Review

Pharmacogenetics and Theratyping in Pulmonology: A Practical Guide

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Pharmacogenetics and Theratyping in Pulmonology: A Practical Guide

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Abstract

Background: Pulmonary diseases are a leading cause of global morbidity and mortality. Heterogeneity in drug response significantly limits treatment success. Pharmacogenetics and genetic testing provides opportunities to personalize therapy based on genetic variants influencing diagnosis, pharmacokinetics and pharmacodynamics. **Objective:** To review recent advances in genetic testing and pharmacogenetics in asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), pulmonary arterial hypertension (PAH), and alpha-1 antitrypsin deficiency (AATD), with emphasis on practical diagnostics for pulmonologists. **Methods:** Analysis of recent literature, integrating recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), and the American College of Medical Genetics and Genomics (ACMG/AMP). **Results:** Variants in *ADRB2*, *CRHR1*, *CYP3A5*, *ALOX5*, *LTC4S*, *CFTR*, *SERPINA1*, *BMPR2*, and *CYP2C9* influence treatment response and drug safety. Diagnostic strategies include targeted genotyping, next-generation sequencing (NGS) panels, whole exome sequencing (WES), and functional theratyping. **Conclusion:** Pharmacogenetics is established in CF and AATD, emerging in asthma, COPD, and PAH. For pulmonologists, integrating genetic testing into clinical practice requires awareness of available diagnostic methods, clear guidelines, and structured clinical decision support.

Keywords: pharmacogenetics; asthma; COPD; cystic fibrosis; pulmonary arterial hypertension; alpha-1 antitrypsin deficiency; drug response; precision medicine

1. Introduction

Respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) are major contributors to morbidity and mortality. Despite standardized guidelines, treatment outcomes vary considerably. For example, while many patients with asthma achieve disease control with inhaled corticosteroids (ICS), a substantial subset remains symptomatic despite high-dose ICS combined with long-acting β2-agonists (LABAs).

Genetic testing and pharmacogenetics, which examines the influence of inherited genetic variation on drug response, provides a scientific basis for tailoring therapy. It is particularly valuable in monogenic conditions such as cystic fibrosis (CF), pulmonary arterial hypertension (PAH), and alpha-1 antitrypsin deficiency (AATD), where specific pathogenic variants directly determine treatment options. For complex disorders such as asthma and COPD, pharmacogenetic testing aids in stratifying therapy and reducing adverse effects [1,2].

2. Pharmacogenetics in Asthma

Asthma is a chronic inflammatory disease of the airways characterized by variable and usually reversible airflow obstruction, affecting more than 350 million people worldwide [3]. Despite the

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availability of effective pharmacological treatments, including inhaled corticosteroids (ICS), β_2-agonists, leukotriene receptor antagonists, and biologics targeting type 2 inflammation, there is substantial interindividual variability in treatment response. Up to 30–40% of patients exhibit suboptimal control of symptoms despite guideline-based therapies, underscoring the urgent need for more personalized approaches [4,5].

In this context, pharmacogenetics has emerged as a critical approach to understanding treatment variability. Genetic polymorphisms contribute significantly to differential drug response. For example, variants in the β_2-adrenergic receptor gene (*ADRB2*), particularly the Arg16Gly polymorphism, have been associated with variability in bronchodilator response and disease control [6,7]. Similarly, polymorphisms in corticosteroid pathway genes, such as *GLCCI1* (rs37973), influence responsiveness to inhaled corticosteroids, with certain genotypes conferring reduced therapeutic benefit [8]. Another relevant biomarker is the *FCER2* gene, where variants have been linked to an increased risk of severe exacerbations during ICS therapy [9]. Moreover, variants in the ALOX5 gene, coding for 5-lipoxygenase, modulate the therapeutic efficacy of leukotriene receptor antagonists, suggesting a role for genotype-guided therapy in selected patients [10].

Pharmacogenetic studies are also entering the field of advanced biologic therapies. Preliminary evidence suggests that genomic and transcriptomic biomarkers might predict differential response to anti-IgE, anti-IL5, or anti-IL4/13 antibodies, thus potentially guiding their cost-effective and rational use in severe asthma [11,12].

Incorporating pharmacogenetics into clinical decision-making could allow for better treatment stratification, reducing the trial-and-error approach to asthma therapy. The integration of genetic markers into multi-omic platforms and electronic health record-based decision support systemsis expected to facilitate clinical implementation and accelerate the translation of pharmacogenomic research into everyday pulmonology [13].

Table 1. Pharmacogenetic testing in pulmonary diseases.

Gene	Polymorphism/Variant	Drug / Drug class	Clinical implication	Reference
ADRB2	Arg16Gly (rs1042713), Gln27Glu (rs1042714)	β_2-agonists (SABA, LABA)	Arg16Arg associated with reduced response to regular β_2-agonist use; differences in long-term asthma control	[6,7]
GLCCI1	rs37973	Inhaled corticosteroids (ICS)	Risk allele linked to diminished response to ICS and persistent symptoms	[8]
FCER2	T2206C (rs28364072)	Inhaled corticosteroids (ICS)	C allele carriers at increased risk of severe exacerbations during ICS therapy	[9]
CRHR1	rs242941, rs1876828	Inhaled corticosteroids (ICS)	Certain haplotypes associated with improved ICS response	[8]
ALOX5	VNTR in promoter region	Leukotriene receptor antagonists	Non-classical promoter alleles linked to weaker therapeutic response	[10]

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		(montelukast, zafirlukast)		
IL4RA	Ile50Val (rs1805010), Gln576Arg (rs1801275)	Omalizumab (anti-IgE); ICS	Variants modulate atopic asthma phenotype and may influence response to biologic treatment	[11]
IL5RA / *IL5* pathway genes	Various associated variants	Mepolizumab, reslizumab (anti-IL5)	Potential role in predicting biologics efficacy in eosinophilic asthma	[11]
IL4/IL13 pathway genes	rs20541 (*IL13*), rs1800925 (*IL13*)	Dupilumab (anti-IL4Rα / anti-IL13)	Variants linked to type 2 inflammation; potential biomarkers for patient stratification	[11,12]

2.1. ADRB2 Variants

The *ADRB2* gene encodes the β2-adrenergic receptor, the target of LABAs. The p.Gly16Arg variant (rs1042713) is the best characterized. Patients homozygous for Arg16 demonstrate reduced bronchodilator response and increased exacerbation risk during LABA use, while Gly16 carriers respond more favorably [4]. Another functional variant, p.Gln27Glu (rs1042714), reduces receptor internalization and is associated with a protective effect [5].

2.2. CRHR1 and Corticosteroid Response

The *CRHR1* gene (corticotropin-releasing hormone receptor 1) modulates corticosteroid response. Certain haplotypes are associated with improved lung function and enhanced ICS efficacy [6].

2.3. CYP3A5 Metabolizer Status

Variants in *CYP3A5*, a cytochrome P450 enzyme, affect systemic exposure to ICS. Poor metabolizers accumulate higher steroid concentrations, increasing risk of osteoporosis and adrenal suppression [7].

2.4. Leukotriene Pathway

Montelukast and other leukotriene receptor antagonists (LTRAs) show variable efficacy. Variants in *ALOX5* and *LTC4S* influence treatment response. GWAS also implicate *MRPP3* in modulating zileuton efficacy [8].

Genetic diagnostics and clinical recommendations in asthma

- Consider pharmacogenetic panel testing in patients with poor asthma control despite ICS/LABA therapy.
- Genotyping of *ADRB2* (p.Gly16Arg, p.Gln27Glu) may guide LABA use.
- Testing for *CRHR1* and *CYP3A5* variants may optimize ICS dosing and reduce side effects.
- In leukotriene-targeted therapy, *ALOX5* and *LTC4S* variants can help predict response.

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3. Pharmacogenetics and Genetics in COPD

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by chronic inflammation, structural remodeling of the airways, and persistent airflow limitation that is not fully reversible. It represents one of the leading causes of morbidity and mortality worldwide, with an estimated prevalence of over 300 million patients and ranking among the top three causes of death globally. Classically, COPD has been considered a complex multifactorial disease, in which environmental exposures, primarily tobacco smoke, occupational dusts and fumes, and air pollution, interact with genetic susceptibility factors to determine an individual's risk and disease trajectory.

Among the genetic determinants of COPD, alpha-1 antitrypsin deficiency (AATD) is the best-established and most clinically relevant example. This inherited condition, caused by pathogenic variants in the *SERPINA1* gene, leads to reduced circulating levels or dysfunctional variants of alpha-1 antitrypsin (AAT), the principal inhibitor of neutrophil elastase. In the absence of adequate AAT activity, unchecked proteolytic activity results in progressive destruction of alveolar walls and early-onset panacinar emphysema, particularly pronounced in the lower lobes of the lungs.

The most severe phenotype is associated with the homozygous PI*ZZ genotype, in which serum AAT levels fall to approximately 10–15% of normal, conferring a markedly increased risk of developing emphysema, often decades earlier than in smoking-related COPD. Compound heterozygotes, such as PI*SZ, and heterozygotes PI*MZ, carry an intermediate risk that is strongly modulated by environmental exposures—especially active cigarette smoking. This gene–environment interaction underscores the importance of systematic genetic testing, as early identification of AATD carriers enables preventive interventions, including smoking cessation, avoidance of occupational exposures, targeted clinical monitoring, and, where appropriate, augmentation therapy with intravenous purified AAT.

While AATD remains the only firmly established monogenic risk factor for COPD, ongoing research is uncovering additional polygenic contributions. Genome-wide association studies (GWAS) have implicated multiple loci associated with lung function trajectories, inflammatory regulation, matrix remodeling, and immune responses. Variation in genes such as *HHIP* (hedgehog-interacting protein), *FAM13A*, *CHRNA3/5* (nicotinic receptor subunits), and *IREB2* has been associated with COPD susceptibility and progression, further confirming the multifactorial genetic underpinnings of the disease. Although their clinical translation is still limited, such discoveries point toward a future in which polygenic risk scores could refine disease prediction and complement traditional risk factors like smoking history, occupational exposures, and imaging markers.

3.1. ICS Response

Inhaled corticosteroids (ICS) constitute a cornerstone of anti-inflammatory treatment in selected phenotypes of chronic obstructive pulmonary disease (COPD), particularly among patients with frequent exacerbations and evidence of type 2 inflammation. However, as in asthma, there is marked interindividual variability in ICS efficacy and safety, underscoring the need for predictive biomarkers and pharmacogenetic insights.

Pharmacogenetic studies indicate that CYP3A5 polymorphisms significantly affect ICS metabolism. Individuals who are poor metabolizers due to loss-of-function *CYP3A5* variants demonstrate higher systemic exposure to corticosteroids. This phenomenon mirrors findings in asthma, where impaired metabolism increases the risk of corticosteroid-related adverse effects such as adrenal suppression, osteoporosis, and metabolic disturbances [10]. Hence, in COPD patients requiring long-term ICS therapy, genotyping for drug metabolism variants could help personalize dosing strategies, balancing the benefits of exacerbation reduction against the risk of systemic complications.

Beyond pharmacogenetics, inflammatory biomarkers play a critical role in predicting ICS responsiveness. Measurement of blood eosinophil counts has emerged as a robust and readily

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available marker to stratify COPD patients likely to benefit from ICS therapy. Elevated eosinophil counts correlate with greater reductions in exacerbation frequency and improved clinical outcomes, whereas patients with persistently low eosinophil levels may derive limited benefit but remain at risk of pneumonia and other adverse events. Integrating eosinophil counts into treatment algorithms alongside pharmacogenetic information offers a more comprehensive predictive model than either factor alone [10].

In clinical practice, this dual approach could be transformative: while biomarkers such as eosinophils identify the inflammatory phenotype likely to respond, pharmacogenetic testing identifies metabolic capacity and thus the optimal therapeutic window for safe and effective ICS use. Together, these tools represent a step toward precision respiratory medicine in COPD, moving beyond the traditional "one-size-fits-all" approach.

3.2. Potassium Channel Genes

Bronchodilator responsiveness (BDR) represents a key clinical parameter in both asthma and chronic obstructive pulmonary disease (COPD), reflecting the degree of reversibility of airflow limitation. Despite its importance in diagnosis and management, BDR varies substantially between patients and is determined by a complex interplay between genetic, molecular, and environmental factors. Pharmacogenetic studies have identified several loci related to BDR, extending beyond the classical genes such as *ADRB2* and steroid-signaling pathways.

Recent evidence points toward a potential role of ion channel genes, including *KCNJ2* and *KCNK1*, in modulating responsiveness to bronchodilators [11]. KCNJ2 encodes the inward rectifier potassium channel Kir2.1, which contributes to setting the resting membrane potential of airway smooth muscle cells. Variants in this gene may influence smooth muscle excitability and thus modify the physiological relaxation response to β_2-agonists. Similarly, *KCNK1* encodes a member of the tandem pore domain potassium channels (K2P family), which regulate baseline potassium conductance and modulate smooth muscle tone. Polymorphisms in *KCNK1* have been associated with differential BDR in genome-wide association studies, suggesting that subtle variations in potassium channel activity could alter the pharmacodynamic response to bronchodilator therapy.

While these findings are intriguing, the translation into routine clinical practice remains experimental. The identified associations require replication in larger, ethnically diverse cohorts and functional studies to establish causal mechanisms. At present, *KCNJ2* and *KCNK1* variants are best regarded as research biomarkers, highlighting novel biological pathways that may underlie variability in drug response but not yet suitable for guiding therapeutic decisions.

Nevertheless, these discoveries expand the pharmacogenetic landscape of obstructive airway diseases and point toward ion channels as potential therapeutic targets. Future studies may determine whether patients carrying specific channel variants exhibit consistent, clinically meaningful differences in bronchodilator efficacy, and whether this knowledge could eventually inform individualized bronchodilator therapy as part of precision respiratory medicine.

Genetic diagnostics and clinical recommendations in COPD

- All patients with early-onset COPD or atypical emphysema should undergo *SERPINA1* testing (at least PI*Z and PI*S alleles).
- NGS panels are recommended if rare *SERPINA1* variants are suspected.
- Pharmacogenetic panels including *CYP3A5* may help refine ICS treatment.

4. Pharmacogenetics in Cystic Fibrosis

Cystic fibrosis (CF) is a prototypical monogenic disorder in which pharmacogenetics has transitioned from research to routine clinical practice. The disease arises from pathogenic variants in the *CFTR* gene, encoding the cystic fibrosis transmembrane conductance regulator protein, a chloride channel crucial for epithelial ion transport. More than 2,000 *CFTR* variants have been described, and these can be grouped into functional classes depending on the molecular defect, such as impaired synthesis, folding, gating, or conductance (http://www.genet.sickkids.on.ca).

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Variants are classified into six groups:

- Class I: no protein production (e.g., nonsense variants)
- Class II: defective processing (e.g., p.Phe508del)
- Class III: defective gating (e.g., p.Gly551Asp)
- Class IV: reduced conductance
- Class V: reduced synthesis
- Class VI: increased turnover at the cell surface [12]

The introduction of CFTR modulators has transformed the therapeutic landscape of CF. Importantly, their efficacy is strictly genotype-dependent, representing one of the clearest demonstrations of precision pharmacogenetics in clinical medicine. For example, the potentiator ivacaftor has shown dramatic clinical benefit in patients carrying Class III gating variants *such as* p.Gly551Asp, by improving the probability of channel opening and thereby restoring chloride transport [13]. In this subgroup, ivacaftor has been associated with substantial improvements in pulmonary function, weight gain, sweat chloride normalization, and survival.

Another milestone was the development of combination therapies designed to address the trafficking defect caused by the most common variant, p.Phe508del. *Initial* double combinations (lumacaftor/ivacaftor or tezacaftor/ivacaftor) demonstrated clinical benefit but were limited by variable efficacy and adverse events. The introduction of the triple modulatory therapy elexacaftor/tezacaftor/ivacaftor represented a significant breakthrough: carriers of at least one p.Phe508del allele now have access to a highly effective treatment that markedly improves lung function, reduces pulmonary exacerbations, enhances quality of life, and prolongs survival [13]. This strategy highlights how precise genetic characterization directly informs therapeutic eligibility and expected benefit.

However, a considerable challenge remains for patients carrying rare or ultra-rare *CFTR* variants, for which randomized trial evidence is lacking. In this context, theratyping, the functional assessment of patient-derived epithelial cells (e.g., nasal epithelial cells or intestinal organoids) exposed to candidate modulators, offers a powerful platform for evaluating potential drug responsiveness. This personalized ex vivo testing has been successfully applied to extend modulator therapy to individuals with rare CFTR genotypes, providing functional evidence to support regulatory approval or compassionate use [14].

Taken together, CF illustrates the full potential of pharmacogenetically guided therapy in respiratory medicine: systematic genotyping directs patient stratification, therapy selection, and provides predictive information about likely clinical outcomes. Moreover, functional assays such as theratyping bridge the gap between genetic diagnosis and real-world drug response, thereby extending the reach of precision medicine to genetically heterogeneous populations.

Genetic diagnostics and clinical recommendations in CF

- All suspected CF patients should undergo CFTR NGS panel testing.
- If negative or inconclusive, WES/WGS is recommended.
- Functional assays, theratyping, are valuable for rare variants to guide CFTR modulator eligibility.

5. Pharmacogenetics in Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a rare but severe disease characterized by progressive remodeling of pulmonary vasculature and right heart failure. From a genetic perspective, PAH may occur in heritable forms, most commonly due to pathogenic variants in the *BMPR2* gene, which are identified in approximately 70% of familial cases and 20% of apparently idiopathic cases [15]. Mutations in *BMPR2* lead to dysregulation of the bone morphogenetic protein signaling pathway, promoting proliferation of pulmonary vascular smooth muscle cells and endothelial dysfunction.

Beyond *BMPR2*, other causative genes include *ACVRL1* and *ENG*, both of which are also implicated in hereditary hemorrhagic telangiectasia, underlining the intersection between vascular malformations and pulmonary vascular disease. Importantly, *EIF2AK4* mutations have been associated with pulmonary veno-occlusive disease (PVOD) and pulmonary capillary

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hemangiomatosis (PCH), two subtypes of PAH that carry a particularly poor prognosis. Identification of such variants therefore has diagnostic, prognostic, and therapeutic implications, as these patients often show atypical treatment responses and may be at higher risk of adverse events from standard PAH therapies.

Pharmacogenetics is emerging as a relevant aspect of drug response variability in PAH. For instance, CYP2C9 polymorphisms significantly influence the metabolic clearance of prostacyclin analogues, such as treprostinil, thereby affecting drug concentrations, therapeutic efficacy, and the risk of toxicity [16]. Individuals carrying reduced-function *CYP2C9* alleles (e.g., *CYP2C9* *2 and *3) display slower drug metabolism and may therefore require adjusted dosing strategies to avoid adverse effects while maintaining efficacy. Although clinical implementation is still in early stages, pharmacogenetic testing could become an important element of precision dosing in PAH management, particularly for therapies with narrow therapeutic windows.

In addition to prostacyclin analogues, ongoing research is examining whether genetic variants in drug transporters, signal transduction pathways, or nitric oxide metabolism influence response to endothelin receptor antagonists, PDE5 inhibitors, or sGC stimulators. While current evidence remains preliminary, these avenues open the possibility for a more personalized therapeutic algorithm in PAH, where molecular diagnostics inform both disease subtype stratification and tailored pharmacological strategies.

Genetic diagnostics and clinical recommendations in PAH

- Genetic testing is recommended in familial or early-onset PAH.
- Multigene panels covering *BMPR2, ACVRL1, ENG, EIF2AK4* should be used.
- *CYP2C9* genotyping may assist in prostacyclin dosing.

6. Pharmacogenetics in Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD) is a hereditary disorder caused by pathogenic variants in the *SERPINA1* gene, encoding the alpha-1 antitrypsin (AAT) protein, a key serine protease inhibitor that protects lung tissue from neutrophil elastase-mediated damage. The disease exhibits marked allelic heterogeneity, with the most clinically relevant pathogenic variants being PI*Z and PI*S. Individuals harboring the homozygous PI*ZZ genotype are at the highest risk of developing early-onset pulmonary emphysema, chronic obstructive pulmonary disease (COPD), and liver disease, while heterozygous PI*MZ and compound heterozygous PI*SZ genotypes confer an intermediate level of risk depending on environmental exposures, particularly cigarette smoking and occupational inhalants [9].

From a pharmacologic perspective, early detection of *SERPINA1* variants has direct therapeutic implications. Patients with confirmed severe deficiency, especially those with the PI*ZZ genotype and airflow obstruction, may qualify for intravenous augmentation therapy with purified AAT protein, which has been shown to slow disease progression by reducing the rate of lung function decline. In addition, pharmacogenetic identification of at-risk individuals allows for personalized preventive recommendations, including smoking cessation, vaccination against respiratory pathogens, and tailored lifestyle modifications to minimize pulmonary damage.

Another essential aspect is the implementation of cascade family screening, which facilitates identification of *SERPINA1* carriers among first-degree relatives. This approach not only uncovers asymptomatic cases but also enables pre-symptomatic intervention, such as smoking avoidance and structured pulmonary follow-up, thereby reducing long-term morbidity. Genetic counseling should accompany all diagnostic and family testing pathways to ensure informed decision-making and patient engagement.

Looking toward innovation, AATD might become a target for precision medicine strategies beyond conventional augmentation. Gene-based approaches, including AAT gene augmentation, mRNA-based therapies, or genome editing, are under investigation as potential curative avenues. Thus, the pharmacogenetics of AATD sits at the intersection of established clinical interventions and

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rapidly evolving molecular therapeutics, underscoring the importance of integrating genetic screening into standard pulmonology practice.

Genetic diagnostics and clinical recommendations in AATD

In alpha-1 antitrypsin deficiency (AATD), genetic testing represents a cornerstone of accurate diagnosis and targeted management. Current guidelines advise that every patient with chronic obstructive pulmonary disease (COPD) should undergo at least one genetic assessment for the most common pathogenic variants of *SERPINA1*, namely PI*Z and PI*S. This approach ensures that individuals with atypical clinical presentations or early-onset disease are not overlooked, and it facilitates timely diagnosis of a condition that remains underrecognized in routine practice.

Beyond the classical PI*Z and PI*S alleles, extended next-generation sequencing (NGS) panels offer the possibility to identify rare or novel pathogenic variants in *SERPINA1*, which might otherwise escape detection by standard genotyping. Employing such broad molecular diagnostics is particularly important in patients with discordant biochemical and clinical findings, as well as in geographic regions where less common variants occur with higher frequency.

Importantly, the genetic diagnosis of AATD has implications that go beyond the index patient. Genetic counseling should be systematically offered, both to educate affected individuals about disease inheritance and to support informed decision-making regarding lifestyle modifications, reproductive options, and clinical monitoring. In addition, cascade genetic testing of biological relatives is strongly recommended, as it enables early identification of carriers and affected family members who may benefit from preventive interventions, structured monitoring, and, in selected cases, augmentation therapy.

Taken together, the integration of routine *SERPINA1* testing, advanced sequencing technologies, and structured family counseling constitutes best practice in AATD care. This combined strategy not only improves diagnostic yield but also promotes preventive medicine by detecting disease risk within families and implementing appropriate clinical surveillance before the onset of irreversible lung damage.

7. Recommended Genetic Tests in Pulmonology

Table 2. Genetic testing in pulmonary diseases significant for therapy and drug dosing.

Disease	Clinical scenario	Recommended test	Genes / variants	Clinical action
Asthma	Poor ICS/LABA response	PGx panel	*ADRB2*, *CRHR1*, *CYP3A5*, *ALOX5*	Adjust therapy, consider biologics
COPD	Early-onset emphysema	Targeted / NGS	*SERPINA1* (PI*Z, PI*S, rare alleles)	Augmentation therapy if PI*ZZ
CF	Bronchiectasis, positive sweat test	CFTR NGS panel / WES	*CFTR* variants (Class I–VI)	Eligibility for modulators
PAH	Familial/early-onset PAH	PAH panel	*BMPR2*, *ACVRL1*, *ENG*, *EIF2AK4*	Genetic counseling, drug selection
AATD	COPD with liver involvement	Targeted or panel	*SERPINA1 PI*Z*, *PI*S*	Augmentation therapy, family testing

PGx - pharmacogentic.

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8. Implementation in Clinical Practice

The successful translation of pharmacogenetics into respiratory medicine depends on its seamless integration into routine workflows. One of the most important steps is the incorporation of pharmacogenetic test results into electronic health records (EHRs), complemented by clinical decision support systems that can provide pulmonologists with real-time prescribing recommendations. Such systems should highlight relevant genotype–drug interactions, propose dose adjustments, or suggest alternative therapies, thereby minimizing reliance on individual clinician memory and reducing the risk of prescribing errors.

Equally crucial is the education and training of pulmonologists. Surveys conducted in various healthcare settings demonstrate that a significant proportion of specialists report insufficient knowledge and low confidence in applying pharmacogenetic results to clinical decision-making [17,18]. Structured educational initiatives, such as continuing medical education (CME) modules, integration of pharmacogenomics into pulmonology residency curricula, and accessible online resources, are necessary to bridge this knowledge gap. These efforts are likely to foster greater clinician acceptance and accelerate adoption.

Another key consideration is the economic justification of testing. Cost-effectiveness analyses have consistently shown that pharmacogenetic-guided prescribing reduces the burden of adverse drug reactions (ADRs), lowers hospitalization rates, and improves long-term treatment efficacy, ultimately leading to net healthcare savings [19]. In respiratory medicine, avoiding unnecessary exposure to ineffective biologics in asthma or optimizing immunomodulatory therapy in COPD represents not only a clinical but also a financial advantage.

Implementation, however, faces practical challenges: availability of accredited laboratories, turnaround time of genetic testing, reimbursement policies, and disparities in infrastructure between healthcare systems across regions. Addressing these barriers requires coordinated strategies at the policy level, including the establishment of standardized testing protocols and reimbursement frameworks that can ensure equitable access.

9. Future Perspectives

The future of precision respiratory medicine will be defined by the integration of multidisciplinary technologies capable of capturing disease complexity across multiple biological layers. Multi-omics approaches, encompassing genomics, transcriptomics, proteomics, metabolomics, and epigenomics, are expected to provide a systems-level understanding of respiratory diseases. By linking molecular signatures with clinical phenotypes, they will allow the identification of novel therapeutic targets, patient subgroups with distinct drug responsiveness, and predictive biomarkers for disease progression.

Parallel to this, artificial intelligence (AI) and machine learning are rapidly advancing as indispensable tools in data-driven medicine. Their application in respiratory genomics is anticipated to optimize variant interpretation, integrate multi-omics data with imaging and clinical variables, and generate real-time treatment recommendations. In particular, digital twin technologies, virtual computational models of an individual patient, hold the promise of simulating disease course, testing drug efficacy in silico, and supporting highly personalized treatment decisions before clinical interventions are initiated.

On the therapeutic frontier, gene therapy and mRNA-based approaches represent transformative opportunities. For monogenic conditions such as cystic fibrosis (CF) and alpha-1 antitrypsin deficiency (AATD), these modalities may move beyond symptomatic control toward durable or even curative interventions [20,21]. Gene editing strategies, ribonucleic acid repair, and mRNA delivery systems are being actively explored to correct underlying genetic defects in relevant tissues, offering the potential to alter disease trajectory fundamentally.

Importantly, future progress will require not only technological breakthroughs but also careful attention to ethical, regulatory, and health-economic aspects. Issues such as equitable access to testing

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and therapies, data privacy in AI-driven models, and cost–benefit validation of advanced biotechnologies will need to be addressed before widespread clinical implementation.

10. Guideline-Based Integration of Pharmacogenetics

The analysis of literature from recent years underscores not only rapid scientific progress but also the growing role of international implementation frameworks in shaping clinical practice. Consensus recommendations from the Clinical Pharmacogenetics Implementation Consortium (CPIC, https://cpicpgx.org), the Dutch Pharmacogenetics Working Group (DPWG, https://www.knmp.nl/kennisgebieden/farmacogenetica), and the American College of Medical Genetics and Genomics (ACMG/AMP, https://www.acmg.net) provide detailed genotype–phenotype translations and evidence-based prescribing guidelines that are directly applicable to pulmonology. These bodies establish harmonized standards on how to interpret pharmacogenetic test results and integrate them into therapeutic decisions, addressing gene–drug pairs such as CYP2C9–prostacyclin analogues, CYP3A5–corticosteroids, or ADRB2–β2-agonists. Importantly, they also set forth recommendations on variant classification, reporting standards, and clinical decision support integration, which are crucial for effective communication of results in clinical settings [17,18].

For respiratory diseases, this means that scientific evidence can be rapidly translated into routine care pathways, provided that pulmonologists are aware of and adhere to these guidelines. Aligning local practice with CPIC, DPWG, and ACMG principles ensures not only scientific validity but also facilitates cross-border harmonization and paves the way toward systematic adoption of pharmacogenetics in respiratory medicine.

11. Conclusions

Pharmacogenetics is progressively shaping respiratory medicine by providing a framework for tailoring therapies to the individual genetic background of patients. In cystic fibrosis (CF) and alpha-1 antitrypsin deficiency (AATD), pharmacogenetic principles have already become an integral part of daily clinical practice, guiding the use of targeted disease-modifying therapies and enabling more accurate prediction of treatment response. In asthma and chronic obstructive pulmonary disease (COPD), the field is evolving at a rapid pace, supported by growing evidence on drug–gene interactions, particularly in the context of bronchodilator response, inhaled corticosteroid sensitivity, and biologic eligibility. Pulmonary arterial hypertension (PAH), although still at an early stage of pharmacogenetic research, represents a promising area where genetic insights may soon refine therapeutic strategies and stratify patients by prognosis and treatment benefit.

For pulmonologists, the translational gap lies not in the discovery of variants but in their clinical adoption. Clear, evidence-based guidelines on which tests should be ordered, at what point in the disease course, and how results should influence drug selection or dosing remain essential. Establishing structured decision-making algorithms, integrating pharmacogenetic testing into routine diagnostic pathways, and promoting multidisciplinary collaboration between pulmonologists, clinical geneticists, and pharmacologists will be critical for full implementation.

Ultimately, the integration of pharmacogenomics into respiratory care has the potential to reduce therapeutic failure, minimize adverse drug reactions, and improve long-term outcomes. The next decade should therefore prioritize not only discovery research, but also harmonization of testing practices, cost-effectiveness studies, and the development of clinical recommendations tailored to everyday pulmonology practice.

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