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Pharmacogenomics of chronic obstructive pulmonary disease

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition, which presents the opportunity for precision therapy based on genetics or other biomarkers.

Areas covered: Alpha-1 antitrypsin deficiency, a genetic form of emphysema, provides an example of this precision approach to diagnosis and therapy. To date, research in COPD pharmacogenomics has been limited by small sample sizes, lack of accessible target tissue, failure to consider COPD subtypes, and different outcomes relevant for various medications. There have been several published genome-wide association studies and other omics studies in COPD pharmacogenomics; however, clinical implementation remains far away. There is a growing evidence base for precision prescription of inhaled corticosteroids in COPD, based on clinical phenotypes and blood biomarkers, but not yet based on pharmacogenomics.

Expert opinion: At this time, there is insufficient evidence for clinical implementation of COPD pharmacogenomics. Additional genome-wide studies will be required to discover predictors of drug response and to identify genomic biomarkers of COPD subtypes, which could be targeted with subtype-directed therapies.

Keywords

alpha-1 antitrypsin deficiency; asthma-COPD overlap; bronchodilator response; gene expression profiling; genome-wide association study; inhaled corticosteroids; precision medicine

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most commonly encountered disorders in respiratory medicine and a major source of morbidity and mortality worldwide [1]. Despite the disease prevalence, there are limited therapies available, most of which are used to treat symptoms and reduce the risk of acute exacerbations. The only treatments shown to reduce mortality include smoking cessation [2], supplemental oxygen in hypoxemic patients [3,4], lung volume reduction surgery in patients with upper lobe predominant emphysema and low exercise capacity [5], and non-invasive ventilation in acute respiratory failure [6,7].

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COPD has been long known to be a heterogeneous condition, with pathologies including emphysema and small and large airway disease. Because of the heterogeneity, COPD could well be considered within the paradigm of precision medicine. The goal of precision medicine is to use biomarkers or other diagnostic tests to categorize patients into disease subtypes [8]. These subtypes can then be targeted with new or existing therapies. The biomarkers and disease subtypes must be evaluated in clinical trials of the proposed treatments to provide appropriate evidence for precision medicine. The above list of COPD treatments shown to reduce mortality highlights that several COPD therapies are already targeted to specific patient subsets, e.g. supplemental oxygen in patients with severe, but not mild hypoxemia [9]. The rationale behind pharmacogenomics is to use genetic data to identify individuals with different outcomes related to either safety or efficacy before prescribing a particular drug. The term “pharmacogenetics” has been traditionally used to denote the effect of a single gene or genetic variant, whereas “pharmacogenomics” indicates a genome-wide approach. Due to the direction of research in the field in general and COPD in particular, “pharmacogenomics” is preferred in this review. Pharmacogenomics is a specific example of precision medicine, where genetic variation or gene expression is used as the biomarker to determine which patients may or may not benefit from a specific treatment. Alpha-1 antitrypsin deficiency (AATD) is a genetic form of emphysema and demonstrates the precision medicine approach to COPD [10].

2. Alpha-1 antitrypsin deficiency and COPD precision therapy

Alpha-1 antitrypsin (AAT) is encoded by the *SERPINA1* gene on chromosome 14. AAT is the major protease inhibitor of neutrophil elastase, so patients with AATD have increased protease activity in the lungs, leading to early-onset emphysema and COPD, especially in cigarette smokers. Severe AATD is usually due to two copies of the Z allele, leading to the ZZ genotype. AATD accounts for approximately 1% of COPD in populations of European descent [11]. There are estimated to be 100,000 AATD individuals in the United States, making it three times as common as cystic fibrosis [12]. However, many patients with AATD are undiagnosed or misdiagnosed [13]. Heterozygous carriers of one Z allele (MZ genotype) have a slightly increased risk of COPD, which appears confined to those with a history of cigarette smoking [14–16]. Increased risk is also seen in those who carry the Z allele in combination with other deficiency alleles, such as the S allele [17] or one of several rare null alleles that do not produce functional AAT protein [18].

The Alpha-1 Foundation and the European Respiratory Society have both recently published guidelines for the diagnosis and management of AATD [19,20]. Both guidelines recommend testing for AATD in all COPD patients, regardless of age or race. Initial testing includes measurement of serum AAT levels, followed by isoelectric focusing of serum or genotyping for the Z and S alleles. Additional genotyping or sequencing is reserved for other variants, including null alleles.

Augmentation therapy with pooled human AAT protein is approved by the United States Food and Drug Administration (FDA) for treatment of COPD due to AATD; augmentation therapy is available in some European nations as well. Observational studies [21–23] and small clinical trials [24,25] initially showed the efficacy of augmentation therapy. The

RAPID study, a randomized clinical trial including 180 subjects with severe AATD (all with AAT level $<11\mu\text{M}$, 93% with ZZ genotype), demonstrated that augmentation therapy at a dose of 60mg/kg weekly slowed the progression of emphysema on quantitative analysis of chest CT scans [26]. AATD can serve as a model of precision medicine in COPD and other respiratory diseases. A clinically-available blood test identifies a subset of individuals with the disease, which can be treated with a specific therapy. AATD can also be viewed through a pharmacogenetics lens. COPD patients with the ZZ genotype have been shown to benefit from augmentation therapy, while augmentation therapy is not indicated in COPD patients without severe AATD, including heterozygous carriers (MZ genotype) [27].

3. Considerations in COPD pharmacogenomics studies

Several considerations are important when attempting a COPD pharmacogenomics study, some of which are specific to COPD and some more generally applicable to pharmacogenomics studies. An example of the latter is the availability of a sufficient sample size of well-characterized subjects treated with the relevant drug. In the past, these samples have most commonly been collected as part of clinical trials, though some pharmacogenomics questions can be addressed in observational studies. Therefore, to reach the necessary numbers many pharmacogenomics studies require commitment from industry sponsors or collaborations with academic investigators. While DNA variants are easily assessed in blood samples, other potentially relevant biomarkers, such as gene expression, may require samples from the appropriate target tissue. For cancer pharmacogenomics studies, this has been less of a limitation, since tissue sampling is a standard part of clinical care. However, invasive procedures such as bronchoscopy and lung biopsy are not routinely performed in the evaluation of COPD patients, limiting the availability of these samples for research and clinical translation.

A wide variety of clinical outcomes have been used in COPD clinical trials and are therefore relevant for pharmacogenomics studies (Table 1) [28,29]. COPD is defined by reduced lung function, specifically the forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC). There is a long history of use of change in FEV_1 as the outcome in COPD clinical trials, as many previous trials have tested inhaled bronchodilator medications [30]. It has been difficult to demonstrate reduction in mortality in most COPD clinical trials [31]. Acute exacerbations, periods of worsening symptoms, have become an important endpoint in recent clinical trials. Exacerbations can be defined based on symptoms of increased dyspnea, cough, and phlegm [32] or based on interactions with the healthcare system, such as prescriptions for antibiotics and/or oral corticosteroids [33]. Multiple medications have been shown to reduce the frequency of COPD exacerbations [34]. Progression of emphysema on quantitative analysis of chest CT scans was used in the RAPID trial of AAT augmentation [26]. This outcome has not been widely applied in other COPD clinical trials, but has future potential for specific therapies targeting emphysema. Patient reported outcomes, such as dyspnea or disease related quality of life, are becoming increasingly widespread in COPD clinical trials as meaningful endpoints [35].

Different COPD medications have been shown to have effects on different COPD outcomes (Table 1), and these medication-outcome pairings must also be considered in

pharmacogenomics studies. It is also important to acknowledge the limitations of current COPD therapies, many of which have only modest effects on outcomes. By definition, airflow obstruction in COPD is not fully reversible with bronchodilators [36]. The reduction in exacerbation frequency from most therapies ranges from 15–25% [37–39].

As mentioned above, COPD is a heterogeneous disease and some of the most effective therapies are only indicated in specific patient subgroups. Disease heterogeneity must be considered in COPD pharmacogenomics studies. Otherwise, studies may not be able to distinguish the effect of a genetic variant on treatment response versus its effect on disease subtype (Figure 1).

4. Genome-wide association studies in COPD pharmacogenomics

There is a long history of candidate gene association studies in common diseases, including COPD and pharmacogenetics [40]. These were largely hampered by small sample sizes, incomplete assessment of genetic variants in a gene, and most importantly, poor reproducibility [41]. Genome-wide association studies (GWAS) overcome many of these limitations of candidate genes studies and have become the predominant study design in human complex disease genetics over the past decade [42]. Although there have been multiple GWAS for COPD susceptibility, now with sample sizes over 250,000 [43], there have been only a few GWAS for COPD pharmacogenomics (Table 2). These GWAS for COPD and other complex traits have demonstrated that most common diseases are influenced by many genetic variants, usually single nucleotide polymorphisms (SNPs), each with a small effect size. Many of these SNPs are thought to affect gene regulation and not protein structure. These small effect sizes, necessitating very large sample sizes for gene discovery, would seem to pose an almost insurmountable obstacle for pharmacogenomics studies. However, pharmacogenetics SNPs may have larger effect sizes, as demonstrated by an analysis of studies in the National Human Genome Research Institute GWAS catalog, with median sample size ~350 [44]. Several explanations have been offered for this observation, including the fact that pharmacogenomics studies may have more careful assessment of clinical outcomes, such as quantitative traits measured in a clinical trial, and the relevant environmental exposure, the drug.

Despite the known limitations of candidate gene association studies, these studies still persist in COPD pharmacogenomics. Most have focused on *ADRB2*, the gene encoding the β_2 -adrenergic receptor. A recent meta-analysis [45] and a large GWAS [46] have failed to show an effect of known coding variants in *ADRB2* on bronchodilator response in COPD. The findings should discourage any additional studies of *ADRB2* coding variants in COPD pharmacogenomics. In most cases, future candidate gene studies should be limited to validation of genes identified through GWAS, such as the extension into COPD [47] of the association between a variant in *GLCCII* and inhaled corticosteroid (ICS) response, which was initially identified in asthma [48].

However, bronchodilator response (BDR) remains an important phenotype for COPD pharmacogenomics studies, since inhaled β -agonists are commonly prescribed for COPD treatment. BDR is assessed in many COPD clinical trials and observational studies, allowing

for adequate sample sizes for GWAS. We have performed a GWAS for BDR in 5789 COPD subjects from four studies [46]: Genetic Epidemiology of COPD Study (COPDGene), Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), Norway GenKOLS Study, and the National Emphysema Treatment Trial. Since different phenotypes may have different genetic influences, we defined BDR by using three quantitative traits [49]; the difference between pre- and post-bronchodilator FEV₁ was expressed as the absolute volume, as percent of baseline FEV₁, and as percent of predicted FEV₁. Results from a GWAS are commonly presented using a Manhattan plot of $-\log_{10}(\text{p-value})$ of each SNP across the human genome and regional association plots focusing on specific genetic loci, both of which are demonstrated in Figure 2. Despite the large sample size and careful phenotyping, no SNP was associated with BDR at the usual threshold for genome-wide significance ($\text{p-value} < 5 \times 10^{-8}$) in the meta-analysis of five populations (COPDGene included non-Hispanic white and African American subjects). However, SNPs in two potassium channel genes, *KCNJ2* on chromosome 17 and *KCNK1* on chromosome 1, showed suggestive evidence for association ($\text{p-values} \sim 2 \times 10^{-7}$). These genes have been shown to affect membrane potential in bronchial smooth muscle and epithelial cells, respectively. SNPs in *CDH13* had genome-wide significant association in African Americans ($\text{p} = 5 \times 10^{-9}$). *CDH13* encodes T-cadherin, which was shown to affect airway hyperresponsiveness in a mouse model [50]. All of these SNP effect sizes were small, and these SNPs alone are unlikely to predict which subjects will respond to β -agonists. However, this genome-wide pharmacogenomics analysis pointed to a potential novel pathway for therapy.

Condreay and co-authors, representing a pharmaceutical company, reported a pharmacogenomics study of the treatment effects of umeclidinium (long-acting anti-muscarinic) and vilanterol (long-acting β -agonist), either alone or in combination [51]. They combined data from 6705 subjects in 17 of their company's clinical trials. There were no SNPs significantly associated with treatment response in the GWAS; they did not provide data on associations below the strict genome-wide threshold. Despite the negative results, this study demonstrates an important commitment to a pharmacogenomics study in COPD on the part of a pharmaceutical company. Industry partners will be necessary to collect large sample sizes of consented subjects for continued research in this area.

Supplemental oxygen is a cornerstone of COPD therapy in patients with severe hypoxemia; however, the Long-term Oxygen Treatment Trial (LOTT) found no benefit in a study of 738 patients with mild resting hypoxemia (oxygen saturation 89–93%) or exertional desaturation [9]. Our group performed a GWAS of the primary LOTT outcome of time to death or first hospitalization in 331 white subjects with available DNA samples, finding 97 SNPs in 15 loci with suggestive evidence of a genotype-by-treatment effect at $\text{p} < 1 \times 10^{-5}$ [52]. We combined the GWAS results with microarray gene expression profiling in whole blood samples in 37 subjects at baseline, 12 months follow-up, or both time points. Examining gene expression of transcripts located nearby (within 100 kb) of the 97 SNPs, we showed that expression of *ARSB* (arylsulfatase B) had a significant interaction with oxygen therapy in association with the primary outcome (Figure 3). RNA sequencing data from the larger COPDGene Study demonstrated that the *ARSB* SNPs affected gene expression depending on oxygen treatment, a context-dependent expression quantitative trait locus (eQTL). *ARSB* expression has been previously shown to be downregulated by hypoxemia based on *in vitro*

and *in vivo* models [53,54]. Without additional validation, it would be premature to use these results for personalized oxygen prescription, but this study highlights the integration of multiple omics data types and the use of a clinical trial and an observational study to overcome the small sample size limitation commonly encountered in COPD pharmacogenomics.

To date, there have been relatively few pharmacogenomics GWAS in COPD. However, there have been multiple GWAS for COPD traits which are relevant for pharmacogenomics studies (Table 3). Most common have been GWAS of lung function, the largest of which included over 400,000 subjects and identified 279 genetic loci [55]. GWAS have been performed for hyperinflation [56] and emphysema distribution [57,58], two phenotypes that are relevant for lung volume reduction therapies. Although exacerbations are an important outcome in clinical trials, no GWAS for COPD exacerbations have been published. Smoking cessation is perhaps the most important therapy to limit the progression of COPD [59]. There has been extensive pharmacogenomics research related to smoking cessation, which has been reviewed elsewhere [60–62].

Another important outcome from pharmacogenomics studies is the identification of variants associated with adverse drug effects. ICS are widely used in the treatment of both COPD and asthma. Adrenal suppression is a concerning adverse effect, especially in children with asthma [63]. Hawcut et al. performed a GWAS in 499 children with asthma in the U.K., of whom 35 (7%) were found to have adrenal suppression based on an adrenocorticotrophic hormone (ACTH) stimulation test [64]. Variants in the Platelet Derived Growth Factor D gene (*PDGFD*) were associated with several phenotypes at a suggestive p-value <1e-6. A single SNP in *PDGFD* was validated based on genotyping in a pediatric asthma study (n=81) and adult COPD study (n=78), both of whom had undergone similar phenotyping. The results were genome-wide significant in a meta-analysis (p=3.5e-10). Though the sample size in this study was small by conventional GWAS standards, they were able to identify a biologically-plausible gene with large effect size in a well-characterized study subjects. It remains to be seen whether this result will replicate in other COPD study populations.

In COPD, pneumonia is considered to be one of the more severe adverse effects of ICS [65]. There has not been a pharmacogenomics GWAS of this adverse effect in ICS users. However, a GWAS for pneumonia in smokers with and without COPD has been published [66]. Despite several suggestive associations, no SNPs were significantly associated with lifetime pneumonia risk.

5. Genetics of COPD heterogeneity and subtypes

After COPD diagnosis and lung function, emphysema has been the most widely studied phenotype in COPD genetics studies. Emphysema can be assessed based on quantitative analysis of chest CT scans [67]. GWAS have identified genome-wide significant associations with quantitative measures of emphysema [68,69], emphysema patterns [70], and emphysema distribution [57,58]. Some of the emphysema associations overlap with COPD GWAS findings, including genes such as *HHIP* and *FAM13A*, which have been demonstrated to influence emphysema in mouse smoking models [71,72]. However, some of

the emphysema associations have not been found in previous COPD GWAS, demonstrating the complementary information which can be obtained from analysis of COPD-related phenotypes. Additional genes for quantitative emphysema have been identified by gene expression profiling in lung tissue samples [73–75].

The initial emphysema GWAS considered COPD subgroups with and without emphysema, based on radiologist assessment in the ECLIPSE, NETT, and Norway GenKOLS studies [76]. A SNP in *BICD1* showed suggestive association with the presence versus absence of emphysema, which was genome-wide significant in the subgroup with moderate to severe emphysema. Recent genetic studies have returned to the analyses of COPD subtypes based on emphysema. Halper-Stromberg et al. performed a GWAS for visually-assessed emphysema on chest CT scans in 1540 subjects in the COPDGene Study [77]. They found a genome-wide significant association with a known COPD locus on chromosome 15q25, which includes the genes *CHRNA3*, *CHRNA5* and *IREB2*. SNPs in 8 of 19 pre-defined COPD GWAS loci were nominally associated with visual emphysema.

Radder and colleagues defined a subset of 65 COPD subjects with emphysema and severe airflow obstruction and compared them to controls without emphysema or airflow obstruction, using whole genome sequencing [78], the state-of-the-art technology in human genetics [79]. A non-synonymous variant in *PTPRO* (protein tyrosine phosphatase, receptor type O) was found in eight subjects with severe COPD with emphysema but in no controls. This variant was also associated with emphysema and FEV₁ in a replication sample of 686 subjects. *In vitro* studies found a potential functional role of this variant in epidermal growth factor signaling.

Asthma-COPD overlap is a common and clinically-relevant COPD subtype, which is associated with increased symptoms, exacerbations and healthcare utilization [80,81]. Despite the clinical importance and multiple publications, there is no clear definition for subtype [82,83]. In the COPDGene Study, we defined asthma-COPD overlap based on spirometric confirmation of COPD (FEV₁/FVC<0.7 and FEV₁<80% predicted) in subjects with a self-reported doctor's diagnosis of asthma before the age of forty [81]. In separate GWAS of 283 non-Hispanic white and 167 African American subjects with asthma-COPD overlap, compared to subjects of each race with COPD alone, no SNPs were genome-wide significant [84]. Several suggestive associations were found, including SNPs in *SOX5* and *CSMD1*, two genes previously associated with COPD and emphysema, respectively [76,85]. It is likely that a more specific subtype definition will be required to find additional genetic associations with asthma-COPD overlap.

6. Other omics technologies in COPD pharmacogenomics

A potential option to overcome the limited sample sizes in COPD pharmacogenomics GWAS is to use other omics data types, such as gene expression profiling, which may have larger effect sizes than genetic variants. For example, Christenson and colleagues used microarray gene expression data from airway brushings and endobronchial biopsies in subjects with asthma to develop a gene expression score indicative of T helper type 2 (Th2) inflammation [86]. They showed that the Th2 score was higher in bronchial brushing

samples from subjects with COPD compared to smoker and non-smoker controls. In bronchial biopsies from the GLUCOLD study, a small clinical trial of inhaled corticosteroids in COPD (N=79), the Th2 expression score was associated with improvement in hyperinflation, measured by the ratio of residual volume to total lung capacity (RV/TLC), in ICS-treated subjects. However, the Th2 score was also associated with baseline airway and blood eosinophil counts, so it may be identifying subjects with eosinophilic COPD, a COPD subtype that is more likely to benefit from ICS [87].

Interleukin (IL)-17 is a pro-inflammatory cytokine, with known or possible roles in multiple chronic inflammatory diseases, including COPD [88]. Drugs targeting IL-17 and its receptor are used to treat autoimmune conditions including psoriasis, psoriatic arthritis, and ankylosing spondylitis [89]. IL-17A associated inflammation may be unresponsive to corticosteroids. To address this question, Christenson et al. defined an airway epithelial IL-17A response gene set *in vitro*, which was refined using data from bronchial brushings from smokers with COPD [90]. The gene set was validated in two datasets of skin biopsies from patients with psoriasis treated with anti-IL-17A therapies. In the GLUCOLD study bronchial biopsies, subjects with a high IL-17 signature were less likely to respond to ICS, based on lack of improvement in FEV₁ at 30 months. Both the IL-17 and Th2 studies demonstrate the strengths of integration of multiple gene expression datasets from relevant COPD tissue samples. However, it remains to be seen whether these pharmacogenomics biomarkers have peripheral blood correlates, which will be necessary for eventual clinical translation, as it would not be feasible to perform bronchoscopies on all COPD patients prior to initiating ICS treatment.

Epigenetics encompasses processes such as DNA methylation, histone modification and regulatory RNAs, all of which lead to changes in gene expression or phenotype, without changes in DNA sequence [91]. Epigenetic effects may explain features of complex disease not explained by DNA sequence variation, particularly related to environmental interactions, including drug treatments [92]. Methylation of cytosine bases at CpG dinucleotide sites is one of the most common epigenetic events and can be assayed using high-throughput genome-wide arrays [93]. Lee et al. performed DNA methylation profiling using Illumina 450k chips in peripheral blood mononuclear cells from 24 COPD patients with acute exacerbations treated with oral corticosteroids, 12 of whom showed improvement in lung function and symptoms at two weeks follow-up [94]. Despite the small sample size, 23 CpG sites in 19 gene regions showed differential methylation between responders and non-responders. For validation, they performed pyrosequencing of four genes with previous evidence of association with COPD in a separate sample of 50 patients. A CpG site in the gene *PSMD8* (26S proteasome non-ATPase regulatory subunit 8) was nominally replicated. Although the biologic role of *PSMD8* in corticosteroid response is not clear, this study shows that DNA methylation data is another type of omics data which can be employed in the small sample sizes typical of COPD pharmacogenomics studies.

Metabolomics, the simultaneous assessment of multiple small molecules usually combining liquid chromatography with mass spectrometry, is being increasingly employed in blood samples in large COPD studies [95,96]. Exhaled breath condensate is a promising non-invasive sample for COPD metabolomics [97]. Metabolomics may have several potential

roles in COPD pharmacogenomics research, beyond increasing our understanding of disease mechanisms, pathways, and drug targets. Metabolomics studies may identify biomarkers predictive of drug response or demonstrate drug effects through analysis of downstream metabolites [98]. Since commonly used metabolomics panels measure levels of multiple xenobiotic molecules including some medications, these large studies may provide the ability to assess inter-individual variation in drug levels, which could be integrated with genetic data for consideration as a pharmacogenomics phenotype.

Moving beyond these analyses of single data types, gene expression or methylation data can be integrated with GWAS, to identify expression or methylation quantitative trait loci, which are genetic variants that influence gene expression or methylation, respectively. These integrative genomics approaches may better define gene regulation as it relates to complex diseases [99]. Network medicine methods consider the simultaneous effects of multiple genes, uncovering potential interacting effects [100]. Beside the LOTT pharmacogenomics study above, these methods have not been applied in COPD pharmacogenomics.

7. Pharmacogenomic labelling and clinical implementation

The U.S. Food and Drug Administration (FDA) maintains a list of drugs with pharmacogenetics biomarkers included in the drug label [101]. The majority of this list includes anti-cancer therapies, though several medications relevant to COPD are included. The labels for several bronchodilators, including arformoterol, formoterol, indacaterol, and umecclidinium, mention pharmacogenetic variants related to their clinical pharmacology; however, none of these variants is felt to be clinically-relevant.

Other drugs on the list with relevance to lung diseases include azathioprine, ivacaftor, lumacaftor, and warfarin. Genetic testing is recommended before starting the first three medications. Studies incorporating pharmacogenetic testing for warfarin dosing have had conflicting results [102].

Codeine is widely prescribed as an analgesic and as an anti-tussive, leading to its relevance for COPD. Codeine's therapeutic effects are due to its metabolism to morphine by cytochrome P450 2D6 [103]. Codeine will be less efficacious in individuals carrying *CYP2D6* genotypes leading to poor metabolism, and may cause serious side effects, including respiratory depression and death [104], in individuals with genotypes leading to ultrarapid metabolism. Both the Clinical Pharmacogenetics Implementation Consortium [103] and the Dutch Pharmacogenetics Working Group [105] make dosing recommendations based on *CYP2D6* metabolizer phenotypes.

However, there remain significant barriers to clinical implementation of pharmacogenomics related not just to codeine or COPD, but for most drugs and diseases. While there is ample time to send samples to reference laboratories for management of chronic conditions like alpha-1 antitrypsin deficiency, more rapid genetic testing will be required for treatment of acute conditions, with warfarin for example. With the rapid expansion of both clinical and direct-to-consumer genetic testing [106], one could envision that these genetic results could be incorporated into the electronic medical record along with decision support tools to aid

the clinician in drug or dose selection [107,108]. Further research is necessary for both the evidence base and the implementation of such practices.

8. Precision treatment with inhaled corticosteroids in COPD

There is substantial interest in identifying COPD patients most likely to respond to ICS, given the increased risk of pneumonia as a serious adverse effect. Current guideline recommend ICS as part of initial therapy in patients with frequent exacerbations, especially in patients with elevated eosinophil counts (> 300 cells/ μ l) or a history of asthma [36]. De-escalation of therapy, specifically ICS withdrawal, is also part of the guidelines. Table 4 shows current and potential future strategies for precision treatment with ICS. Subtypes based on patient history or blood counts can easily be implemented into clinical practice. However, many hurdles must be overcome prior to the use of genomic data to target ICS prescriptions in COPD. Additional studies must be performed to confirm the previous studies, and clinically-applicable tests must be developed, so implementation of ICS pharmacogenomics remains a future direction for the field.

9. Conclusion

Despite the high prevalence of COPD, with associated morbidity and mortality, COPD pharmacogenomics research remains in its early stages. COPD pharmacogenomics studies have been limited by small sample sizes, lack of access to lung tissue, and the variety of outcomes used for COPD clinical trials. The current literature includes GWAS for response to several COPD therapies, including bronchodilators and supplemental oxygen, as well as GWAS for traits relevant to pharmacogenomics, such as lung function and asthma-COPD overlap. Studies are beginning to integrate other omics data types, which is a potential approach to overcome the limited sample sizes. Besides AAT deficiency, pharmacogenomics information is not currently implemented in the treatment of COPD.

10. Expert opinion

COPD is a heterogeneous disease, yet current treatment paradigms are only beginning to incorporate patient subtypes into therapeutic decisions. Subtype directed therapies, such as inhaled corticosteroids for patients with frequent exacerbations, have had only moderate success. This is likely due to the imprecise phenotype categorization, the limited number of medication classes available to treat COPD, and the generally modest effects of most of these drugs. The ultimate goal is to provide precision therapies for patients with specific COPD subtypes, based on specific biomarkers. In the near future, these biomarkers will most likely be derived from current clinical tests, such as complete blood counts and chest CT scans.

The diagnosis and treatment of alpha-1 antitrypsin deficiency is the only fully developed application of COPD “pharmacogenomics”, although the disease was discovered based on protein phenotyping before the gene was identified. A substantial research effort is still needed to provide additional evidence for further COPD pharmacogenomics. Discovery-based studies, including GWAS, gene expression profiling, and whole genome sequencing,

will be required to identify predictors of drug response. These studies will need appropriate subject consent and sample collections in COPD clinical trials. Ideally this research will leverage existing data from large COPD observational studies, such as COPDGene [109] and SPIROMICS [110], and from population-based studies, such as the U.K. Biobank [111], for discovery and validation. Large-scale COPD pharmacogenomics studies will require collaborations between academic and industry partners.

Perhaps a more feasible intermediate goal would be to identify genomic biomarkers of COPD subtypes such as asthma-COPD overlap or Th2-high COPD, which could be targeted with subtype-directed therapies. Although not true “pharmacogenomics”, this strategy exemplifies precision medicine. The most power may come from combination of clinical phenotyping with genomic biomarkers. This implementation will require incorporation of genetic results into the electronic medical record, along with decision support tools. This paradigm is already being applied for pharmacogenomics in other conditions [112], so respiratory physicians could follow along in this infrastructure, as a COPD pharmacogenomics evidence base is established.

Besides the treatment of alpha-1 antitrypsin deficiency, other pharmacogenomics-based treatments of COPD are more than five years away. However, subtype-directed therapies may be expected in that time frame. Mepolizumab is an anti-IL-5 monoclonal antibody, which is approved for use in asthma. Mepolizumab has been shown to be effective in reducing exacerbations in patients with COPD with peripheral eosinophilia [113], but it was not approved by the FDA, largely due to the lack of a beneficial effect in unselected COPD patients. It is likely that additional data will support its use in eosinophilic COPD. Other medications, such as ICS and roflumilast [114], can also be directed at the eosinophilic COPD subtype.

More research is needed to identify additional COPD subtypes, biomarkers, and drugs. Biobank studies will allow for large sample sizes, which will lead to increased genetic discoveries related to COPD susceptibility and phenotypes. For pharmacogenomics, these large studies will need to be linked to the electronic medical record, to provide detailed information about medication usage and treatment outcomes.

To date, most of the genetics and pharmacogenomics studies in COPD have been performed in populations of European ancestry. As demonstrated in our GWAS [46], bronchodilator response phenotypes differed between non-Hispanic white and African American subjects, as did the genetic association results. Future studies will need to include non-European populations, as the COPD epidemic is a worldwide concern.

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Article Highlights

- Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease, with pathologies including emphysema, large and small airway disease.
- The goal of precision medicine is to use biomarkers to divide a heterogeneous disease into relevant subtypes, which can be targeted with specific therapies.
- All COPD patients should be tested for alpha-1 antitrypsin (AAT) deficiency, a genetic subtype of COPD which can be treated with intravenous pooled human AAT protein.
- COPD pharmacogenomics studies have been limited by small sample sizes and limited access to lung or airway tissue.
- COPD pharmacogenomics studies may be confounded by disease subtypes, if not addressed in the study design.
- Different COPD therapies have differing effects on COPD outcomes, which must be considered in pharmacogenomics studies.
- Genome-wide association studies (GWAS) have been performed for response to short-acting and long-acting bronchodilators and supplemental oxygen, with limited success.
- Multiple GWAS have also been performed for traits relevant for COPD pharmacogenomics, such as lung function and asthma-COPD overlap.
- Pharmacogenomics studies have started to use other omics data types, including gene expression profiling and DNA methylation data. Multi-omics integration is potential avenue to overcome limitations of small sample sizes.
- Besides AAT deficiency, pharmacogenomics information is not currently used in the treatment of COPD. However, there is a growing evidence base for precision prescription of inhaled corticosteroids in COPD, based on disease biomarkers and subtypes.
- Future research in COPD pharmacogenomics and precision medicine should incorporate large biobank data linked to the electronic medical record, as well as studies in non-European derived populations.

Figure 1.

Confounding by disease subtype in COPD pharmacogenetics studies. (A) The standard pharmacogenetics paradigm of a genetic variant affecting treatment response. (B) A variant may actually be influencing risk of a disease subtype, and the subtype determines treatment response.

Figure 2.

Genome-wide association study for bronchodilator response in COPD. (a) Manhattan plot of $-\log_{10}(\text{p-value})$ across all chromosomes. Absolute bronchodilator response is defined by change in FEV_1 in liters. (b) Regional association plot for the association between variants near *KCNJ2* and absolute bronchodilator response. Adapted from [46].

Figure 3.

Association between arylsulfatase B (*ARSB*) gene and response to supplemental oxygen in the Long-term Oxygen Treatment Trial. (a) Kaplan-Meier plot of time to death or hospitalization, stratified by *ARSB* single nucleotide polymorphism (SNP) rs7732088 and oxygen treatment. (b) Kaplan-Meier plot of *ARSB* gene expression in blood samples. (c) Regional association plot for genome-wide time-to-event analysis for SNPs near *ARSB*. Reprinted from [52] with permission.

Table 1.

COPD treatments and their effects on disease outcomes. I=Increase; D=Decrease; ?=possible effect; -- no effect.

Drug/class	Pulmonary function*	Acute exacerbations	Mortality	Emphysema progression	PROs**
LAMA	I	D	--	--	I
LAMA/LABA	I	D	--	--	I
LABA/ICS	I	D	D?	--	I
LAMA/LABA/ICS	I	D	--	--	I
Roflumilast	I?	D	--	--	--
Azithromycin	--	D	--	--	I
Oxygen	--	--	D	--	--
AAT augmentation	--	I?	--	D	--

* Short-term and/or long-term change in forced expiratory volume in 1 second (FEV₁).

** Patient-reported outcomes, such as dyspnea or quality of life

Abbreviations: AAT = alpha-1 antitrypsin; LAMA = long-acting anti-muscarinic; LABA = long-acting beta-agonist; ICS = inhaled corticosteroid

Table 2.

Genome-wide association studies (GWAS) in COPD pharmacogenomics

Treatment	Primary Outcome	Study subjects	Main results	Reference
Short acting beta-agonists	Bronchodilator response	5789 COPD subjects in 4 studies	SNPs in <i>KCNK1</i> and <i>KCNJ2</i> suggestive in meta-analysis ($p \sim 2 \times 10^{-7}$). <i>CDH13</i> significant in African Americans ($p = 5 \times 10^{-9}$)	[46]
LAMA/LABA	Trough FEV ₁	6075 COPD subjects in 17 clinical trials	No significant results in GWAS	[51]
Supplemental oxygen	Death or hospitalization	331 COPD with moderate hypoxemia at rest or exertional desaturation	97 SNPs in 15 loci with genotype-by-treatment interaction ($p < 1 \times 10^{-5}$). <i>ARSB</i> validated using gene expression data.	[52]
Inhaled corticosteroids	Adrenal suppression	499 children with asthma. Validation in 81 children with asthma and 78 adults with COPD	Intronic SNP in <i>PDGFR</i> significant in meta-analysis ($p = 3.5 \times 10^{-10}$)	[64]

Abbreviations: LAMA/LABA = long-acting anti-muscarinic/long-acting beta-agonist; FEV₁ = forced expiratory volume in 1 second; SNP = single nucleotide polymorphism

Table 3.

Genome-wide association studies of selected traits relevant for COPD pharmacogenomics

Trait	Study subjects and phenotypes	Associated Genes*	Reference
Lung function	400,102 individuals of European ancestry	279 significant loci	[55]
Quantitative Emphysema	12,031 with and without COPD, 2 measures of emphysema (LAA950 and 15 th percentile)	Significant: <i>HHIP</i> , <i>CHRNA3</i> , <i>AGER</i> , <i>DLCL1</i> , <i>SERPINA10</i>	[69]
Emphysema distribution	11,532 with and without COPD, 2 measures of emphysema distribution	Significant: <i>HHIP</i> , <i>CHRNA5</i> , <i>SOWAHB</i> , <i>TRAPPC9</i> , <i>KIAA1462</i>	[57]
Airway thickening	12,031 with and without COPD, measurement of wall area percent	Significant: <i>MIR2054</i>	[69]
Total lung capacity (TLC)	4543 COPD, TLC measured by chest CT scan	Significant: <i>DNAH5</i>	[56]
Hypoxemia	5420 COPD, pulse oxygen saturation	Significant in AA: Chr 14 and 15 (<i>TTCRR</i> , <i>KIF7</i>)	[115]
Chronic bronchitis (CB)	1662 COPD with CB vs. 3520 smokers with normal spirometry	Significant: Chr 4q22.1 (<i>FAM13A</i>), 11p15.5 (<i>EFCAB4A</i> , <i>CHIDI</i> , <i>AP2A2</i>)	[116]
Asthma-COPD overlap (ACO)	450 ACO vs. 3120 COPD	Suggestive in NHW: <i>CSMD1</i> , <i>SOX5</i> Suggestive in meta-analysis of NHW and AA: <i>GPR65</i>	[84]
Pneumonia	Smokers with and without COPD; 3766 ever pneumonia vs. 5659 never pneumonia	Suggestive: <i>LOC339862</i> , <i>RAPGEF2</i> , <i>PHACTRI</i> , near <i>PRR27</i> , near <i>MCPHI</i>	[66]
Pulmonary artery enlargement (PAE)	1266 COPD with PAE vs. 3775 COPD without PAE	Significant: <i>IREB2</i> , <i>GALC</i>	[117]
Airway hyperresponsiveness	2814 COPD subjects with measurement of continuous PC20	Significant: <i>LINGO2</i> Suggestive: <i>MYH15</i> , <i>SGCD</i> , <i>PDSS2</i>	[118]

AA = African American subjects; NHW = non-Hispanic white subjects

* Genome-wide significance at standard threshold of p-value<5e-8. Suggestive association at p-value<5e-6.

Table 4.

Precision prescription of inhaled corticosteroids in COPD

COPD Subtype/phenotype	Biomarker	Possible outcome of ICS	Ready for Clinical Implementation?	Reference
Frequent exacerbator	History of 2 exacerbations in the prior year	Reduction in exacerbation frequency	Yes	[36]
Eosinophilic COPD	Blood eosinophil count >300 cells/ μ l	Reduction in exacerbation frequency	Yes	[36]
Asthma-COPD overlap	History of asthma diagnosed before age 40	Reduction in exacerbation frequency? Improved FEV ₁ ?	Possible	No clinical trials available
Th2 high	Th2 gene expression score in airway brushings	Reduced hyperinflation	No	[86]
IL-17 high	IL-17 gene expression signature in airway brushings	Lack of improvement in FEV ₁	No	[90]
Adrenal suppression	<i>PDGFD</i> genotype	Increased risk of adrenal suppression	No	[64]
High risk of pneumonia	Clinical: current smoker, increasing age, low BMI, more severe COPD, lack of vaccination Genetic: several suggestive SNPs	Increased risk of pneumonia	Clinical factors: yes Genetic: No	[36]

BMI = body mass index; ICS = inhaled corticosteroids; SNP = single nucleotide polymorphism