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PHARMACOGENETICS OF INHALED CORTICOSTEROID RESPONSE IN CHILDREN AND ADOLESCENTS WITH ASTHMA

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ABSTRACT

Variability in response to inhaled corticosteroids in childhood asthma reflects a combination of genetic characteristics, inflammatory endotype, and actual drug exposure, in which the risk of exacerbation during prescribed treatment does not always characterize biological drug sensitivity. The aim of the review is to critically compare clinical publications on pharmacogenetic and regulatory response markers in children and adolescents, assessing the reproducibility of associations and the evidence supporting personalized treatment; an analysis was conducted with a targeted audit of 25 sources, and the synthesis of quantitative findings was restricted to publications with accessible full texts. Genotype-phenotype observations, genome-wide associations, pharmacoepigenetic markers, prediction models, and treatment-selection trials were considered separately. Russian and Belarusian observations are limited by heterogeneous exposure and the composition of comparator groups, while several international genomic signals received only nominal support; in independent validation of a model combining clinical characteristics with three microRNAs, the area under the receiver operating characteristic curve was 0.72 versus 0.65 for the clinical model. The association of *PDGFD* with adrenal suppression was replicated in a pediatric validation cohort, although clinical selection and concomitant systemic steroids limit the generalizability of the estimate. Trials of genotype-guided treatment escalation did not identify a significant improvement in the primary symptom-control outcome, while retaining a favorable signal for the secondary exacerbation outcome. Three analytical matrices distinguish outcomes, exposure, replication, and clinical utility; published associations support further independent evaluation of markers but do not, by themselves, justify genotype-based treatment changes.

KEYWORDS: Asthma; Children; Adolescents; Inhaled corticosteroids; Pharmacogenetics; Personalized therapy

INTRODUCTION

Variation in the effectiveness of inhaled corticosteroids (ICS) requires a distinction between biological drug sensitivity and the clinical course of asthma during prescribed treatment, since an exacerbation in a patient who has been prescribed an inhaler does not establish steroid resistance: interpretation depends on actual drug use, inhalation technique, concomitant treatment, and outcome definitions. A pharmacogenetic marker becomes clinically relevant when it helps select among treatment strategies and improves outcomes beyond the capabilities of routine clinical assessment.

The PiCA consortium described by N. Farzan et al. included 14,227 patients aged up to 25 years, but only 7,619 received ICS. Among 5,769 participants with the relevant information, 1,929, or 33%, used systemic steroids as rescue treatment for exacerbations. The authors emphasized the multidimensional nature of response: agreement between symptoms and exacerbations remained low; we regard discordant outcomes as an important source of differences between genetic associations, and the total consortium size as a feature of the research platform rather than a single cohort evaluating ICS response. (Farzan et al., 2017)

This review aims to critically compare clinical studies of genetic and regulatory determinants of pediatric ICS response, assessing independent replication, incremental predictive value, and the evidence supporting clinical use.

MATERIAL AND METHODS

A narrative review was conducted with critical comparison of clinical publications. A targeted audit covered 25 sources: the full texts of 21 articles and a draft Russian guideline document were read, whereas access to three articles was restricted to abstracts. Quantitative results from publications without accessible full texts were excluded from the main analysis; the draft guideline was not used as a source of epidemiological estimates, and the verified articles appeared in journal issues published in 2016-2025; the availability audit was completed on October 19, 2026. No systematic review protocol, PRISMA flow diagram, or quantitative pooling of effects was used.

The journal issue year was distinguished from the online publication date, and publication periods from participant recruitment periods. Total cohorts, analytical subsets, and independent validation stages were considered separately; repeated use of CAMP, PiCA, PACT, and PUFFIN did not increase the number of independent confirmations, and when a source contained inconsistencies, disputed values were not reconstructed by assumption; specific discrepancies are recorded in Supplementary Material S1.

Age, sample composition, design, drug exposure, response definitions, effect sizes, multiple testing, and independent replication were compared. OR denotes odds ratio; CI, confidence interval; and FEV_1, forced expiratory volume in one second. AUC denotes the area under the receiver operating characteristic curve; SNP, single-nucleotide polymorphism; GWAS, genome-wide association study; and FDR, false discovery rate, while genetic quality control is abbreviated as QC. CAMP, PiCA, PACT, PUFFIN, GACRS, BAMSE, BARD, INFANT, and PASS are retained as cohort and trial identifiers.

RESULTS

Clinical studies differed in age, treatment regimens, and response definitions; sample characteristics and published estimates are summarized in Table 1.

Table 1. Characteristics and findings of clinical studies

Publication	Sample	Outcome or marker	Estimate	Limitation
(Fitzpatrick et al., 2016)	300 randomized; 230 evaluable	Comparative response to three regimens	170/230 with differential response	Phenotyping, not genotyping
(Fedorova et al., 2019)	236 patients + 194 healthy controls	*GLCCI1*; subgroup versus healthy controls	OR 1.74 [1.07-2.83]	Not a comparison of response between regimens
(Minina et al., 2020)	60 children; 27 receiving ICS	*GLCCI1*; functional phenotype	*AG* versus *GG*; p=0.009 for the proportion with FEV_1 ≥80%	Heterogeneous treatment
(Gafurova and Faizullina, 2022)	82 adolescents; *TC* 24, *CC* 58	*FCER2*; treatment step	Steps 3-4 in 19/24 *TC* carriers	No *TT* genotype
(Xu et al., 2017)	418 adults	*GLCCI1*; FEV_1 after 24 weeks	*AA* +0.18 L; *GG* +0.09 L	Combined with salmeterol
(Leusink et al., 2016)	110 children	Nonresponse by FEV_1 / hyperresponsiveness	15 / 10; overlap 3	Published online in 2015
(Hernandez-Pacheco et al., 2019)	1347 → 1697	*rs5995653*; exacerbations	OR 0.66 → 0.76	Nominal replication
(Hernandez-Pacheco et al., 2021a)	2681 → 538	*rs67026078*; exacerbations	Replication: OR 1.83 [1.16-2.90]	Non-European validation unsuccessful
(Hernandez-Pacheco et al., 2021b)	166 → 175	Inadequate FEV_1 improvement	OR 7.01 [3.29-14.93]	Original SNP not replicated
(Dijk et al., 2020)	2412 in total	*IL1RL1*; any exacerbation	OR 1.31; p=0.02	Outcome during treatment
(Voorhies et al., 2024)	111 → 217	*GSDMB*/*ORMDL3*; aggregate test	p=0.003 → 0.02	Effect in White subgroups

Publication	Sample	Outcome or marker	Estimate	Limitation
(Ortega et al., 2021)	249 children; 267 adolescents/adults	Local ancestry at a chr12 region	OR 3.95 [2.02-7.72]	Not an allelic SNP estimate
(Wang et al., 2019a)	152 children	Methylation and expression	ρ=0.25; p=0.02	Not a correlation with FEV_1 improvement
(Wang et al., 2019b)	154 + 72 + 168	*IL12B* / *CORT*	Q=0.028 / 0.035	*CORT*: only two cohorts
(Li et al., 2020)	462 overall; 188 receiving ICS	miRNA; extreme quartiles	AUC 0.86 in 86 participants	No independent replication
(Sharma et al., 2023)	580 → 187	Three models; independent test	AUC 0.65 / 0.64 / 0.72	Composite CASTER outcome
(Piparia et al., 2025)	168 participants	Eosinophil subgroups	AUC 0.54 / 0.61 / 0.72	Estimates within the original cohort
(Hawcutt et al., 2018)	407 after QC → 81	*PDGFD*; cortisol <350 nmol/L	OR 7.32 → 3.86	Selection for suspected suppression
(Slob et al., 2025b)	193 participants	Secondary exacerbation outcome	-0.080 [-0.155 to -0.004]; p=0.038	Primary outcome not significant
(Slob et al., 2025a)	Same PACT/PUFFIN trials	Six-month costs	€771.07 versus €827.31	Dutch prices

Note. Arrows indicate progression to a validation sample. Overlapping cohorts are not summed; ORs and AUCs refer to different outcomes. The reported p and FDR-Q values are reproduced without recalculation.

Clinical phenotype and response assessment

In INFANT, A.M. Fitzpatrick et al. randomized 300 children aged 12-59 months; comparative response could be evaluated in 230, of whom 170, or 74%, benefited more from one treatment strategy than from the others. Aeroallergen sensitization increased the probability of the best response to daily ICS; the combination with blood eosinophils ≥300 cells/μL strengthened prediction in an exploratory analysis. The authors linked personalization to readily available inflammatory characteristics; the trial is not pharmacogenetic but provides a clinical benchmark: genetic models should demonstrate benefit beyond phenotyping, while the participants' age limits extrapolation to adolescents. (Fitzpatrick et al., 2016)

Russian and Belarusian clinical observations

Yu.Yu. Fedorova et al. examined 236 children with asthma and 194 healthy children. In the Tatar subgroup, the G allele of *GLCCI1 rs37973* was associated with uncontrolled asthma relative to healthy controls: OR 1.74, 95% CI 1.07-2.83. The authors highlighted interethnic differences. This estimate does not directly compare controlled with uncontrolled asthma; at least three months of ICS treatment does not eliminate differences in susceptibility and baseline severity. No significant associations between the investigated loci and disease risk were found in the combined analysis. (Fedorova et al., 2019)

E.S. Minina et al. enrolled 60 children aged 3-17 years, but only 27 received ICS, while nine received a leukotriene modifier alone. Spirometry was performed on the second day of hospitalization. Children with the *AG* genotype of *GLCCI1 rs37973* had more favorable lung function than those with *GG*; the difference in the proportion with FEV_1 ≥80% reached p=0.009. The authors proposed a prognostic role for the genotype. We classify the report as a genotype-phenotype observation: heterogeneous treatment and the absence of a standardized comparison of changes in lung function preclude interpreting it as an ICS efficacy trial involving all participants. (Minina et al., 2020)

R.R. Gafurova and R.M. Faizullina examined 82 adolescents: the *TC* genotype of *FCER2* T2206C was present in 24 and *CC* in 58; *TT* was absent. Treatment corresponded to steps 3-4 in 19 of the 24 *TC* carriers. The authors associated the genotype with a need for more intensive treatment. Because every participant carried the C allele, its independent effect relative to noncarriage could not be estimated; the prescribed treatment step reflects clinical need and physician decision-making but cannot replace direct measurement of pharmacological response. (Gafurova and Faizullina, 2022)

Genomic associations and independent replication

The adult study by Y. Xu et al. analyzed 418 patients after 24 weeks of fluticasone/salmeterol treatment; mean age was 44.4 years. FEV_1 increased by 0.18±0.28 L in participants with the *AA* genotype of *rs37973* and by

0.09±0.28 L in those with *GG*. The authors linked these differences to *GLCCI1* by comparing clinical findings with cellular expression; mechanistic support informs the pediatric hypothesis, but combination treatment and the adult sample limit conclusions about an ICS-specific effect in children. (Xu et al., 2017)

M. Leusink et al. analyzed 110 children aged 6-16 years receiving stepwise treatment. Inadequate response was identified in 15 by lung function and in ten by airway hyperresponsiveness; only three met both criteria. No novel chip-wide significant associations were found, although the 17q12-21 region showed individual signals. The authors emphasized the dependence of findings on the phenotype selected. The journal issue was dated 2016 and online publication 2015; the inconsistent exact p value for *KRT25* in the abstract and tables is not reproduced here. (Leusink et al., 2016)

In 2019, N. Hernandez-Pacheco et al. combined 1,347 patients of admixed ancestry; European validation cohorts included 1,697 participants. The A allele of *rs5995653* between *APOBEC3B* and *APOBEC3C* was associated with lower odds of exacerbation: OR 0.66 at discovery and 0.76 at validation, p=0.00752. The authors discussed a possible role in antiviral defense, but replication was nominal and did not withstand the relevant multiple-testing correction; functional interpretation relied on external resources rather than a separate clinical experiment. (Hernandez-Pacheco et al., 2019)

In the 2021 European analysis by N. Hernandez-Pacheco et al., discovery included 2,681 patients and independent validation 538; assessment in non-European groups included 1,773. The C allele of *CACNA2D3-WNT5A rs67026078* received nominal support in European validation: OR 1.83, 95% CI 1.16-2.90, p=0.010. Strict genome-wide significance was not achieved, and non-European replication was unsuccessful. The cohorts included young adults up to 25 years of age. The authors linked the locus to inflammation and remodeling; heterogeneous exacerbation definitions and incomplete ascertainment of ICS use limit drug-specific interpretation. (Hernandez-Pacheco et al., 2021a)

In the *ROBO2* analysis of 166 SLOVENIA participants, cases were defined by an FEV_1 increase of less than 8% after six weeks of treatment. The G allele of *rs1166980* increased the odds of inadequate response: OR 7.01, 95% CI 3.29-14.93. The original SNP was not replicated in 175 CAMP participants. Support for a different regional variant associated with exacerbations in Europeans is not equivalent to reproducing the original association. The authors proposed *ROBO2* as a promising locus; we regard the signal as exploratory because direct replication was absent and the effect estimate was imprecise. (Hernandez-Pacheco et al., 2021b)

F.N. Dijk et al. evaluated *IL1RL1* across several cohorts comprising 2,412 participants. The C allele of *rs13431828* was associated with any exacerbation, OR 1.31, p=0.02. The authors discussed both a more severe inflammatory phenotype and direct interaction with steroid response. Reproducibility varied between independent groups, and significant longitudinal effects were absent in SLOVENIA. *IL1RL1* should be considered a candidate marker of residual risk during treatment rather than an established criterion for dose selection. (Dijk et al., 2020)

K. Voorhies et al. used two pediatric biobanks: PrecisionLink included 91 White and 20 Black children, while BIG included 83 and 134, respectively. An aggregate test of *GSDMB*/*ORMDL3* variants was associated with emergency visits or hospitalization in White children: p=0.003 and p=0.02 in independent validation. The authors emphasized the potential of biobanks. An aggregate regional test does not provide a ready-to-use individual threshold; small subgroups and potential failure to capture visits to other institutions limit generalizability. (Voorhies et al., 2024)

In BARD, V.E. Ortega et al. analyzed 249 children and 267 adolescents/adults of African descent. In children, local African ancestry at a chromosome 12 region was associated with a greater benefit from increasing ICS than from adding salmeterol: OR 3.95, 95% CI 2.02-7.72. The allelic estimate for *rs73399224* was a separate finding, with nominal independent support. The authors attributed the findings to age- and population-related differences. Comparing alternative treatments brings the design closer to a clinical treatment decision, while independent confirmation of the pediatric effects remains necessary. (Ortega et al., 2021)

The relationship between molecular markers, measured outcomes, and the limits of clinical interpretation is presented in Table 2.

Table 2. Matrix for interpreting molecular associations

Area	Marker	Outcome	Limit of interpretation
Russian observations	*GLCCI1* / *FCER2* (Fedorova et al., 2019)	Lung function; treatment step	Susceptibility, severity, and response are conflated; limited comparator groups
GLCCI1 regulation	*rs37973* (Xu et al., 2017)	Adult combination treatment	Age and concomitant salmeterol limit pediatric applicability
Cross-population validation	*APOBEC3B-APOBEC3C* (Hernandez-Pacheco et al., 2019)	Exacerbations / functional response	Nominal replication, without strict genome-wide significance
European GWAS	*CACNA2D3-WNT5A* (Hernandez-Pacheco et al., 2021a)	Exacerbations during prescribed treatment	No non-European replication; incomplete ascertainment of actual use
Direct functional response	*ROBO2* (Hernandez-Pacheco et al., 2021b)	Inadequate FEV_1 improvement	Original SNP not replicated; another variant and outcome provide regional support
Inflammatory signaling	*IL1RL1* (Dijk et al., 2020)	Residual exacerbation risk	Risk during treatment does not establish a specific interaction with ICS
Aggregate variants	*GSDMB*/*ORMDL3* (Voorhies et al., 2024)	Emergency visits / hospitalizations	Regional test without an established individual threshold
Alternative strategies	*RNFT2*/*NOS1*, ancestry (Ortega et al., 2021)	Advantage of one regimen over another	Local ancestry differs from a specific allelic effect
Epigenetic discovery	*BOLA2* (Wang et al., 2019a)	FEV_1 after eight weeks	Nominal tests; no independent replication
Epigenetic validation	*IL12B* / *CORT* (Wang et al., 2019b)	Emergency visits / systemic steroids	Different numbers of cohorts by outcome; temporal sequence unresolved
MicroRNAs	miR-155-5p / miR-532-5p (Li et al., 2020)	Long-term FEV_1 change	Extreme groups; AUC within the original cohort
Integrated prediction	Clinical characteristics + three microRNAs (Sharma et al., 2023)	CASTER	Independent testing available; no trial of model-guided prescribing
Endotype modification	T / *GLCCI1* + eosinophils (Piparia et al., 2025)	Tertiles of FEV_1 change	Exploratory AUCs; no external validation
Safety	*PDGFD* (Hawcutt et al., 2018)	Adrenal suppression	Selection for suspected suppression; possible systemic steroid exposure
Test application	*ADRB2* (Slob et al., 2025b)	Treatment escalation on top of ICS	Favorable secondary outcome; primary outcome not significant

Note. Residual risk during prescribed treatment is distinguished from a specific marker-drug interaction; no formal GRADE rating was assigned.

Epigenetic markers and prediction models

A.L. Wang et al. analyzed 152 CAMP children; response was assessed after eight weeks of budesonide. Hypermethylation at cg27254601 was associated with improved lung function and *BOLA2* expression. The correlation ρ=0.25, p=0.02 described methylation and expression, rather than the magnitude of FEV_1 improvement itself. The authors proposed a pharmacoepigenetic mechanism; independent replication was absent, and the initial search used nominal thresholds, so the marker remains hypothesis-generating. (Wang et al., 2019a)

Another report by A.L. Wang et al. included 154 children from CAMP, 72 from BAMSE, and 168 from GACRS. Hypomethylation at cg00066816 near *IL12B* was associated with the absence of emergency visits or hospitalizations across all three cohorts, FDR-Q=0.028. Hypermethylation at cg04256470 near *CORT* was associated with the absence of systemic steroid use only in CAMP and GACRS, Q=0.035; the corresponding outcome was not measured in BAMSE. The authors emphasized regulation of sensitivity, but the temporal relationship between methylation and treatment remained unresolved; interaction relative to placebo was assessed only in CAMP. (Wang et al., 2019b)

J. Li et al. in 2020 analyzed 462 CAMP participants, including 188 receiving budesonide. The miR-155-5p and miR-532-5p model achieved an AUC of 0.86 when comparing 43 participants in the highest response quartile with 43 in the lowest; the AUC was 0.78 when the highest quartile was compared with the remainder, and the authors considered microRNAs promising markers while acknowledging the absence of independent replication. Selecting extreme groups may have facilitated classification; the directions of clinical and cellular effects did not align straightforwardly, precluding a simple causal interpretation. (Li et al., 2020)

In the 2023 report by R. Sharma et al., models were trained in 580 GACRS participants and tested without refitting in 187 CAMP participants. Three microRNAs were confirmed with consistent directions of association. External AUC was 0.65 (95% CI 0.57-0.73) for the clinical-demographic model, 0.64 (0.56-0.72) for microRNAs, and 0.72 (0.65-0.79) for the combined model. The authors reported a difference between the combined and clinical models, p=0.0022. The composite CASTER outcome represents an inferred response rather than prospectively measured benefit from changing treatment. (Sharma et al., 2023)

Independent validation of the clinical and molecular models is compared in Figure 1.

Figure 1. External validation of models predicting ICS response. Published AUCs and intervals; training in GACRS and independent testing in CAMP. An AUC of 0.72 does not mean that 72% of treatment decisions were correct. File: рисунок_1.tiff. (Sharma et al., 2023)

S. Piparia et al. analyzed 168 CAMP participants, stratifying eosinophils at 300 cells/μL. The T and *GLCCI1* variant model had an AUC of 0.54 in the low-eosinophil group, 0.61 overall, and 0.72 in the high-eosinophil group. Classification compared the upper and lower tertiles of FEV_1 change. The authors linked enhanced prediction to endotyping; independent validation was absent, a difference in significance between subgroups does not, by itself, establish a statistical interaction, and the published AUCs should be interpreted as exploratory estimates within the original cohort. (Piparia et al., 2025)

Exploratory AUC estimates by eosinophil subgroup are presented in Figure 2.

Figure 2. Inflammatory endotype and prediction using T / *GLCCI1*. The upper and lower response tertiles within CAMP were compared; intervals and independent validation are unavailable. File: рисунок_2.tiff. (Piparia et al., 2025)

Safety and clinical utility

D.B. Hawcutt et al. recruited 499 children into PASS, of whom 407 passed genetic quality control; the pediatric validation cohort comprised 81 participants. *PDGFD rs591118* was associated with adrenal suppression: OR 7.32 (95% CI 3.15-16.99) and 3.86 (1.19-12.50), respectively; the authors emphasized independent validation, but recruitment was prompted by clinical suspicion of suppression, and some children received systemic steroids. The finding concerns the safety of corticosteroid exposure that included ICS, rather than complication prevalence during isolated inhaled treatment. (Hawcutt et al., 2018)

Replication of the *PDGFD* association is shown in Figure 3.

Figure 3. Association of *PDGFD rs591118* with adrenal suppression. ORs and 95% CIs are shown for two PASS stages; the pediatric outcome was peak cortisol <350 nmol/L after a stimulation test. Discovery controls were supplemented with WTCCC2 population participants; no new pooled estimate was calculated. File: рисунок_3.tiff. (Hawcutt et al., 2018)

E.M.A. Slob et al. combined PUFFIN and the uncontrolled-asthma subgroup of PACT, totaling 193 participants. The primary outcome, symptom control, did not differ significantly. For the secondary exacerbation outcome, Table 4 reports an adjusted difference of -0.080 (95% CI -0.155 to -0.004), p=0.038. The authors acknowledged that favorable secondary outcomes alone were insufficient to change recommendations. *ADRB2* concerns β_2-agonists, and the evaluated strategy selected treatment escalation on top of ICS. The result does not establish direct corticosteroid sensitivity. (Slob et al., 2025b)

The economic analysis by E.M.A. Slob et al. used the same trials; estimated six-month costs were €771.07 with genotype-guided management and €827.31 in the control group, a difference of €56.24; the authors considered

the strategy potentially cost-saving, and cost ranges were generated by varying reference prices to 80-120% of baseline and are not statistical confidence intervals; the model uses Dutch prices, school absence, and estimates of parental productivity loss, so transferring the monetary effect to Russian practice requires a separate calculation. (Slob et al., 2025a)

DISCUSSION

Comparison across publications shows that the strength of marker validation depends not only on the p value but also on whether the design addresses the clinical question. Genotype-phenotype association, changes in lung function after treatment, interaction with alternative therapy, and benefit from applying a test represent different levels of evidence. Changing the outcome or SNP during replication may extend a biological hypothesis but does not reproduce the original effect.

The strongest route toward better prediction combines clinical and molecular characteristics with independent validation, although a high AUC within extreme response groups may overestimate discrimination in practice. External validation should assess calibration, classification errors, and incremental benefit over a comprehensive clinical model, since numerical differences without better decisions do not establish clinical utility.

Our proposed interpretation matrix distinguishes outcome, exposure, reproducibility, and applicability. The conceptual framework is not a validated score and does not specify treatment by genotype; its purpose is to make the transition from a laboratory association to a clinical decision testable, with separate assessments of efficacy and safety.

Requirements for progression from association to clinical benefit are presented in Table 3.

Table 3. Proposed matrix for progression toward clinical utility

Observation	Required assessment	Next stage	Limitation
Genotype associated with severity	Independence from age, ancestry, severity, and treatment	Assess drug response	Does not establish dose selection
Marker associated with change after ICS	Standardized exposure and before/after measurement	Independent replication of the original effect	Does not establish comparative benefit of alternatives
Treatment interaction identified	Formal marker × strategy interaction test	Prospective assessment of the algorithm	Subgroup significance is insufficient
Prediction model developed	External AUC, calibration, and comparison with a clinical baseline	Assess decisions and outcomes	AUC does not establish test utility
Test-guided prescribing improves an outcome	Randomized comparison with a prespecified outcome	External reproducibility and implementation	Secondary outcomes require caution
Cost savings estimated	Actual resources, prices, and uncertainty	Local budget and accessibility assessment	Foreign prices cannot be transferred directly

Note. The rows describe a sequence of evidence assessment; the matrix is neither a clinical recommendation nor a validated score.

The conceptual framework for marker evaluation is presented in Figure 4.

Figure 4. Proposed conceptual framework for assessing marker applicability. Clinical context and actual exposure are considered together with genetic and regulatory characteristics, while efficacy and safety are evaluated separately. The framework sets no treatment thresholds and requires independent clinical validation. File: рисунок_4.tiff.

LIMITATIONS

A targeted audit of the original publication set does not provide the completeness of a systematic search. Full texts of three articles were unavailable, limiting their use, and publications differ in age, drug exposure, and outcomes; internal discrepancies occur between abstracts, text, and tables. Overlapping cohorts prevent summing participants or treating every article as independent confirmation; no formal GRADE assessment or overall meta-analytic effect was calculated.

CONCLUSION

Genetic and regulatory markers explain individual components of variability in ICS response, but their readiness for clinical use differs; priorities are independent reproduction of the original effect, assessment of treatment interactions, and prospective demonstration of benefit from testing; personalization must account for clinical phenotype, actual exposure, and safety, while a published association alone does not justify changing treatment.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL CAPTIONS

Supplementary Material S1. Audit log for 25 sources, documenting full-text availability, identified discrepancies, and corrections adopted. Bibliographic records for publications excluded from the main analysis are included in S1.