial and ethnic disparities in the quality of asthma care. Chest 2007;132(5 Suppl):810S–7S
5. Lakhanpaul M, Bird D, Manikam L, et al. A systematic review of explanatory factors of barriers and facilitators to improving asthma management in South Asian children. BMC Public Healt 2014;14:403
6. Wechsler ME, Castro M, Lehman E, et al. Impact of race on asthma treatment failures in the Asthma Clinical Research Network. Am J Respir Crit Care Med 2011;184:1247–53
7. Cantarero-Arévalo L, Ersbøll AK, Holstein BE, et al. Ethnic and migrant differences in the use of anti-asthmatic medication for children: the effect of place of residence. Pharmacoepidemiol Drug Saf 2014;23:95–104
8. Ortega VE, Meyers DA. Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. J Allergy Clin Immunol 2014;133:16–26

•• **Paper that explains the rationale for pharmacogenetics in the management of asthma in different ethnic groups.**

9. Xie HG, Kim RB, Wood AJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. Annu Rev Pharmacol Toxicol 2001;41:815–50
10. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev 2012;64:450–504

•• **A broad review that describes bronchodilators in all their aspects, including genetic factors that affect their pharmacotherapeutic responses.**

11. Chung LP, Waterer G, Thompson PJ. Pharmacogenetics of β2 adrenergic receptor gene polymorphisms, long-acting β-agonists and asthma. Clin Exp Allergy 2011;41:312–26
12. Lima JJ. Do genetic polymorphisms alter patient response to inhaled bronchodilators? Expert Opin Drug Metab Toxicol 2014;10:1231–40
13. Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet 2009;374:1754–64
14. Bleecker ER, Nelson HS, Kraft M, et al. Beta2-receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate. Am J Respir Crit Care Med 2010;181:676–87
15. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 2004;364:1505–12
16. Maxwell TJ, Ameyaw MM, Pritchard S, et al. Beta-2 adrenergic receptor genotypes and haplotypes in different ethnic groups. Int J Mol Med 2005;16:573–80
17. Burchard EG, Avila PC, Nazario S, et al. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. Am J Respir Crit Care Med 2004;169:386–92
18. Naqvi M, Thyne S, Choudhry S, et al. Ethnic-specific differences in bronchodilator responsiveness among African Americans, Puerto Ricans, and Mexicans with asthma. J Asthma 2007;44:639–48
19. Choudhry S, Ung N, Avila PC, et al. Pharmacogenetic differences in response to albuterol between Puerto Rican and Mexican asthmatics. Am J Respir Crit Care Med 2005;171:563–70
20. Weir TD, Mallek N, Sandford AJ, et al. β2-adrenergic receptor haplotypes in mild, moderate and fatal/near fatal asthma. Am J Respir Crit Care Med 1998;158:787–91
21. Basu K, Palmer CN, Tavendale R, et al. Adrenergic β2-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. J Allergy Clin Immunol 2009;124:1188–94
22. Ortega VE. Pharmacogenetics of beta2 adrenergic receptor agonists in asthma management. Clin Genet 2014;86:12–20

• **That describes candidate gene studies which have contributed to our understanding of the pharmacogenetics of β-agonists in asthma management and discusses approaches recently used to identify novel biomarkers which could be used in future genetic profiles to predict β-agonist responsiveness in asthma.**

23. Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of β2-adrenergic receptor polymorphism on response to long acting β2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet 2009;374:1754–64
24. Ortega VE, Hawkins GA, Moore WC, et al. Effect of rare variants in ADRB2 on risk of severe exacerbations and symptom control during longacting β agonist treatment in a multiethnic asthma population: a genetic study. Lancet Respir Med 2014;2:204–13
25. Drake KA, Torgerson DG, Gignoux CR, et al. A genome-wide association study of bronchodilator response in Latinos implicates rare variants. J Allergy Clin Immunol 2014;133:370–8

•• **A very important study documenting that rare variation contributes to**

**individual differences in response to salbutamol in Latinos, notably in solute carrier genes that include membrane transport proteins involved in the transport of endogenous metabolites and xenobiotics.**

26. Himes BE, Jiang X, Hu R, et al. Genome-wide association analysis in asthma subjects identifies SPATS2L as a novel bronchodilator response gene. PLoS Genet 2012;8:e1002824
27. Kim SH, Ye YM, Lee HY, et al. Combined pharmacogenetic effect of ADCY9 and ADRB2 gene polymorphisms on the bronchodilator response to inhaled combination therapy. J Clin Pharm Ther 2011;36:399–405
28. Rogers AJ, Tantisira KG, Fuhlbrigge AL, et al. Predictors of poor response during asthma therapy differ with definition of outcome. Pharmacogenomics 2009;10:1231–42
29. Chan MT, Leung DY, Szefler SJ, Spahn JD. Patients suffering from steroid-insensitive asthma are more likely to be African-American compared with those with steroid-sensitive asthma. J Allergy Clin Immunol 1998;101:594–601
30. Federico MJ, Covar RA, Brown EE, et al. Racial differences in T-lymphocyte response to glucocorticoids. Chest 2005;127:571–8
31. Maranville JC, Baxter SS, Torres JM, Di Rienzo A. Inter-ethnic differences in lymphocyte sensitivity to glucocorticoids reflect variation in transcriptional response. Pharmacogenomics J 2013;13:121–9
32. Rosenwasser L, Klemm JD, Klemm DJ, et al. Association of asthmatic steroid insensitivity with an IL-4 gene promoter polymorphism [abstract 771]. J Allergy Clin Immunol 2001;107:S235
33. Burchard EG, Silverman EK, Rosenwasser LJ, et al. Association between a sequence variant in the IL-4 gene promoter and FEV1 in asthma. Am J Respir Crit Care Med 1999;160:919–22
34. Gould W, Peterson EL, Karungi G, et al. Factors predicting inhaled corticosteroid responsiveness in African American patients with asthma. J Allergy Clin Immunol 2010;126:1131–8
35. Blake K, Cury JD, Hossain J, et al. Methacholine $PC_{20}$ in African Americans and whites with asthma with homozygous genotypes at ADRB2 codon 16. Pulm Pharmacol Ther 2013;26:342–7
36. Qiu Y, Zhang D, Qin Y, Yin KS. Effect of β2-adrenergic receptor gene Arg16Gly polymorphisms on response to long-acting β2-agonist in Chinese Han asthmatic patients. Multidiscip Respir Med 2014;9:22
37. Tantisira KG, Lasky-Su J, Harada M, et al. Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. N Engl J Med 2011;365:1173–83
38. Lima JJ, Zhang S, Grant A, et al. Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. Am J Respir Crit Care Med 2006;173:379–85
39. Weiss ST, Litonjua AA, Lange C, et al. Overview of the pharmacogenetics of asthma treatment. Pharmacogenomics J 2006;6:311–26
40. Tcheurekdjian H, Via M, De Giacomo A, et al. ALOX5AP and LTA4H polymorphisms modify augmentation of bronchodilator responsiveness by leukotriene modifiers in Latinos. J Allergy Clin Immunol 2010;126:853–8
41. Mougey E, Lang JE, Allayee H, et al. ALOX5 polymorphism associates with increased leukotriene production and reduced lung function and asthma control in children with poorly controlled asthma. Clin Exp Allergy 2013;43:512–20
42. Obase Y, Shimoda T, Kawano T, et al. Polymorphisms in the CYP1A2 gene and theophylline metabolism in patients with asthma. Clin Pharmacol Ther 2003;73:468–74
43. Klein K, Winter S, Turpeinen M, et al. Pathway-targeted pharmacogenomics of CYP1A2 in human liver. Front Pharmacol 2010;1:129
44. Galetin A, Brown C, Hallifax D, et al. Utility of recombinant enzyme kinetics in prediction of human clearance: impact of variability, CYP3A5, and CYP2C19 on CYP3A4 probe substrates. Drug Metab Dispos 2004;32:1411–20
45. Lazarus SC, Chinchilli V, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukoriene receptor antagonists in asthma. Am J Respir Crit Care Med 2007;175:783–90
46. Bossley CJ, Saglani S, Kavanagh C, et al. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. Eur Respir J 2009;34:1052–9
47. Stapleton M, Howard-Thompson A, George C, et al. Smoking and asthma. J Am Board Fam Med 2011;24:313–22
48. Barnes PJ. Mechanisms and resistance in glucocorticoid control of inflammation. J Steroid Biochem Mol Biol 2010;120:76–85
49. Green RH, Brightling CE, Woltmann G, et al. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. Thorax 2002;57:875–9
50. Zahran HS, Bailey C. Factors associated with asthma prevalence among racial and ethnic groups - United States, 2009–2010 Behavioral Risk Factor Surveillance System. J Asthma 2013;50:583–9
51. Chan MT, Leung DY, Szefler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. J Allergy Clin Immunol 1998;101:594–601
52. Naqvi M, Tcheurekdjian H, DeBoard JA, et al. Inhaled corticosteroids and augmented bronchodilator responsiveness in Latino and African American asthmatic patients. Ann Allergy Asthma Immunol 2008;100:551–7
53. Wang Z, Chen C, Niu T, et al. Association of asthma with $beta_2$-adrenergic receptor gene polymorphism and cigarette smoking. Am J Respir Crit Care Med 2001;163:1404–9
54. Cazzola M, Segreti A, Calzetta L, Rogliani P. Comorbidities of asthma: current knowledge and future research needs. Curr Opin Pulm Med 2013;19:36–41
55. Cazzola M, Calzetta L, Bettoncelli G, et al. Asthma and comorbid medical illness. Eur Respir J 2011;38:42–9
56. Kim S, Camargo CA Jr. Sex-race differences in the relationship between obesity and asthma: the behavioral risk

factor surveillance system, 2000. Ann Epidemiol 2003;13:666–73

57. Bender BG, Fuhlbrigge A, Walders N, Zhang L. Overweight, race, and psychological distress in children in the Childhood Asthma Management Program. Pediatrics 2007;120:805–13
58. Gergen PJ, Togias A. Inner city asthma. Immunol Allergy Clin North Am 2015;35:101–14
59. Borrell LN, Nguyen EA, Roth LA, et al. Childhood obesity and asthma control in the GALA II and SAGE II studies. Am J Respir Crit Care Med 2013;187:697–702
60. Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007;101:2240–7
61. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. Eur Respir J 2006;27:495–503
62. Gowers AM, Cullinan P, Ayres JG, et al. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. Respirology 2012;17:887–98
63. Nishimura KK, Galanter JM, Roth LA, et al. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. Am J Respir Crit Care Med 2013;188:309–18
64. Boehmer TK, Foster SL, Henry JR, et al. Residential proximity to major highways - United States, 2010. MMWR Surveill Summ 2013;62(Suppl 3):46–50
65. Lewis TC, Robins TG, Dvonch JT, et al. Air pollution-associated changes in lung function among asthmatic children in Detroit. Environ Health Perspect 2005;113:1068–75
66. Hernández-Cadena L, Holguin F, Barraza-Villarreal A, et al. Increased levels of outdoor air pollutants are associated with reduced bronchodilation in children with asthma. Chest 2009;136:1529–36
67. Lewis TC, Robins TG, Mentz GB, et al. Air pollution and respiratory symptoms among children with asthma: vulnerability by corticosteroid use and residence area. Sci Total Environ 2013;448:48–55
68. Dima AL, Hernandez G, Cunillera O, et al. Asthma inhaler adherence determinants in adults: systematic review of observational data. Eur Respir J 2015;45(4):994–1018
69. Farber HJ, Capra AM, Finkelstein JA, et al. Misunderstanding of asthma controller medications: association with nonadherence. J Asthma 2003;40:17–25
70. Williams LK, Joseph CL, Peterson EL, et al. Race-ethnicity, crime, and other factors associated with adherence to inhaled corticosteroids. J Allergy Clin Immunol 2007;119:168–75
71. Koster ES, Raaijmakers JA, Vijverberg SJ, Maitland-van der Zee AH. Inhaled corticosteroid adherence in paediatric patients: the PACMAN cohort study. Pharmacoepidemiol Drug Saf 2011;20:1064–72
72. Sheikh A, Halani L, Bhopal R, et al. Facilitating the recruitment of minority ethnic people into research: qualitative case study of South Asians and asthma. PLoS Med 2009;6:e1000148
73. Sheikh A, Netuveli G, Kai J, Panesar SS. Comparison of reporting of ethnicity in US and European randomised controlled trials. BMJ 2004;329:87–8
74. National Institutes of Health. NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research – amended. Available from: http://grants.nih.gov/grants/funding/wom en_min/guidelines_amended_10_2001.htm [Last Accessed 29 December 2014]
75. Chung KF. New treatments for severe treatment-resistant asthma: targeting the right patient. Lancet Respir Med 2013;1:639–52
76. Wechsler ME, Castro M, Lehman E, et al. Impact of race on asthma treatment failures in the asthma clinical research network. Am J Respir Crit Care Med 2011;184:1247–53
77. Chang TS, Lemanske RF Jr, Mauger DT, et al. Childhood asthma clusters and response to therapy in clinical trials. J Allergy Clin Immunol 2014;133:363–9
78. Park HW, Tantisira KG, Weiss ST. Pharmacogenomics in asthma therapy: where are we and where do we go? Annu Rev Pharmacol Toxicol 2015;55:129–47

• **An intriguing article documenting that asthma pharmacogenomics is still not able to predict clinical outcomes with sufficient precision to be of clinical utility.**

79. Meyers DA, Bleecker ER, Holloway JW, Holgate ST. Asthma genetics and personalised medicine. Lancet Respir Med 2014;2:405–15

## Affiliation

Mario Cazzola[†1], Paola Rogliani[2], Alessandro Sanduzzi[3] & Maria Gabriella Matera[4]
[†]Author for correspondence
[1]Professor,
University of Rome Tor Vergata, Department of Systems Medicine, Respiratory Clinical Pharmacology Unit, Via Montpellier 1, 00133 Rome Italy
E-mail: mario.cazzola@uniroma2.it
[2]University of Rome Tor Vergata, Department of Systems Medicine, Rome, Italy
[3]University Federico II, Monaldi Hospital, Department of Respiratory Diseases, Naples, Italy
[4]Second University of Naples, Department of Experimental Medicine, Naples, Italy