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REVIEW

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Translating Asthma Pharmacogenomics into Practice: Evidence Synthesis, Clinical Implementation, and Future Directions

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ABSTRACT

Asthma presents substantial global variability in treatment response, much of which remains unexplained by conventional clinical and biomarker-based assessment. Pharmacogenomics offers a promising avenue for understanding this heterogeneity; however, its translation into routine practice has been slow. This review synthesizes current evidence up to 2025 on key pharmacogenomic markers involved in responses to inhaled corticosteroids, beta-agonists, leukotriene modifiers, and biologics. A structured methodology incorporating risk-of-bias assessment, quantitative and narrative evidence synthesis, and GRADE evaluation was applied. Among available markers, GLCCI1 and CRHR1 show the most consistent associations with corticosteroid responsiveness, though effect sizes are modest and lack large randomized validation. ADRB2 and leukotriene pathway variants demonstrate limited and inconsistent clinical value, while pharmacogenomic predictors of biologic therapy remain preliminary. An integrated clinical implementation pathway is proposed, emphasizing the need to interpret genetic results alongside inflammatory endotypes, adherence patterns, environmental exposures, and real-world treatment behaviour. Equity and ancestry considerations highlight the limited external validity of current findings, especially in underrepresented populations such as those in South Asia. Digital health technologies, pragmatic trials, and multi-omics integration represent promising directions for future research. Overall, while pharmacogenomics enhances mechanistic understanding of asthma, its present clinical utility is limited; meaningful translation will require expanded population diversity, stronger real-world evidence, and multi-dimensional predictive models that integrate genetics with biomarkers and digital health data.

Keywords: Asthma pharmacogenomics, precision medicine, inhaled corticosteroid response, genetic variability, clinical implementation

INTRODUCTION

Asthma remains a major global respiratory disorder, with prevalence and morbidity remaining high despite improved diagnostics and therapies. Many patients continue to experience poor control due to environmental triggers, microbial factors, genetic susceptibility, adherence issues, and diverse inflammatory pathways. These variations highlight the need for approaches beyond uniform treatment strategies. Patients receiving similar therapies—corticosteroids, beta-agonists, leukotriene antagonists, or biologics—often show markedly different outcomes. Variability in bronchodilator response, leukotriene activity, and biologic effectiveness reflects underlying genetic influences on drug metabolism, receptor sensitivity, and inflammatory signaling. Although numerous variants such as ADRB2, GLCCI1, CRHR1, and CYP450 polymorphisms have been studied, inconsistent replication across populations and limited real-world validation create uncertainty regarding their clinical use. This review evaluates key pharmacogenomic markers, examining their analyti-

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cal and clinical validity, potential utility, and implications for practice. It also outlines an implementation framework integrating genomics with biomarkers, endotypes, adherence, and health-system factors to support more precise and equitable asthma management (1).

Beyond genetic variation, interpretation of treatment response in asthma increasingly relies on real-world data, digital health tools, and data-driven clinical decision support systems. Integration of pharmacogenomic information with adherence monitoring, environmental exposure data, and longitudinal clinical outcomes may improve the contextualization and translational relevance of genetic associations.

METHODS

This review followed a structured approach consistent with pharmacogenomic evidence-synthesis standards, incorporating key elements of PRISMA with modifications for genomic heterogeneity. A predefined protocol outlining objectives, eligibility criteria, and analytical methods was archived on an open-access platform to enhance transparency (2).

Search Strategy and Data Sources

A comprehensive search of PubMed, Embase, Scopus, Web of Science, and the Cochrane Library was conducted for studies published from January 2000 to January 2025. Grey literature and cross-referenced studies were also screened. Search terms combined MeSH and free-text keywords related to asthma, pharmacogenomics, drug response, and variants such as ADRB2, GLCCI1, and CRHR1 (3).

Eligibility Criteria

Using the PICO framework, eligible studies included asthma patients of any age receiving ICS, beta-agonists, leukotriene antagonists, or biologics. Outcomes required genotype-linked therapeutic response. Randomized trials, cohort, case-control, and genome-wide studies were included; animal and mechanistic studies were excluded (4).

Animal and mechanistic studies were excluded because the primary aim of this review was to evaluate clinical validity and real-world applicability of pharmacogenomic markers in asthma management. Although mechanistic studies provide biological plausibility, they do not directly inform therapeutic decision-making in patients.

Study Processes

Two reviewers independently screened studies and extracted data on genetic variants, outcomes, and validity measures. Risk of bias was assessed using RoB 2, QUIPS, and Human Genome Epidemiology criteria. Narrative synthesis and random-effects meta-analysis were performed where applicable, with evidence certainty graded using GRADE (5).

PATHOPHYSIOLOGY AND ENDOTYPES RELEVANT TO PHARMACOGENOMICS

Asthma is a heterogeneous disorder shaped by genetic predisposition, environmental exposures, immune pathways, and age. Symptom-based classifications cannot explain variability in treatment response; instead, endotype-based models rooted in molecular pathways provide a more accurate framework for interpreting pharmacogenomic effects. Because many variants act within specific inflammatory contexts, understanding underlying biology is essential for gene-drug interpretation (6).

Inflammatory Pathways and Genetic Determinants of Asthma Heterogeneity

Asthma is a complex and heterogeneous respiratory disorder driven by the interaction of genetic susceptibility, immune dysregulation, and environmental exposures. Conventional symptom-based classification inadequately captures the biological diversity underlying asthma, particularly with respect to variability in therapeutic response. Molecular and immunological mechanisms, therefore, provide a more robust framework for understanding disease heterogeneity and for contextualizing pharmacogenomic effects (6).

Airway inflammation is initiated by epithelial responses to allergens, pollutants, viral infections, and microbial stimuli. Activation of epithelial-derived cytokines, including thymic stromal lymphopoietin, interleukin-25, and interleukin-33, orchestrates downstream immune pathways that shape asthma phenotypes. Type 2 (T2) inflammation, characterized by eosinophilic infiltration, elevated immunoglobulin E levels, and increased expression of interleukin-4, interleukin-5, and interleukin-13, represents the predominant endotype and generally exhibits favorable responsiveness to inhaled corticosteroids. Nonetheless, substantial interindividual variability persists within T2-high asthma, indicating that inflammatory phenotype alone does not fully explain treatment outcomes (7).

In contrast, non-T2 asthma encompasses neutrophilic and paucigranulocytic patterns driven by alternative immune mechanisms, including interleukin-17 signaling, interferon-mediated pathways, and innate immune activation. These endotypes are frequently associated with reduced corticosteroid responsiveness and a higher burden of persistent symptoms, highlighting the potential relevance of non-steroid pathways and alternative pharmacogenomic targets (8).

Genetic variation contributes to asthma pathogenesis at multiple biological levels. Polymorphisms in genes such as *IL33*, *TSLP*, *ORMDL3*, and *ADAM33* influence epithelial barrier integrity, airway remodeling, and immune activation. Additionally, variants affecting glucocorticoid receptor signaling, beta-2 adrenergic receptor function, and leukotriene synthesis pathways modulate pharmacological response. These genetic effects interact with inflammatory context, underscoring the necessity of integrating biological mechanisms with pharmacogenomic interpretation (8).

Endotype-Specific Pharmacogenomic Effects and Gene-Environment Interactions

Endotype-based classification provides a biologically grounded approach for interpreting differential drug response in asthma and offers essential context for evaluating pharmacogenomic associations. Because many genetic variants exert their influence within specific inflammatory environments, pharmacogenomic markers cannot be considered independently of underlying endotype (9).

In T2-high asthma, variants involved in glucocorticoid signaling—particularly within *GLCCI1*, *CRHR1*, and *NR3C1*—demonstrate more consistent associations with inhaled corticosteroid responsiveness. These associations reflect modulation of steroid-mediated anti-inflammatory pathways rather than direct effects on disease severity. Conversely, in T2-low asthma, where corticosteroid efficacy is diminished, genetic variation within beta-adrenergic and leukotriene pathways may assume greater relative importance, although current evidence remains inconsistent and insufficient for clinical application (9).

Gene-environment interactions further modify pharmacogenomic effects and contribute to interindividual and population-level variability. Environmental exposures such as air pollution, tobacco smoke, allergens, and respiratory infections influence immune activation and epigenetic regulation, potentially altering the functional impact of genetic variants. Age-related biological factors also play a critical role; developmental changes in immune function and receptor expression may explain why certain pharmacogenomic associations—particularly those related to corticosteroid response—are more pronounced in pediatric populations than in adults (10).

These interactions help explain the inconsistent replication of pharmacogenomic findings across studies and populations. Consequently, genetic associations with drug response should be interpreted within a multidimensional framework that incorporates inflammatory endotype, environmental exposures, and age, rather than as universal predictors of therapeutic efficacy. Such an integrated approach provides a more accurate foundation for evaluating pharmacogenomic markers and supports their potential role in personalized asthma management (10).

PHARMACOGENOMIC MARKERS: EVIDENCE REVIEW AND META-ANALYTIC SUMMARY

Research from candidate gene studies, genome-wide analyses, and genotype-stratified trials has identified several variants influencing asthma drug response, though only a few show consistent clinical relevance (11).

Pharmacogenomic Evidence Across Major Asthma Therapeutic Pathways

Pharmacogenomic research in asthma has focused primarily on genetic variation influencing response to beta-2 agonists, inhaled corticosteroids, leukotriene modifiers, and biologic therapies. Evidence derives from candidate-gene studies, genome-wide association analyses, and genotype-stratified clinical trials, although the strength and consistency of associations vary substantially across drug classes (11).

Variants within the ADRB2 gene, particularly Arg-16Gly (rs1042713) and Gln27Glu (rs1042714), were among the earliest pharmacogenomic markers investigated in asthma. Initial studies suggested altered bronchodilator responsiveness and potential tachyphylaxis with regular short-acting beta-agonist use in specific genotypes. However, subsequent large-scale trials evaluating long-acting beta-agonists in combination with inhaled corticosteroids failed to demonstrate clinically meaningful genotype-dependent differences. Genome-wide analyses further indicate that the contribution of ADRB2 variants to treatment response is modest when compared with clinical factors

such as baseline lung function and medication adherence. Consequently, ADRB2 polymorphisms currently lack sufficient clinical relevance for guiding therapy (12).

In contrast, pharmacogenomic associations related to inhaled corticosteroid responsiveness demonstrate greater reproducibility. The GLCCI1 rs37972 variant has been consistently associated with reduced improvement in lung function following corticosteroid therapy, while CRHR1 rs242941 has been linked to enhanced corticosteroid response. Variants in NR3C1 and FKBP5, which regulate glucocorticoid receptor signaling, have shown biologically plausible but inconsistent associations across studies. Although GLCCI1 and CRHR1 represent the most robust markers identified to date, effect sizes remain modest and insufficient for standalone clinical prediction (13).

Genetic variation within leukotriene synthesis and signaling pathways, including polymorphisms in ALOX5, LTC4S, CYSLTR2, and cytochrome P450 enzymes, has been investigated in relation to leukotriene receptor antagonist response. While several studies suggest genotype-dependent differences in treatment efficacy, findings are heterogeneous and frequently limited by small sample sizes and inconsistent replication. As a result, leukotriene pathway pharmacogenomics currently offers mechanistic insight rather than actionable clinical guidance (14).

Pharmacogenomic predictors of biologic therapy response remain in an early exploratory phase. Preliminary studies evaluating response to anti-IgE and anti-interleukin-5 therapies have identified potential genetic modifiers; however, none demonstrate sufficient predictive accuracy or validation to inform treatment selection. At present, biologic therapy decisions remain primarily guided by phenotypic and biomarker-based criteria rather than genotype (15).

Modifying Factors: Age, Ancestry, and Population-Level Variability

The clinical relevance of asthma pharmacogenomic markers is further influenced by age-related biology and genetic ancestry, contributing to variability in observed associations across studies and populations. Several variants associated with inhaled corticosteroid response, including GLCCI1, demonstrate stronger and more consistent effects in pediatric cohorts than in adults, suggesting developmental modulation of drug-response pathways. Differences in immune maturation, receptor expression, and epigenetic regulation may underlie these age-dependent effects (16).

Population-level differences in allele frequency and linkage disequilibrium patterns also affect the reproducibility and external validity of pharmacogenomic findings. Variants within ADRB2, GLCCI1, and drug-metabolizing enzymes show substantial frequency variation across ancestry groups, influencing effect estimates and study outcomes. Underrepresentation of non-European populations in genomic research further limits generalizability and underscores the need for diverse cohorts to accurately assess clinical relevance (16).

Collectively, these modifying factors highlight the complexity of translating pharmacogenomic associations into practice. Genetic effects on drug response are context-dependent and shaped by developmental, biological, and population-specific influences. Consequently, pharmacogenomic markers should be interpreted within a broader clinical framework that integrates age, ancestry, inflammatory endotype, and real-world treatment behavior rather than as isolated predictors of therapeutic response.

Age-Dependent Pharmacogenomic Effects in Asthma

Age significantly modifies pharmacogenomic associations in asthma, particularly for inhaled corticosteroid responsiveness. Pediatric cohort studies consistently report stronger associations between *GLCCI1* variants and reduced corticosteroid response, with children carrying the rs37972 risk allele demonstrating smaller improvements in lung function compared with non-carriers. In adult populations, these associations are weaker or less reproducible, likely reflecting greater disease heterogeneity, cumulative environmental exposures, and age-related differences in immune regulation. Pediatric asthma is more frequently characterized by type 2-driven inflammation, a biological context in which corticosteroid-related genetic effects are more readily observed. These findings underscore the importance of age-stratified interpretation of pharmacogenomic markers and caution against direct extrapolation of pediatric genetic effects to adult asthma without population-specific validation.

EVIDENCE SUMMARY

Overall, GLCCI1 and CRHR1 show the most reproducible associations; other markers remain inconsistent. Pharmacogenomics offers promise but currently cannot

guide treatment independently of clinical and biomarker assessment (17).

Summary of Analytical Validity

Analytical validity for major asthma pharmacogenomic markers—including ADRB2, GLCCI1, CRHR1, and ALOX5—is generally high. Most studies used reliable genotyping methods such as PCR-based assays, SNP arrays, and next-generation sequencing, with consistent quality-control metrics and call rates above 95%. Although early studies showed methodological variation, recent work demonstrates strong standardization, supporting confidence in genotyping accuracy across studies (18).

Clinical Validity and Strength of Associations

Clinical validity varies by gene-drug pair. ADRB2 shows only modest and inconsistent associations with bronchodilator response, particularly when ICS are used concurrently. GLCCI1 rs37972 has more reproducible links to reduced ICS responsiveness, especially in early-onset asthma (19). CRHR1 rs242941 similarly shows consistent associations with improved steroid response (20). Leukotriene pathway variants, including ALOX5, offer mechanistic plausibility but inconsistent clinical evidence. Genetic predictors of biologic therapy response remain preliminary with limited validity (21).

Quantitative Synthesis and Effect Estimates

Meta-analyses show that GLCCI1 rs37972 risk allele carriers experience 15-25% smaller improvements in FEV1 after ICS therapy, with moderate heterogeneity. CRHR1 rs242941 demonstrates smaller but more consistent benefits. Insufficient uniform data prevented meta-analysis for ADRB2 and leukotriene genes, which showed mixed or null results (22).

GRADE Assessment of Evidence Certainty

Using the GRADE framework, GLCCI1 and CRHR1 show moderate certainty due to reproducible associations and biological plausibility. ADRB2 and leukotriene pathway genes show low certainty because of inconsistent findings and modest effect sizes. Predictors of biologic therapy response have very low certainty due to limited and unvalidated evidence. These results highlight the need for larger, standardized studies before pharmacogenomics can be widely adopted in asthma care (23) (Table I).

Overall Interpretation of Evidence

Taken together, the evidence shows that while pharmacogenomics provides important mechanistic insights into asthma heterogeneity, its clinical utility remains limited by inconsistent outcomes and insufficient validation in real-world settings. GLCCI1 and CRHR1 are the most promising markers for informing corticosteroid therapy, but current evidence does not yet support broad implementation of genotyping into routine asthma management. For other pathways, particularly beta-agonists and leukotriene modifiers, the variability in effect estimates indicates the need for larger, harmonized studies that incorporate endotype classification, environmental exposures, and adherence assessment.

This synthesis highlights a continuing translational gap: although many genetic associations are biologically plausible and supported by mechanistic data, few meet the threshold for clinical implementation. Bridging this gap will require integrated approaches that combine pharmacogenomics with biomarkers, phenotyping, and data from real-world practice (29).

CLINICAL UTILITY AND PRACTICE RECOMMENDATIONS

Although many gene-drug associations have been described in asthma, only a few shows consistent evidence that could influence treatment decisions. This section summarizes the practical relevance of key pharmacogenomic markers.

Table I: GRADE assessment of evidence certainty for major pharmacogenomics markers in asthma

Gene	Drug Class	Effect	Population	Clinical Utility
GLCCI1	ICS	↓ FEV1 improvement	Children & adults	Moderate (24,25)
CRHR1	ICS	↑ steroid response	Early-onset asthma	Moderate (26)
ADRB2	SABA/LABA	Inconsistent	Mixed populations	Low (27)
ALOX5	LTRA	Variable	Small cohorts	Low (28)

Framework for Evaluating Clinical Utility

Clinical utility depends on three elements: reliable genotyping (analytical validity), consistent genotype-response associations (clinical validity), and meaningful benefit when applied to treatment decisions (clinical relevance). Few asthma pharmacogenomic markers currently meet all three criteria (30).

Clinical Implications of GLCCI1 and CRHR1

GLCCI1 rs37972 carriers often show weaker improvement with inhaled corticosteroids, suggesting the need for closer monitoring or earlier step-up therapy. CRHR1 rs242941 is associated with enhanced steroid responsiveness. While neither marker supports routine genotyping, both may add value when combined with biomarkers like eosinophils or fractional exhaled nitric oxide, especially in early-onset or high-risk asthma (31).

Limited Utility of ADRB2 Variants

Despite extensive study, ADRB2 polymorphisms provide little actionable information. Variability in bronchodilator response is driven more by clinical and environmental factors than genotype, and combination ICS-LABA therapy reduces genotype-related differences. Thus, ADRB2 genotyping is not recommended for treatment selection (32).

Leukotriene Pathway Genetics

Variants in ALOX5, LTC4S and related genes offer mechanistic insight but inconsistent clinical evidence. Differences in montelukast metabolism via CYP450 enzymes have not translated into validated dosing adjustments. Therapy selection should therefore rely on clinical phenotype (e.g., atopy, aspirin sensitivity) rather than genotype (33).

Pharmacogenomics for Biologic Therapy

Current biologics—omalizumab, mepolizumab, benralizumab and dupilumab—are guided primarily by phenotypic markers such as IgE and eosinophils. Genetic predictors remain exploratory and insufficient for clinical use, though they may gain importance as multi-omics research evolves (34).

Integrating Genetics with Biomarkers and Endotypes

Single markers have limited predictive power; combining pharmacogenomics with biomarkers and endotype classification is more promising. For example, GLCCI1 may refine ICS response prediction when paired with eosinophil counts. Such integrated approaches may assist in therapy escalation for patients with variable or discordant responses.

Practice Recommendations for 2025

Routine pharmacogenomic testing is not recommended. Selective genotyping may be considered only in severe or suspected corticosteroid non-response cases. Genetic results must always be interpreted alongside biomarkers, clinical features and real-world factors, which currently exert greater influence on treatment outcomes (Table II).

Table II: Practice recommendations for pharmacogenomic use in asthma management (2025)

Recommendation Area	Practical Guidance for 2025
Routine testing	Routine pharmacogenomic testing is not recommended for general asthma management at this time (35).
GLCCI1 and CRHR1 genotyping	May be considered in research settings or in selected patients with severe, difficult-to-control asthma where early identification of corticosteroid non-response may influence treatment planning (35).
ADRB2 genotyping	Should not be used to guide beta-agonist selection or dosing due to insufficient clinical utility (36).
Leukotriene pathway genotyping	Remains investigational; current evidence does not support its use in therapeutic decision-making (36).
Interpretation of results	Pharmacogenomic findings should be interpreted with consideration of patient age, genetic ancestry, inflammatory endotype, and adherence patterns (37).
Integrated approaches	Combining genetic markers with biomarkers and clinical phenotyping may provide greater predictive value and should be prioritized in future research (38).
Real-world context	Pharmacogenomic data should be complemented with real-world factors such as adherence monitoring, environmental exposures, and exacerbation history, as these often exert stronger influence on outcomes than genotype alone (38).

Summary of Clinical Utility

Pharmacogenomics has improved understanding of asthma heterogeneity, but its clinical use remains limited due to variable evidence and modest predictive strength. GLCCI1 and CRHR1 show the greatest promise for guiding corticosteroid therapy, yet neither supports routine testing. The most effective future approach will integrate genetic insights with biomarkers, endotypes, and clinical assessment. Longitudinal and real-world studies are essential to determine whether pharmacogenomics can meaningfully improve therapeutic decision-making in the coming years.

CLINICAL IMPLEMENTATION PATHWAY

Translating pharmacogenomic findings into practice requires structured decision models that combine genetics with clinical, biomarker, and environmental information. Although single markers offer limited standalone value, they can contribute within a broader personalized care strategy.

Rationale for A Structured Pathway

Asthma response varies widely even among patients with similar clinical profiles. A structured pathway ensures that genetic data—when available—enhances standard care by identifying patients with poor corticosteroid response, refining decisions for uncontrolled asthma, reducing unnecessary medication exposure, and improving outcomes in severe disease (39).

Digital health technologies, including electronic health records, adherence-monitoring devices, and emerging artificial intelligence-based decision support tools, can facilitate the integration of pharmacogenomic data into routine asthma care. Such systems enable real-time interpretation of genetic findings alongside biomarkers, adherence patterns, and clinical response, supporting more informed and adaptive treatment decisions.

Initial Clinical Assessment

The first step remains comprehensive evaluation, including symptoms, spirometry, exacerbations, comorbidities, and environmental exposures. Before considering genetic testing, clinicians must optimize inhaler technique, adherence, and management of comorbid conditions, as these factors strongly influence treatment response (40).

Biomarker and Endotype Classification

Biomarkers such as blood eosinophils, fractional exhaled nitric oxide, serum IgE, and sputum profiles help distinguish T2-high from T2-low inflammation. These endotypes guide therapy and provide context for interpreting genetic effects, as many pharmacogenomic associations operate through inflammation-related pathways (41).

Integration of Pharmacogenomic Information

Pharmacogenomic results should be used only after clinical and biomarker evaluation. Three situations may benefit from genetic insights:

1. **Suspected corticosteroid non-response:** GLCCI1 rs37972 or non-responsive CRHR1 genotypes may support earlier step-up therapy or closer monitoring.
2. **Discordant biomarker profiles:** Genetics may help explain poor steroid response despite high inflammation.
3. **Severe or refractory asthma:** Pharmacogenomics may contribute to characterizing phenotype, though it cannot yet guide biologic selection.
4. In all cases, genetic findings should complement—not determine—treatment decisions (42).

Stepwise Decision Algorithm

The integrated pathway shown in Figure 1 outlines six sequential steps from diagnosis to ongoing reassessment. Each stage highlights the interaction between clinical evaluation, biomarker interpretation, therapeutic response, and pharmacogenomic information. This structured flow supports personalized, adaptable, and clinically grounded asthma management.

Clinical Interpretation of Pharmacogenomic Insights in Asthma

Pharmacogenomic information is most useful when combined with structured clinical assessment. For example, a child with strong type-2 inflammation but weak corticosteroid response may carry GLCCI1 variants, supporting earlier treatment escalation. Adults with persistent symptoms despite good adherence may benefit from genetic insights that help explain treatment resistance and justify progression to biologics. In contrast, ADRB2 genotyping offers little value for patients with variable bronchodilator response; improving adherence, inhaler technique,

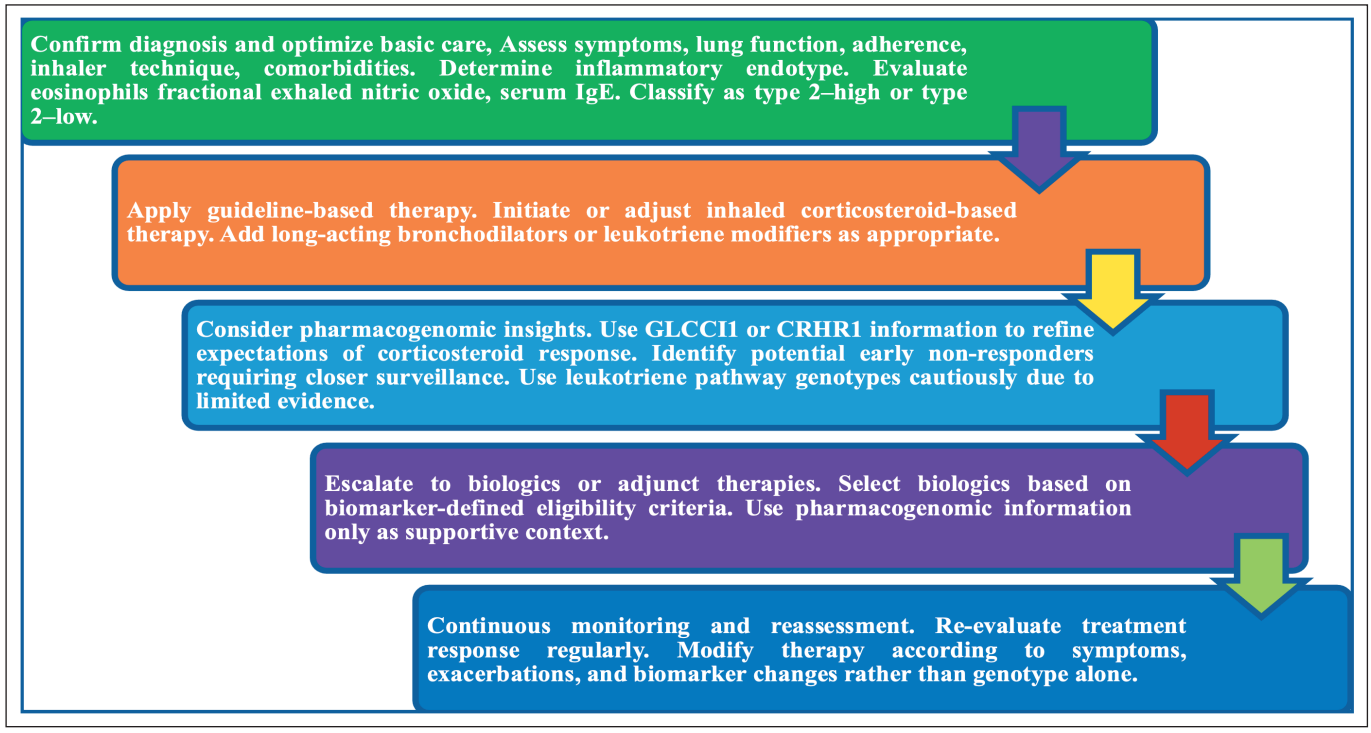

Figure 1: Integrated asthma management pathway illustrating the stepwise progression from diagnosis to personalized treatment decisions incorporating clinical assessment, biomarkers, and pharmacogenomic insights.

or stepping up to combination therapy remains more effective. These scenarios demonstrate that genetics should complement—not replace—clinical judgement (43).

Limitations in Current Implementation

Several barriers limit pharmacogenomic-guided asthma therapy, including testing cost, limited access, clinician unfamiliarity, and the absence of standardized interpretation frameworks. Many genetic associations also have small effect sizes and are influenced by environment, adherence, and comorbidities. Consequently, pharmacogenomic markers cannot yet substitute for objective inflammatory measures or established clinical assessments (44).

Future Directions for Implementation

As multi-omics studies expand and real-world research integrates pharmacogenomics with biomarker patterns, adherence data, and machine-learning methods, asthma care is expected to become increasingly personalized. In the future, electronic health record-based decision-support tools may automatically incorporate genomic data for risk stratification and therapy planning. Until such systems mature, pharmacogenomic testing should remain selective, applied mainly to complex or refractory cases. Figure 2 summarizes this framework, illustrating how genetic information adds value when layered onto clinical evaluation and biomarker-defined endotypes, with GLCCI1 and CRHR1 providing the most meaningful refinement of corticosteroid expectations (45).

EQUITY, ANCESTRY, AND EXTERNAL VALIDITY

Equitable implementation of pharmacogenomics requires accounting for ancestry, diversity, and the external validity of genetic associations. Most asthma pharmacogenomic findings come from European or North American cohorts, limiting their applicability to genetically diverse populations. Because allele frequencies, linkage disequilibrium patterns, and gene-environment interactions differ widely, the predictive value of variants cannot be assumed to generalize globally.

Genetic Ancestry, Environmental, and Social Factors

Key variants such as ADRB2 Arg16Gly, GLCCI1 rs37972, and CRHR1 rs242941 show substantial frequency

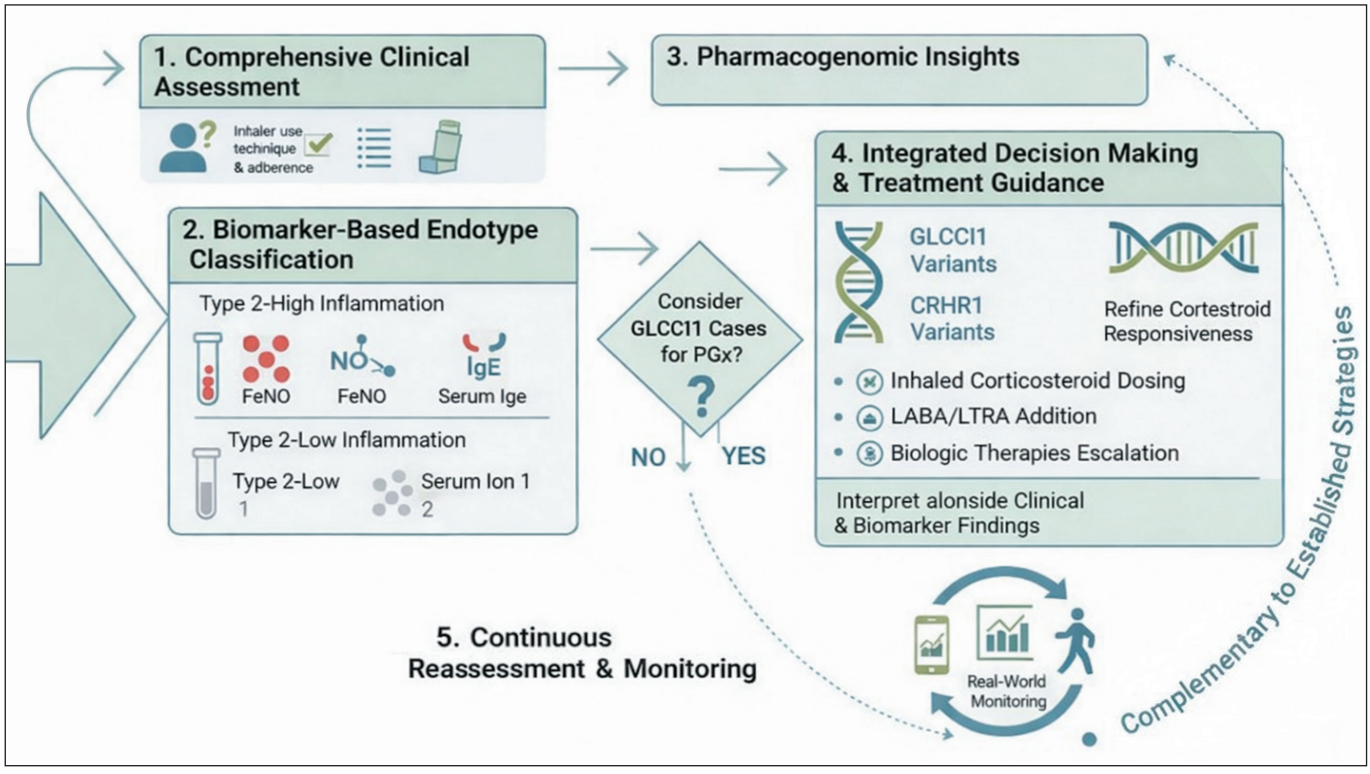

Figure 2: Stepwise Clinical Implementation Pathway for Personalized Asthma Management.

differences across ancestry groups, influencing effect size and replication. Environmental exposures—air pollution, tobacco smoke, allergens—and social determinants such as healthcare access, inhaler technique, and medication affordability modify therapeutic response and may outweigh genetic influences (46).

Race-Based Limitations

Findings from the SAPPHIRE study demonstrate that self-identified race does not predict corticosteroid response once clinical variables are considered. This underscores the need to interpret pharmacogenomic data based on genetic ancestry and individual-level variation rather than race categories (47).

Underrepresentation and Regional Research Needs

South Asian, African, and Latin American populations remain underrepresented in genomic research, limiting external validity and the applicability of markers such as GLCCI1 and ADRB2. Developing regional genomic databases and locally relevant pharmacogenomic studies—especially in India—will improve accuracy and support context-specific treatment models (48).

Ethical and Translational Implications

Ethical considerations include privacy, data ownership, and equitable distribution of benefits. In resource-limited settings, testing should not overshadow access to basic asthma care. Expanding research inclusivity and integrating environmental and social determinants are essential to ensure pharmacogenomics improves outcomes without reinforcing disparities.

REAL-WORLD DATA, ADHERENCE, and DIGITAL HEALTH

Real-world evidence and digital health tools are essential for understanding therapeutic variability in asthma, as pharmacogenomic effects operate within a broader context shaped by adherence, environment, and daily symptom patterns. These data sources help translate genetic findings into meaningful clinical practice.

Real-World Evidence

Randomized trials cannot fully capture routine-care variability. Real-world datasets provide insight into factors such as adherence, comorbidities, and environmental

exposures—often stronger determinants of outcomes than single genetic markers. Poor adherence to inhaled corticosteroids contributes more to treatment failure than known pharmacogenomic variants (49). Such data also help identify true non-responders and validate genetic associations in diverse populations.

Objective Adherence Monitoring

Electronically monitored inhalers show actual adherence is frequently lower than reported. Smart inhalers distinguish biological non-response from behavioral non-adherence, refining interpretation of pharmacogenomic effects and improving study accuracy.

Digital Health and Remote Monitoring

Apps, wearables, and environmental alerts offer continuous symptom data and can improve adherence and reduce exacerbations. When combined with genetic information, digital biomarkers may enhance prediction of treatment response.

Electronic Health Records

EHRs enable integration of genotype results with clinical workflows. Decision-support tools could recommend alternative therapies when genetic markers suggest reduced responsiveness, paralleling applications already used in oncology and anticoagulation (50).

Pragmatic Trials

Pragmatic and stepped-wedge designs can evaluate pharmacogenomic-guided therapy within real clinical settings. Trials comparing standard care with GLCCI1- or CRHR1-informed care may clarify real-world benefit.

Cost-Effectiveness

Testing may be most cost-effective in patients with persistent symptoms despite high adherence

FUTURE DIRECTIONS

Asthma pharmacogenomics is rapidly advancing as genomics, multi-omics, computational biology, and precision-medicine approaches evolve. Although routine clinical use remains limited, several emerging developments may transform personalized asthma therapy.

Multi-Omics Integration

Genomics alone cannot explain asthma complexity. Epigenomic, transcriptomic, proteomic, and metabolomic data reveal mechanisms underlying T2-high and T2-low inflammation and may refine prediction of corticosteroid responsiveness (51). Combining these layers is expected to outperform single-variant analyses.

Polygenic Response Scores

Polygenic response scores, integrating many variants with small effects, may improve prediction of ICS or bronchodilator response. Early studies suggest multi-gene models outperform single markers, though validation requires large, diverse cohorts.

Machine Learning and AI

Machine-learning models can analyze complex genomic, biomarker, and environmental datasets to predict exacerbations, classify endotypes, and optimize biologic selection. Integrating pharmacogenomics into these systems may reveal new treatment-response signatures.

Gene Editing and Therapeutic Innovation

CRISPR-based tools allow functional testing of pharmacogenomic variants and could eventually support gene-targeted therapies, though clinical application remains distant (52). New biologics and small molecules targeting upstream inflammatory mediators will also require pharmacogenomic evaluation.

Expanding Diverse Datasets

Greater inclusion of South Asian, African, Latin American, and Indigenous populations is essential for accurate, equitable prediction tools. Global genomic initiatives are beginning to address this gap.

Health-System Integration

Future implementation depends on standardized reporting, clinician education, and EHR-based decision support. Combining genomic data with adherence monitoring and biomarkers may enhance precision management.

Ethical Considerations

Privacy, consent, equitable access, and avoidance of race-based misinterpretation remain critical concerns as pharmacogenomics expands (53).

Outlook

Over the next decade, integrated multi-dimensional models may enable meaningful clinical use of pharmacogenomics, supporting more personalized and effective asthma care.

CONCLUSION

Asthma pharmacogenomics has provided important insights into variable drug response, though only a few markers—particularly GLCCI1 and CRHR1—show consistent clinical relevance, and none yet justify routine testing. Meaningful implementation will require integrating genomics with biomarkers, endotypes, adherence, environment, and digital health data, as these factors often influence outcomes more than genotype alone. Greater inclusion of diverse populations is essential to ensure equitable applicability. As multi-omics, machine learning, and real-world research advance, pharmacogenomics is poised to become a key component of future precision asthma care, supporting more personalized and effective treatment strategies.

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