

THE ROLE OF PHARMACOGENOMICS IN PERSONALIZING PHARMACOTHERAPY FOR AUTOIMMUNE –ASSOCIATED INTERSTITIAL LUNG DISEASE [ILD]

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Article Received on: 17/09/2026

Article Revised on: 06/10/2026

Article Published on: 01/11/2026

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<https://doi.org/10.5281/zenodo.23797782>



How to cite this Article: Nakka Hemalatha^{*1}, Sara venkatalakshmi², Esamsetti Sowmya², Yedida Divya², Chintapalli Srikar Reddy², Pabbineedi Manoj. (2026). The Role of Pharmacogenomics In Personalizing Pharmacotherapy For Autoimmune -Associated Interstitial Lung Disease [Ild]. International Journal of Modern Pharmaceutical Research, 10(11), 33–41.

ABSTRACT

Pharmacogenomics (PGx) is an important component of precision medicine that explores how genetic differences between individuals can influence their response to drug therapy. Autoimmune-associated interstitial lung disease (AI-ILD) represents a diverse group of conditions characterized by variations in disease progression, treatment effectiveness, and susceptibility to adverse drug reactions. These differences can make conventional approaches to immunosuppressive and antifibrotic therapy less predictable. This review examines the potential application of pharmacogenomics in developing individualized treatment strategies for patients with AI-ILD. Particular emphasis is placed on genetic variations that may influence drug metabolism, transport, molecular targets, therapeutic response, and treatment-related toxicity. The pharmacogenomic relevance of commonly used therapies, including mycophenolate mofetil, azathioprine, cyclophosphamide, methotrexate, glucocorticoids, biologic therapies, and antifibrotic agents, is discussed. Established biomarkers, particularly TPMT and NUDT15 in thiopurine treatment, are highlighted alongside emerging genetic findings for other therapies. Despite its potential, clinical application remains limited by the scarcity of ILD-specific evidence, small study populations, variable genetic associations, and insufficient prospective validation. Combining pharmacogenomic data with clinical, radiological, and molecular information may facilitate more individualized therapeutic decision-making. Further research is necessary to establish clinically validated pharmacogenomic strategies for routine use in AI-ILD.

KEYWORDS: Pharmacogenomics; Autoimmune-associated interstitial lung disease; Precision medicine; Drug response; Pharmacogenetic variability; Personalized therapy.

1. INTRODUCTION

Pharmacogenomics (PGx) examines how genetic differences affect drug response and Pharmacogenetics involves the investigation of genetic variations that affect drug-metabolizing pathways and consequently contribute to interindividual differences in therapeutic response and susceptibility to adverse drug reactions.^[1] Supports individualized treatment by identifying factors that influence drug exposure and therapeutic effects.^[2] Because population-based dosing may not suit every patient, genetic variation can contribute to inadequate response, expected therapeutic effects, or increased toxicity.^[3]

Pharmacogenomics can be defined as the study of how inter-individual genetic variation governs drug response, wherein gene expression patterns and single-nucleotide polymorphisms (SNPs) are correlated with the

therapeutic efficacy and toxicological profile of pharmaceutical agents.^[4]

A crucial element of personalized and precision medicine is pharmacogenomics. Unlike the conventional one-size-fits-all approach, personalized medicine emphasizes therapeutic interventions tailored to the biological differences among patients. Here, genetic insights aid in selecting appropriate drugs, optimizing dosages, and evaluating toxicity risk. Ultimately, it aims to enhance therapeutic success while limiting avoidable adverse drug reactions.^[5]

Pharmacogenetics and pharmacogenomics are related concepts. Pharmacogenetics traditionally emphasizes the effect of individual genetic variants on drug response, whereas pharmacogenomics considers broader genetic information and multiple biological pathways. Genetic

differences may influence pharmacokinetics through drug metabolism and transport or pharmacodynamics through drug targets, receptors, and downstream signalling pathways.^[6]

Autoimmune-associated ILD develops in the setting of systemic autoimmune disease and includes several clinical entities such as systemic sclerosis-associated ILD, rheumatoid arthritis-associated ILD, inflammatory ILD, Sjögren myopathy-associated Disease-associated ILD, systemic lupus erythematosus-associated ILD, and mixed or undifferentiated connective-tissue disease-associated ILD. The disorders differ in clinical phenotype, radiological pattern, progression, and treatment response.^[7]

Because AI-ILD is heterogeneous, a uniform treatment strategy may not produce the same outcome in every patient. Pharmacogenomic information could complement clinical assessment by identifying genetic factors associated with altered drug exposure, efficacy, or susceptibility to toxicity. However, genetic information should be interpreted together with disease phenotype and other patient-specific characteristics rather than used as an isolated determinant of treatment.^[8]

The objective of this review is to summarize the role of pharmacogenomics in personalizing pharmacotherapy for AI-ILD and to distinguish established clinical applications from promising but still investigational drug-gene associations.^[9]

2. OVERVIEW OF PHARMACOGENOMICS

Pharmacogenomics (PGx) examines how inherited genetic variation contributes to differences in an individual's response to medicines. The response to a drug is influenced not only by the prescribed dose but also by processes that determine drug exposure and the biological response to that exposure. Genetic differences can therefore contribute to interindividual variability in treatment efficacy, drug disposition, and susceptibility to adverse drug reactions. Pharmacogenomic research aims to identify such genetic determinants and use clinically relevant information to support more individualized drug selection and dosing.^[10]

The influence of genetic variation on drug response can broadly be considered through pharmacokinetic (PK) and pharmacodynamic (PD) mechanisms.^[11]

Human genetic variation occurs in several forms, including single-nucleotide variants, insertions and deletions, copy-number variation, and larger structural changes. These variants may influence the expression, structure, stability, or function of proteins involved in drug disposition and response.^[12] A single-nucleotide polymorphism is a variation at a single nucleotide position in DNA that occurs in a Population at a frequency generally considered polymorphic. In pharmacogenomics, SNPs are important Because even a

single base substitution can modify gene expression, RNA processing, protein structure or Enzyme activity. SNPs are among the most commonly studied forms of human genetic variation.^[13]

2.1 Drug-Metabolizing Enzymes

Phase I metabolism primarily involves oxidation, reduction, or hydrolysis, predominantly mediated by the cytochrome P450 (CYP) family. These enzymes metabolize a large proportion of commonly used drugs. Genetic polymorphisms in CYP genes lead to distinct metabolizer phenotypes, which become clinically significant when drug exposure is highly dependent on a specific isoform. Phase II metabolism involves conjugation of drugs or metabolites with endogenous substrates to facilitate elimination. Key enzymes include thiopurine S-methyltransferase (TPMT) and UDP-glucuronosyltransferases (UGTs). Variation in these enzymes can alter drug activation or clearance. Pharmacogenomic testing is therefore clinically relevant for selected drug-gene pairs with established genotype-outcome associations.^[14]

2.2 Cytochrome P450 System

The cytochrome P450 system is a major example of pharmacogenomic variability. CYP enzymes contribute to the metabolism of numerous drugs, and interindividual genetic differences result in altered enzymatic activity. Some variants reduce activity, while others increase it or result in non-functional enzyme. Such differences influence drug concentrations and contribute to therapeutic variability. CYP2D6, CYP2C9, CYP2C19 and CYP3A5 have been extensively studied. CYP2D6 is particularly notable due to its wide range of metabolic capacity among individuals. Altered CYP activity may change exposure to parent drug or its active metabolite.^[15]

2.3 Phase II Enzymes

Phase II enzymes mediate conjugation and elimination of many therapeutic agents. Genetic variation can modify metabolic capacity, thereby affecting drug exposure and toxicity. TPMT and UGT family enzymes are clinically important examples where genetic differences affect drug handling. The clinical utility of Phase II pharmacogenomics depends on the strength and reproducibility of genotype-outcome relationships. While some associations have been incorporated into clinical guidelines, others remain investigational. A statistically significant association alone does not guarantee that genetic testing will improve outcomes.^[16]

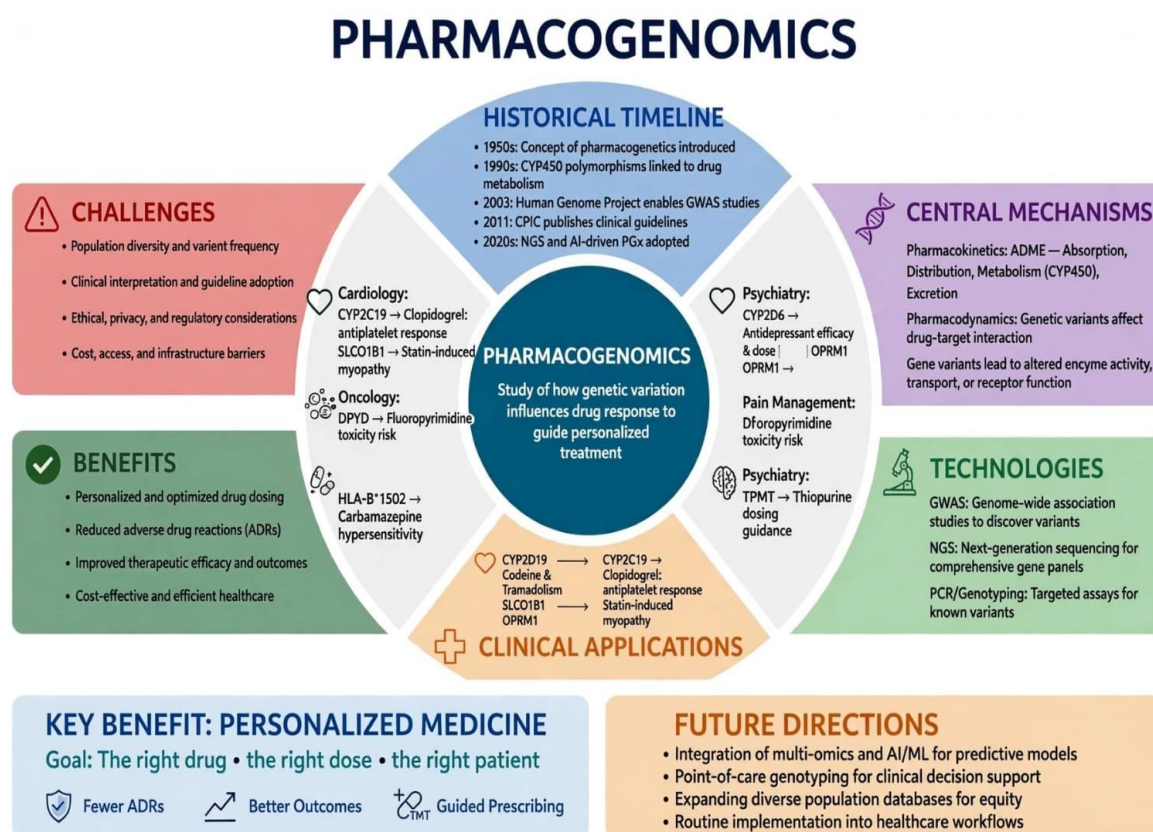
2.4 Drug Transporters

Drug transporters from ABC and SLC families regulate absorption, distribution, and elimination of drugs. Genetic variation can alter their expression or function, changing systemic and intracellular drug concentrations.^[17]

2.5 Drug Targets and Receptors

Besides drug disposition, genetic variants in drug targets like receptors, enzymes, and ion channels can modify

target expression or activity, altering individual drug sensitivity despite similar drug levels.^[18]



2.6 From Pharmacogenomic Variants to Personalized Therapy

Pharmacogenomics is to translate clinically relevant genetic variants into actionable prescribing decisions. This requires robust evidence that a genotype is consistently linked to drug response and that using this information improves drug selection, dosing, efficacy or safety. Implementation relies on validated drug-gene associations, standardized phenotype interpretation and evidence-based guidelines. Consortia such as CPIC provide frameworks to convert genetic results into therapeutic recommendations, facilitating integration into clinical practice.^[19]

Despite progress, PGx implementation remains limited by variable access to testing, complex result interpretation, HER integration challenges, cost, clinician awareness and underrepresentation of diverse populations. These issues are particularly relevant for complex diseases where multiple genetic and clinical factors influence response.^[20] For autoimmune-associated ILD, these principles offer a conceptual basis to explore how genetic variation may affect efficacy and toxicity of immunosuppressive and antifibrotic therapies, but evidence in AI-ILD remains less mature than in other

fields and should be considered an emerging approach requiring further validation before routine use.^[21]

3. AUTO IMMUNE ASSOCIATED INTERSTITIAL LUNG DISEASE

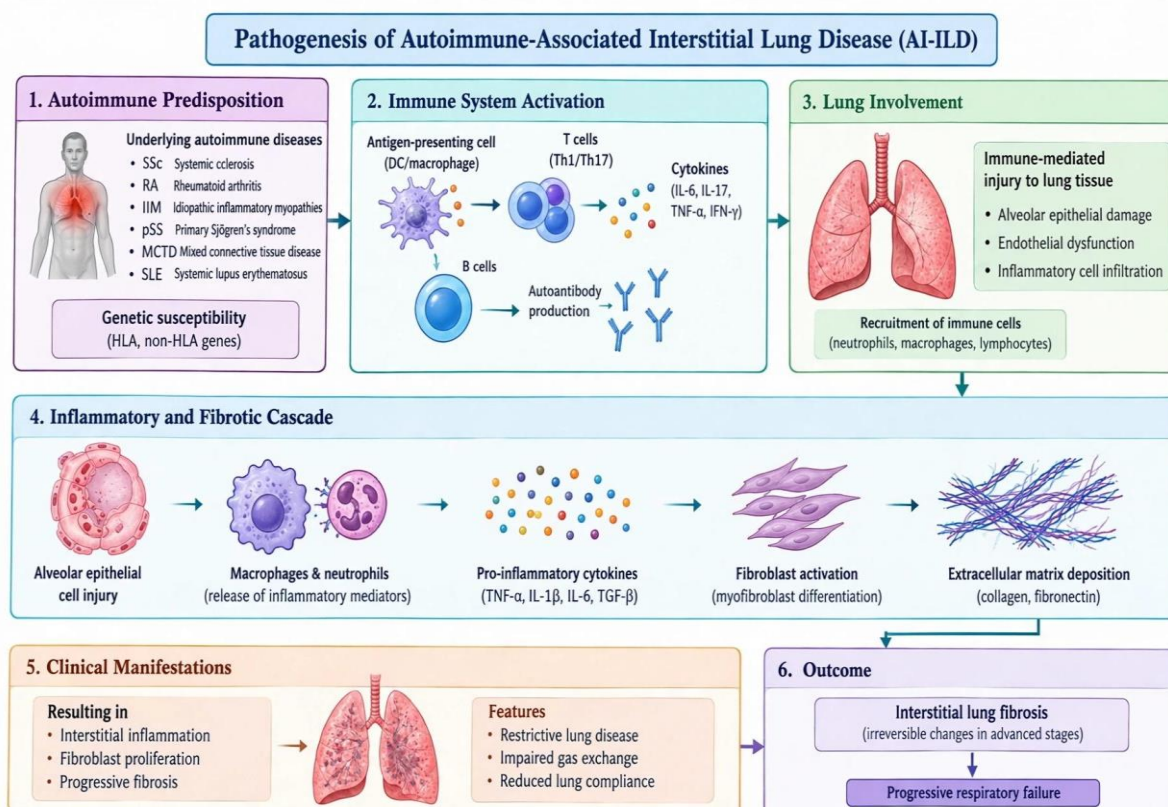
Autoimmune-associated ILD refers to interstitial pulmonary involvement in systemic autoimmune rheumatic or connective tissue diseases, including systemic sclerosis, rheumatoid arthritis, idiopathic inflammatory myopathies, Sjögren syndrome and mixed connective tissue disease. Pulmonary manifestations are heterogeneous in radiological pattern, severity, progression rate and treatment response, and classification is based on the underlying systemic disease. Patients with interstitial pneumonia and autoimmune features not fulfilling defined CTD criteria may be categorized as interstitial pneumonia with autoimmune features (IPAF) as a research entity.^[22] Among these, SSc-ILD is characterized by immune dysregulation, vasculopathy and progressive fibrosis, often with an NSIP pattern but variable course, while RA-ILD frequently shows a UIP pattern though NSIP and organizing pneumonia can also occur, and lung disease may develop independent of joint activity, underscoring the need for individualized assessment.^[23]



3.1 Pathogenesis

Autoimmune-associated ILD arises from interplay of genetic predisposition, environmental exposures, epithelial injury, immune dysregulation and abnormal repair, where environmental triggers cause alveolar injury in susceptible individuals, activating immune responses that release inflammatory mediators affecting

epithelial cells, macrophages and fibroblasts, and repeated injury drives aberrant fibrosis, with variable inflammatory versus fibrotic dominance influencing phenotype and treatment, while genetic variation further modulates immune regulation and therapeutic response.^[24]



3.2 Treatment Approaches in Autoimmune-Associated ILD

Management of AI-ILD depends on underlying disease, severity, inflammatory vs fibrotic pattern and progression. Conventional therapy includes

glucocorticoids with immunosuppressants like mycophenolate, cyclophosphamide and azathioprine, supplemented by biologics and antifibrotics in progressive cases.^[25] Scleroderma Lung Study II showed mycophenolate and cyclophosphamide equally improved

lung function over 24 months in SSc-ILD, but cyclophosphamide had more toxicity-related discontinuations. SENSICIS trial demonstrated nintedanib slowed FVC decline in SSc-ILD, supporting antifibrotic use. Per ACR/CHEST, treatment must be disease-specific — glucocorticoids are discouraged as first-line in SSc-ILD but remain a conditional option in other SARD-ILDs.^[26]

several pharmacogenomic pathways have been investigated for drugs commonly used in autoimmune diseases. For mycophenolate mofetil, variants in genes involved in drug metabolism and transport, including UGT1A9, UGT1A8, UGT2B7, SLCO1B1, SLCO1B3, and ABCC2, have been studied. For azathioprine, TPMT and NUDT15 are important pharmacogenes because reduced activity can increase the risk of thiopurine-related myelosuppression. Methotrexate response and toxicity have also been investigated in relation to genes such as SLC19A1, MTHFR, ATIC, and TYMS.^[27]

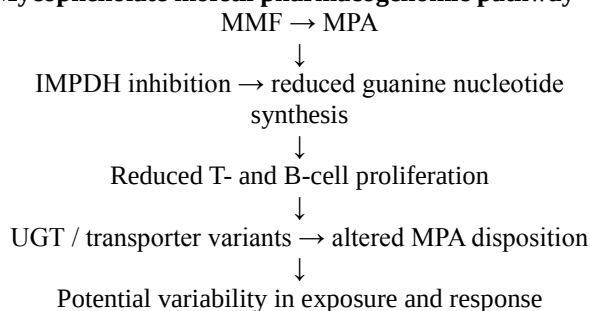
Pharmacogenomics may also have an important role in predicting treatment-related toxicity. The clearest example is thiopurine therapy, for which TPMT and NUDT15 genotyping can be used to identify patients at increased risk of severe toxicity and to guide initial dosing. This represents one of the established clinical applications of pharmacogenomics relevant to immunosuppressive therapy.^[28]

4. PHARMACOGENOMICS OF THERAPIES USED IN AUTOIMMUNE-ASSOCIATED ILD

4.1 Mycophenolate mofetil (MMF)

MMF is prodrug converted to mycophenolic acid (MPA), a potent inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH) that blocks de novo guanine nucleotide synthesis essential for activated T and B lymphocytes, mediating immunosuppression. MPA undergoes extensive glucuronidation via UGT1A9, UGT1A8 and UGT2B7, while transporters SLCO1B1, SLCO1B3, ABCC2 and ABCB1 influence disposition. Although variants in these genes correlate with pharmacokinetic changes, evidence is inconsistent for clinical efficacy to support routine genotype-guided dosing in AI-ILD.^[29]

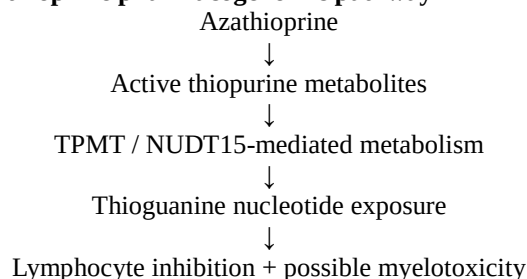
Mycophenolate mofetil pharmacogenomic pathway



4.2 Azathioprine

Azathioprine is intracellularly metabolized to active thiopurine metabolites that disrupt purine synthesis and lymphocyte proliferation.^[30] Its pharmacogenomics is mainly determined by TPMT and NUDT15, which regulate metabolite activity and toxicity. Loss-of-function variants in TPMT/NUDT15 markedly raise myelotoxicity risk; CPIC recommends genotype-based dose adjustment. In AI-ILD, these markers predict toxicity but not pulmonary efficacy.^[31]

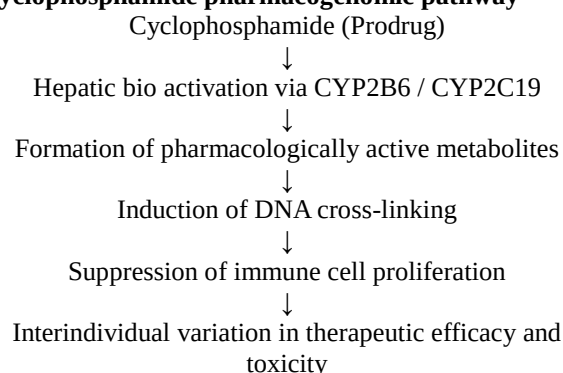
Azathioprine pharmacogenomic pathway



4.3 Cyclophosphamide

Cyclophosphamide is administered as an inactive prodrug that undergoes metabolic activation in the liver. Its active metabolites exert their therapeutic effect by inducing DNA cross-links, thereby inhibiting the proliferation of immune cells.^[32] The bio activation process is primarily mediated by the cytochrome P450 enzymes CYP2B6 and CYP2C19, which are considered potential targets for pharmacogenomic studies. Although genetic polymorphisms influencing cyclophosphamide metabolism have been linked to variations in pharmacokinetics, no validated genotype-based dosing guideline currently exists for autoimmune-associated interstitial lung disease (AI-ILD). Hence, the available data remains investigational at this stage.^[33]

Cyclophosphamide pharmacogenomic pathway

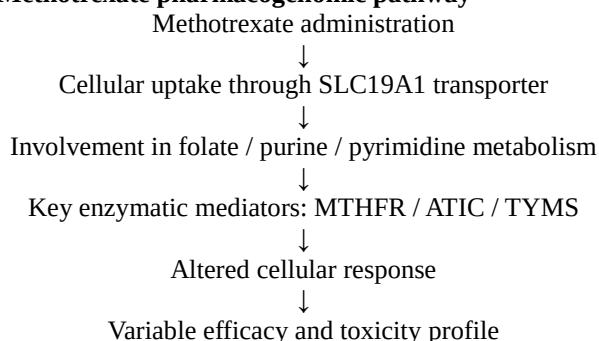


4.4 Methotrexate

Methotrexate is an immunomodulatory agent that acts as a folate antagonist.^[34] Several genes associated with folate transport and intracellular metabolism, such as SLC19A1, MTHFR, ATIC, and TYMS, have been investigated for their potential role in influencing therapeutic response and adverse effects. However, the associations between specific genetic variants and

methotrexate outcomes have shown inconsistency across different studies. Variability in study populations, underlying diseases, treatment protocols, and clinical endpoints has limited the reproducibility of findings. Consequently, no single genetic marker has been validated for routine genotype-guided use of methotrexate in AI-ILD.^[35]

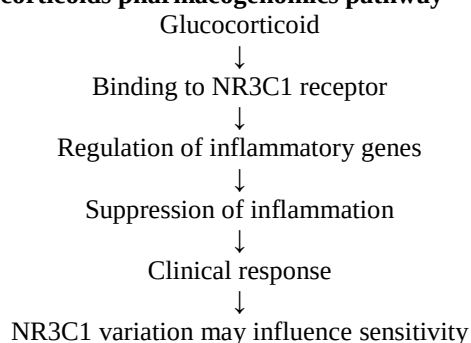
Methotrexate pharmacogenomic pathway



4.5 Glucocorticoids

Glucocorticoids exert their action via the glucocorticoid receptor, which is encoded by the NR3C1 gene. Activation of this receptor modulates the expression of inflammatory genes and results in suppression of inflammatory responses. Genetic variants in NR3C1 have been suggested to influence individual sensitivity to glucocorticoids. At present, there is insufficient evidence to support routine genotype-guided dosing of glucocorticoids based on NR3C1 status in AI-ILD. Therefore, pharmacogenomic exploration in this area remains investigational, and corticosteroid therapy continues to be guided by clinical parameters.^[36]

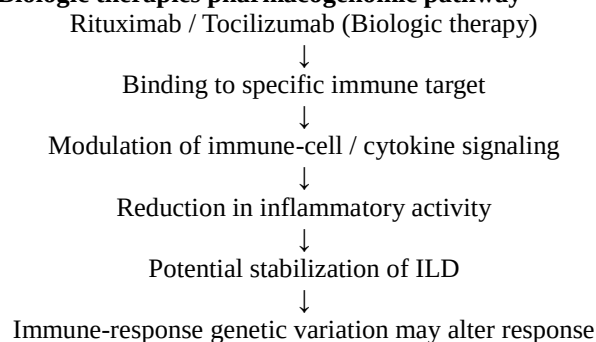
Glucocorticoids pharmacogenomics pathway



4.6 Biologic therapies

Biologic agents such as rituximab and tocilizumab are selectively utilized in autoimmune-associated ILD based on the underlying disease and clinical context.^[37] Pharmacogenomic research has explored immune-response-related genes and Fc-receptor polymorphisms as potential predictors of therapeutic response. Variation in the FCGR3A gene has been linked to differences in rituximab efficacy in autoimmune conditions; however, data specific to ILD remains scarce. At present, these genetic variants are not routinely employed to guide the selection of biologic therapy.^[38]

Biologic therapies pharmacogenomic pathway

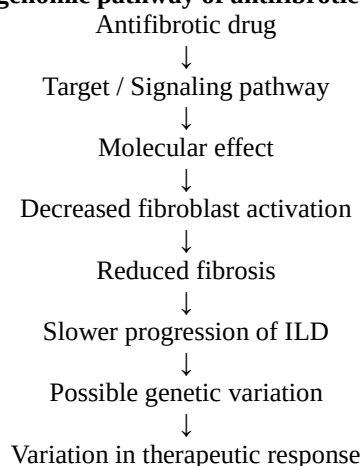


4.7 Antifibrotic Therapies

Nintedanib and pirfenidone are antifibrotic drugs administered to selected patients with progressive fibrotic ILD. Nintedanib acts by inhibiting multiple tyrosine kinase pathways associated with fibroblast activation, whereas pirfenidone exhibits both antifibrotic and anti-inflammatory properties. However, validated pharmacogenomic biomarkers for guiding drug selection or dosing in autoimmune-associated ILD are currently not available.^[39]

Exploratory research in ILD, especially idiopathic pulmonary fibrosis, has evaluated genetic variants that might affect treatment response. While these observations lay the groundwork for future pharmacogenomic studies, they cannot be directly extrapolated to autoimmune-associated ILD due to limited disease-specific evidence.^[40]

Pharmacogenomic pathway of antifibrotic therapy



5. PHARMACOGENOMICS TECHNOLOGIES

Pharmacogenomic technologies enable the identification and evaluation of genetic variants that may influence drug disposition, efficacy, and toxicity. Common approaches include polymerase chain reaction (PCR)-based genotyping, SNP analysis, microarrays, and next-generation sequencing. These methods can identify variants in drug-metabolizing enzymes, transporters, receptors, and immune-related genes. In autoimmune-associated ILD, such technologies are mainly being used in research to investigate differences in treatment

response and adverse effects rather than for routine clinical decision-making.^[41]

5.1 Clinical Implementation of Pharmacogenomics

Clinical implementation of pharmacogenomics involves translating genetic information into treatment decisions, such as drug selection, dose adjustment, or identification of patients at increased risk of toxicity. Established examples in pharmacotherapy include TPMT and NUDT15 testing before thiopurine treatment. However, for most drugs used in autoimmune-associated ILD, pharmacogenomic evidence is still insufficient to support routine genotype-guided prescribing.^[42]

For autoimmune-associated ILD, implementation requires integration of genetic findings with disease subtype, severity, organ involvement, concomitant medications, and patient-specific clinical characteristics. Pharmacogenomic testing should therefore complement rather than replace conventional clinical assessment. Standardization of testing, interpretation of genetic results, accessibility, cost, and availability of validated clinical guidelines remain important considerations for wider clinical adoption.^[43]

CONCLUSION

Pharmacogenomics provides a promising framework for moving autoimmune-associated ILD treatment from a predominantly empirical approach toward more individualized therapy. Genetic variation in drug-metabolizing enzymes, transporters, drug targets, and immune-response pathways may contribute to differences in treatment efficacy and toxicity. At present, however, only a limited number of pharmacogenomic markers have sufficient evidence for routine clinical use, while most applications in autoimmune-associated ILD remain investigational.

Continued research combining pharmacogenomics with clinical, genomic, and molecular information may help establish more precise treatment strategies for autoimmune-associated ILD. Future validation of clinically relevant biomarkers will be essential before routine genotype-guided therapy can be incorporated into ILD management.

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