Available online www.ijpras.com

International Journal of Pharmaceutical Research & Allied Sciences, 2026, 15(1):99-109
https://doi.org/10.51847/08gMSCS3fZ

Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Polygenic Pharmacotherapy beyond Single-Gene Rules: An Evidence Map of Scores, Interactions, Ancestry Transferability, and Clinical Utility

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ABSTRACT

Pharmacogenomics has traditionally translated inherited variation into treatment guidance through individual genes or compact variant panels. This framework remains clinically important but incompletely represents drug response when many variants, treatment exposures, disease states, concomitant medicines, environmental influences, and population-specific genomic structures act together. This evidence-mapping review examines how polygenic information is being developed and evaluated for precision pharmacotherapy, with emphasis on score construction, pharmacokinetic and pharmacodynamic applications, interaction effects, ancestry transferability, incremental prediction, and clinical utility. Peer-reviewed literature was identified through structured searches of biomedical and multidisciplinary databases, verified against prespecified eligibility criteria, and charted across model class, therapeutic application, endpoint, population, validation level, evidence maturity, and translation domain. The mapped landscape shows comparatively developed methodological work on score construction, reporting, and general risk prediction, alongside emerging treatment-specific applications involving cardiovascular therapies, psychotropic-drug exposure, medication-use phenotypes, and genome-wide pharmacogenomic methods. Evidence is more fragmented for dynamic phenoconversion, drug–drug–gene interactions, multi-ancestry pharmacotherapy models, dose individualization, prospective decision support, and patient-outcome evaluation. Predictive performance, pharmacological mechanism, treatment interaction, and clinical utility are frequently treated as adjacent but are not interchangeable forms of evidence. The principal gaps concern drug-response phenotype quality, representative discovery populations, external calibration, individual-level agreement, integration with clinical predictors, and prospective evaluation of score-guided decisions. Polygenic pharmacotherapy may extend precision treatment beyond isolated gene rules, but translation requires sequential evidence connecting genomic models to exposure, response, treatment choice, and patient-relevant benefit without obscuring uncertainty or equity concerns.

Key words: *Pharmacogenomics, Precision pharmacotherapy, Genotype, Phenoconversion, Clinical implementation, Dose individualization*

Received: 15 January 2026; **Revised:** 10 March 2026; **Accepted:** 11 March 2026

INTRODUCTION

Pharmacogenomics examines how inherited genomic variation contributes to variability in drug exposure, response, toxicity, and treatment selection. Its translational scope includes biological discovery, assay interpretation, prescribing guidance, clinical informatics, and evaluation of patient consequences rather than the application of isolated genetic associations alone [1]. Single-gene rules remain appropriate where a well-characterized variant has a substantial and reproducible effect, but many clinically important drug phenotypes are influenced by multiple genetic and non-genetic determinants.

Clinical implementation therefore depends on more than identification of an associated locus. Relevant evidence must be converted into interpretable results, embedded within prescribing workflows, communicated to clinicians and patients, and evaluated against existing care processes. Experience from implementation programs shows that laboratory systems, clinical decision support, professional education, evidence governance, and outcome assessment are interdependent components of pharmacogenomic translation [2]. These requirements become more complex when a score aggregates numerous variants whose weights, provenance, and validity may differ across populations and therapeutic settings.

Pre-emptive pharmacogenomic programs further demonstrate that genotype-guided treatment requires coordinated processes linking testing, interpretation, electronic records, prescribing decisions, and continuing evidence review [3]. However, most established implementation architectures were designed around actionable genes or panels. Polygenic pharmacotherapy introduces additional questions concerning score construction, phenotype specificity, calibration, interaction effects, ancestry transferability, and the extent to which a probabilistic model can improve a concrete treatment decision.

Polygenic scores combine information across multiple variants to estimate a relative propensity for a phenotype. Their movement from research tools to clinical instruments requires clear definitions, reproducible computation, appropriate validation, and evaluation in the population and decision context in which they would be used [4]. This evidence-mapping review charts the literature linking polygenic information to pharmacotherapy, distinguishes evidence presence from validity or readiness, and identifies where methodological development has or has not progressed toward treatment-specific utility.

Evidence-map questions and scope

The central mapping question is how polygenic evidence is distributed across the pharmacotherapy pathway, from score construction to patient-relevant treatment use. The review therefore examines which therapeutic applications, model types, populations, endpoints, validation designs, and implementation contexts are represented. It also considers whether studies evaluate discrimination alone, assess calibration and transportability, compare scores with clinical predictors, connect scores to pharmacokinetic or pharmacodynamic mechanisms, or test treatment-related consequences. A score is treated as a context-dependent predictive instrument rather than an immutable biological property [4].

The scope distinguishes pharmacogenomics from several overlapping concepts. Pharmacogenomics encompasses genomic influences on treatment, whereas genotype-guided therapy refers to the use of genetic information within a treatment decision. Precision pharmacotherapy is broader because it may combine genomic, clinical, environmental, behavioural, and longitudinal information. Dose individualization concerns selection or adjustment of treatment intensity, while clinical decision support concerns how evidence is delivered at the point of care. These concepts may overlap, but evidence supporting one cannot automatically establish another [1].

Polygenic pharmacotherapy was operationally defined as research in which information from multiple inherited variants contributes to an analysis of medication exposure, pharmacokinetics, pharmacodynamics, efficacy, toxicity, dose, prescribing, treatment benefit, or a decision pathway with direct therapeutic relevance. General disease-risk scores were considered only when they informed treatment allocation, comparison with clinical predictors, ancestry transferability, or standards for evaluating utility. Single-gene and multigene-panel studies were retained only when they clarified mechanisms, implementation benchmarks, or limitations that polygenic models must address.

The evidence map was organized around six questions: where evidence is concentrated; which development and validation stages dominate; where evidence is sparse or fragmented; which domains show movement toward treatment evaluation; which methodological weaknesses constrain interpretation; and which research priorities follow directly from those gaps. The map does not estimate pooled treatment effects or infer effectiveness from publication presence. Inclusion within a map cell indicates that a type of evidence exists, not that it is sufficiently replicated, transferable, clinically useful, or ready for routine deployment.

Search strategy, eligibility, and charting framework

Structured searches were designed around combinations of pharmacogenomic, polygenic-score, drug-response, pharmacokinetic, pharmacodynamic, phenoconversion, interaction, ancestry, validation, clinical-utility, dose-individualization, implementation, and decision-support terms. Information sources included PubMed/MEDLINE and multidisciplinary bibliographic databases, supplemented by publisher-record verification and backward and forward citation tracing. Search logic combined broad pharmacogenomic terminology with application-specific terms so that general score-method studies, treatment-specific analyses, interaction studies, transferability research, and implementation evidence could be identified without treating them as a single evidence class.

Eligible records were peer-reviewed articles in journals verified as Q1 in a relevant category for the applicable publication period, contained a verifiable DOI, and contributed extractable evidence to at least one prespecified review domain. Records were excluded when they were non-peer-reviewed, lacked direct therapeutic relevance, could not be assigned to the classification framework, or would require interpretation beyond the population, endpoint, or validation design examined. Duplicate removal used DOI, title, authorship, and publication-form comparisons. Eligibility was verified sequentially at title–abstract and full-text levels, followed by a claim-fit check requiring each retained article to support a defined synthesis statement, table element, figure component, or methodological judgment.

Charting fields included study or article type, model class, therapeutic context, drug-related phenotype, data source, population and ancestry description, construction method, validation stage, comparator, pharmacokinetic or pharmacodynamic endpoint, interaction context, translation domain, key contribution, limitation, and decision boundary. Evidence maturity was represented descriptively through demonstrated study design features rather than numerical scores. **Figure 1** presents the original conceptual synthesis for evidence map of polygenic pharmacotherapy applications, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

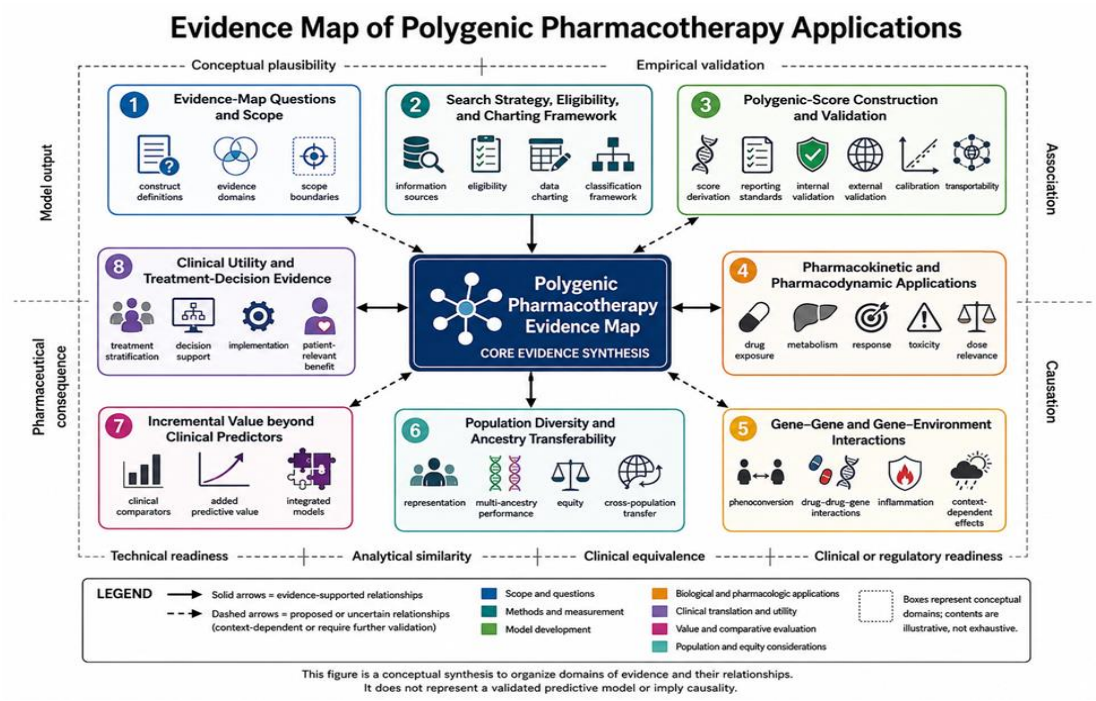

Figure 1. Evidence Map of Polygenic Pharmacotherapy Applications.

The figure is an original conceptual synthesis developed for "Polygenic Pharmacotherapy beyond Single-Gene Rules: An Evidence Map of Scores, Interactions, Ancestry Transferability, and Clinical Utility." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

Polygenic-score construction and validation

Polygenic-score construction begins with a precisely defined phenotype and an appropriate source of genetic effect estimates. Analytical choices include the discovery dataset, variant-quality controls, linkage-disequilibrium treatment, allele harmonization, variant inclusion, effect-size weighting, ancestry composition, and separation of development from evaluation data. These decisions influence both apparent performance and interpretation, particularly when the discovery phenotype differs from the pharmacological outcome of interest. Standard analytical guidance therefore treats score construction as a reproducible modeling workflow rather than a simple summation of risk alleles [5].

Transparent reporting is necessary because two scores bearing the same phenotype label may differ materially in source data, ancestry composition, included variants, computational parameters, and intended use. Reproducibility requires reporting the score identifier or complete specification, genome build, effect alleles, weights, construction method, target population, performance measures, and limitations. Reporting standards improve traceability and comparison but cannot themselves establish analytical validity, clinical validity, or utility [6]. A well-documented score may still be poorly calibrated, weakly transferable, or irrelevant to the treatment decision under consideration.

Pharmacogenomic score construction adds an important phenotype problem. Genetic determinants of disease susceptibility may overlap with determinants of drug response, yet the two are not equivalent. Pharmacogenomic methods may combine information from disease risk, treatment response, or related biological traits, but the resulting model must be evaluated against the drug-specific endpoint it is intended to predict. PRS-PGx methods illustrate how genome-wide information can be adapted for drug-response prediction, while also showing that performance depends on phenotype definition, discovery-sample properties, and the availability of appropriate validation data [7]. Improvement in a statistical metric does not establish a pharmacokinetic mechanism, treatment interaction, or clinical benefit.

Ancestry-diverse construction strategies may improve prediction by integrating population-specific and shared genetic information, but methodological improvement does not remove the need for external evaluation. Linkage-disequilibrium patterns, allele frequencies, environmental structures, healthcare access, and phenotype measurement can differ across development and target populations. Multi-ancestry methods therefore require assessment of discrimination, calibration, individual-level uncertainty, and clinically relevant performance within each intended context [8]. Polygenic-score validation should consequently be understood as a sequence of evidence requirements, not a single performance result or universal declaration of transportability.

Pharmacokinetic and pharmacodynamic applications

Polygenic pharmacotherapy becomes pharmacologically meaningful when genomic information is connected to an exposure, response, toxicity, or treatment-outcome phenotype. In clopidogrel-treated populations, a pharmacogenomic polygenic response score was associated with ischemic events and cardiovascular mortality, illustrating treatment-specific stratification rather than general disease prediction [9]. Such observational evidence identifies a potentially useful signal but does not establish that score-guided prescribing improves outcomes.

Pharmacokinetic evidence can clarify one pathway between inherited variation and treatment response. CYP2D6 genotype was associated with exposure and effectiveness differences for risperidone and aripiprazole, demonstrating how altered metabolism may influence treatment consequences [10]. This evidence is primarily gene-specific, however, and cannot by itself validate a genome-wide polygenic dosing model.

Longitudinal therapeutic-monitoring data provide stronger temporal linkage among dose, exposure, genomic variation, and clinical context. A clozapine analysis combining repeated concentration measurements with genome-wide data identified genetic contributions to pharmacokinetic variability in an ancestrally diverse clinical sample [11]. Nevertheless, drug-specific associations require replication, calibration, and comparison with non-genetic determinants before they can support dose individualization.

Biobank-scale analyses can broaden discovery by linking genomic data to prescribing records and medication-use phenotypes. Genetic analyses of simvastatin use demonstrate the scale and exploratory potential of this approach [12]. Medication use may also reflect indication, access, clinician preference, persistence, or adverse effects, so it should not be treated automatically as a pharmacodynamic response or treatment-benefit endpoint.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for evidence-map eligibility, classification, and data-charting framework for polygenic pharmacotherapy beyond single-gene rules.

Table 1. Evidence-map eligibility, classification, and data-charting framework for Polygenic Pharmacotherapy beyond Single-Gene Rules.

Evidence domain or review construct	Review question	Eligible evidence type	Key extraction fields	Appraisal or relevance criterion	Synthesis role	Main limitation	Interpretation boundary
Polygenic construction	How was genomic information combined?	Reproducible score-development study	Phenotype, variants, weights, ancestry, validation split	Transparent construction and non-overlapping evaluation [5]	Defines model provenance	Method-dependent results	Construction quality is not clinical utility
Reporting and traceability	Can the score be reconstructed and compared?	Reporting-standard or fully specified empirical study	Genome build, alleles, weights, parameters, population	Sufficient metadata for reproducibility [6]	Supports cross-study interpretation	Reporting does not ensure validity	Documentation is not performance evidence
Drug-response scoring	Does the score target a treatment-related phenotype?	Pharmacogenomic score-development or validation study	Drug, exposure, response, comparator, endpoint	Direct relationship to a drug-specific outcome [7]	Maps pharmacodynamic applications	Sparse treated samples	Statistical prediction is not treatment benefit
Pharmacokinetic evidence	Is genomic variation linked to exposure?	Concentration, clearance, metabolism, or dose study	Dose, concentration, sampling, covariates, genotype	Mechanistically interpretable exposure endpoint [11]	Connects genotype to drug disposition	Drug-specific transferability	Exposure association is not a dosing rule
Medication-use phenotype	What does the recorded outcome represent?	Biobank or electronic-record analysis	Indication, initiation, persistence, discontinuation	Explicit distinction between use and response [12]	Maps scalable discovery	Confounding by care processes	Medication use is not equivalent to efficacy
Interaction context	Can non-genetic factors change the predicted phenotype?	Phenoconversion or interaction study	Co-medication, disease state, inflammation, timing	Context temporally linked to exposure or response [13]	Extends static genotype models	Interaction misclassification	Interaction is not necessarily causal
Population transfer	Does performance persist in the target population?	External or multi-ancestry evaluation	Ancestry, calibration, discrimination, uncertainty	Population-specific validation [8]	Maps transportability	Under-representation	Multi-ancestry development is not universal validity
Clinical utility	Does using the information improve a decision or outcome?	Prospective treatment-strategy evaluation	Decision, comparator, action, patient consequence	Direct evaluation of score-guided care	Highest translation domain	Limited direct evidence	Prediction alone cannot establish utility

Gene–gene and gene–environment interactions

Genotype does not always correspond to the metabolic phenotype expressed during treatment. CYP2D6 inhibitors can reduce functional enzyme activity and produce phenoconversion, so a genetically predicted normal metabolizer may behave as a poorer metabolizer during concomitant therapy [13]. Static score interpretation may therefore misrepresent exposure when medication timing and inhibition are ignored.

Large electronic-health-record and biobank datasets permit systematic searches for drug–gene interactions across routinely used therapies. Such analyses can generate pharmacologically relevant hypotheses at scales unavailable

to conventional single-cohort studies [14]. Their interpretation remains vulnerable to confounding by indication, incomplete exposure measurement, multiple testing, and heterogeneous clinical documentation.

Disease state can also modify pharmacokinetics. Inflammation may regulate drug-metabolizing enzymes and transporters, changing clearance or exposure without any alteration in inherited genotype [15]. These mechanisms support the inclusion of time-varying clinical context, but heterogeneous biomarkers, disease severity, and treatment histories complicate prediction of the magnitude and direction of phenoconversion.

Drug–drug–gene interactions further show that genomic and treatment effects may combine rather than act independently [16]. A polygenic model may eventually represent several interacting pathways, yet greater complexity does not guarantee better transportability or clinical usefulness. Statistical interaction, biological interaction, and actionable treatment modification must therefore remain distinct evidence categories.

Population diversity and ancestry transferability

Polygenic scores frequently perform less consistently when transferred from their predominant discovery populations to populations with different genetic architectures. Uncritical cross-population use may therefore widen health disparities by producing less accurate estimates for groups already underrepresented in genomic research [17]. This concern applies directly to pharmacotherapy when a score influences treatment intensity, eligibility, or monitoring.

The distribution of polygenic-score research remains uneven across global populations, with substantial concentration in European-ancestry datasets [18]. Limited representation affects variant discovery, effect-size estimation, calibration, and uncertainty assessment. It also restricts evaluation of environmental, social, and healthcare factors that may alter treatment-related phenotypes.

Increasing diversity requires more than adding participants to existing study structures. Representative cohorts, equitable research partnerships, appropriate population descriptors, local scientific leadership, and relevant clinical outcomes are needed to improve genomic translation [19]. Diversity in development data remains necessary but is not sufficient evidence that a model performs equitably in practice.

Transferability depends on allele frequencies, linkage disequilibrium, effect-size portability, phenotype definition, environmental context, and target-population calibration [20]. These factors should be evaluated rather than inferred from broad ancestry labels. Transferability is constrained jointly by population representation, cross-population performance, and the methodological adequacy of target-population validation [17, 18, 20].

Incremental value beyond clinical predictors

A polygenic score should be evaluated against the information already available at the intended decision point. In coronary-artery-disease prediction, adding genomic information to a clinical model altered predictive performance, but the magnitude and relevance of improvement depended on the comparator and evaluation metric [21]. Genetic-only performance is therefore insufficient for judging incremental value.

Other comparative analyses have shown that established clinical risk factors may already capture substantial predictive information, leaving limited additional gain from a polygenic score in some populations [22]. These findings do not establish that polygenic information lacks value universally; they show that added value must be demonstrated for each clinical context.

Integrated tools combining clinical and polygenic predictors may outperform models based on either information source alone in defined populations [23]. Such integration is more consistent with precision pharmacotherapy than genetic replacement of clinical judgment. Nevertheless, improved discrimination must be accompanied by calibration, reclassification, decision analysis, and external validation.

Large-cohort genomic prediction can identify prevention-relevant risk strata, but risk stratification alone does not establish that treatment allocation based on the score improves benefit–harm balance [24]. The incremental contribution of polygenic information varies with the comparator, population, outcome, and integration strategy [21-23].

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for distribution of evidence across article-specific domains, systems, populations, and outcomes.

Table 2. Distribution of evidence across article-specific domains, systems, populations, and outcomes.

Method, platform, or evidence category	Representative application	Reported strength	Validation context	Generalization concern	Contradictory evidence	Evidence gap	Review interpretation

Pharmacogenomic response score	Clopidogrel-treated outcomes	Treatment-specific association [9]	Treated cardiovascular cohorts	Therapy and population specificity	Causal decision effect untested	Prospective score-guided comparison	Emerging pharmacodynamic evidence
Genotype–exposure analysis	Antipsychotic pharmacokinetics	Mechanistically interpretable exposure relationship [10]	Retrospective clinical cohort	Single-gene rather than polygenic	Non-genetic exposure determinants	Polygenic external validation	Strong mechanistic relevance, limited score utility
Longitudinal genomic PK	Clozapine concentration variability	Repeated-measure exposure evidence [11]	Clinical monitoring data	Drug-specific calibration	Environmental and adherence effects	Prospective dose evaluation	Developing PK application
Biobank pharmacogenomics	Simvastatin medication use	Scalable discovery [12]	Linked genomic and healthcare data	Use may not equal response	Care processes may explain associations	Direct efficacy and toxicity phenotypes	Discovery evidence only
Interaction-aware interpretation	Phenoconversion	Clinically plausible dynamic phenotype [13]	Drug-inhibition context	Timing and exposure uncertainty	Genotype may retain partial value	Dynamic prospective models	Necessary contextual modifier
Cross-ancestry modeling	Multi-population prediction	Potentially improved portability [8]	Diverse genomic cohorts	Residual calibration differences	No universal transfer	Treatment-specific validation	Methodological progression, not readiness
Clinical-plus-polygenic model	Cardiovascular prediction	Context-dependent incremental value [21]	External cohort comparison	Comparator and endpoint dependence	Limited gains reported elsewhere [22]	Treatment-decision evaluation	Added value must be demonstrated
Treatment-benefit stratification	Preventive or lipid-lowering therapy	Trial-derived interaction hypothesis [25]	Secondary genetic analyses	Post hoc and therapy-specific	Prognostic risk may mimic prediction	Prospective strategy trial	Closest link to utility, still conditional

Clinical utility and treatment-decision evidence

Clinical utility requires evidence that using genomic information produces a more appropriate treatment decision or a patient-relevant benefit compared with existing care. In primary-prevention analyses, higher polygenic risk was associated with greater observed relative benefit from statin therapy [25]. Because this was a secondary analysis, it supports treatment-effect hypotheses rather than a validated prescribing rule.

A genetic-risk analysis within the FOURIER trial suggested that polygenic information could identify patients with differing observed benefit from evolocumab [26]. Randomized treatment assignment strengthens evaluation of treatment interaction, but post hoc score analysis remains susceptible to multiplicity, model-selection, and transportability limitations.

A parallel analysis of ODYSSEY OUTCOMES reported differential observed benefit from alirocumab across polygenic-risk strata [27]. The recurrence of this pattern across related therapies is scientifically informative, yet it does not establish that prospective score-guided allocation would improve outcomes, affordability, or equity in routine care.

Prospective panel-guided prescribing has reduced clinically important adverse drug reactions in a multicentre implementation study, providing a benchmark for direct pharmacogenomic utility evidence [28]. That result concerns a defined gene panel rather than a polygenic score. Evidence for treatment-benefit stratification is concentrated in therapy-specific cardiovascular analyses and remains dependent on the design and context of the underlying trials [25-27].

Evidence-density and maturity mapping

The mapped literature contains clear methodological activity but uneven application-level development. A systematic analysis of polygenic scores in pharmacogenomics found heterogeneity in outcomes, methods, validation practices, and reporting [29]. Evidence presence is therefore insufficient for classifying a domain as mature.

Pharmacogenomic genome-wide studies face distinctive constraints because adequately phenotyped treated populations are often smaller than disease-risk cohorts. Exposure definition, adherence, treatment changes, outcome heterogeneity, and replication limitations further complicate discovery [30]. These constraints help explain why general score methodology has advanced faster than treatment-specific validation.

Reproducibility infrastructure has improved through standardized score deposition and searchable metadata. The Polygenic Score Catalog supports identification, reconstruction, and systematic comparison of published scores [31]. Catalog availability does not guarantee complete reporting, external validity, or suitability for a pharmacotherapy decision.

Recent methodological synthesis identifies opportunities for adapting polygenic approaches to pharmacogenomic GWAS while emphasizing phenotype scarcity, validation limitations, and translation challenges [32]. The resulting evidence landscape is best described through demonstrated stages rather than numerical maturity grades. **Table 3** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for validation maturity, translational readiness, and major evidence gaps in polygenic pharmacotherapy beyond single-gene rules.

Table 3. Validation maturity, translational readiness, and major evidence gaps in Polygenic Pharmacotherapy beyond Single-Gene Rules.

Cross-study pattern or configuration	Context or boundary condition	Mechanism or explanatory factor	Observed or reported outcome	Rival explanation	Certainty or rigour concern	Implication	Research priority
Method development exceeds utility testing	General and pharmacogenomic scores	Large discovery datasets favor model development	Extensive construction methodology [5]	Publication emphasis	Limited prospective evaluation	Performance cannot establish utility	Prospective decision trials
Treated cohorts are comparatively constrained	Drug-response GWAS	Exposure-dependent phenotyping	Fragmented replication [30]	Outcome and adherence heterogeneity	Low power and selection bias	Cross-study comparison is difficult	Harmonized treatment phenotypes
PK evidence is drug specific	Monitored therapies	Genomic effects on metabolism or transport	Exposure associations [11]	Dose, adherence, inflammation	External calibration limited	Mechanistic support may not generalize	Multi-centre longitudinal validation
Interaction evidence is context dependent	Polypharmacy and disease	Phenoconversion and pathway modification	Genotype–phenotype discordance [13]	Measurement error or unrecorded exposure	Timing often incomplete	Static rules may misclassify phenotype	Time-varying interaction models
Ancestry performance is unequal	Cross-population transfer	LD, frequency, effect-size and context differences	Reduced portability [17]	Dataset and phenotype differences	Underrepresented target cohorts	Equity is a validity issue	Representative external validation
Incremental prediction is inconsistent	Existing clinical models	Overlap between genomic and clinical information	Variable added value [22]	Comparator choice	Metric-dependent interpretation	Clinical baseline must be explicit	Decision-curve and calibration studies
Treatment-benefit evidence is concentrated	Cardiovascular trial analyses	Baseline risk may alter absolute benefit	Therapy-specific subgroup patterns [26]	Prognostic rather than predictive effect	Secondary analysis	Utility remains conditional	Predeclared treatment-interaction testing
Individual score agreement may be poor	Multiple scores for one condition	Different variants and weights	Discordant classifications [33]	Threshold selection	Population metrics conceal individual error	Score choice affects decisions	Agreement and uncertainty standards

Research gaps and validation priorities

Responsible clinical use requires clear specification of intended context, potential benefits, limitations, uncertainty, equity consequences, and communication needs [34]. Research priorities should therefore extend beyond maximizing discrimination to include calibration, individual-level reliability, treatment relevance, and consequences of acting on the result.

Professional guidance emphasizes analytical validity, clinical validity, clinical utility, appropriate reporting, and cautious interpretation of polygenic scores [35]. Empirical comparison of coronary-risk scores further shows that similar population-level performance can coexist with substantial disagreement for individual classifications [33]. Validation should therefore examine score agreement, uncertainty, threshold stability, and decision consequences rather than relying on a single summary metric.

Translation barriers span reporting, score selection, technical systems, professional education, workflow integration, population generalizability, and clinical guidance [36].

Review limitations

The evidence map depends on prespecified terminology and inclusion boundaries. Studies using unconventional descriptions of polygenic drug response may have been difficult to identify, while broad disease-risk studies were included only when they informed treatment allocation, transferability, comparative prediction, or utility.

The literature is heterogeneous in phenotype definition, score construction, ancestry reporting, comparator choice, and validation design. This heterogeneity limits direct comparison and makes publication presence an unreliable indicator of evidence strength or maturity [29].

The map is qualitative and does not provide pooled effects, numerical evidence-density estimates, or formal readiness grades. It therefore identifies represented and underrepresented evidence configurations without ranking therapies or determining whether a particular score should be used clinically.

Publication bias, overlapping cohorts, selective reporting, and concentration in well-resourced health systems may affect the mapped landscape. Translation evidence also changes as reporting, infrastructure, and clinical guidance develop, so the map should be treated as a structured synthesis rather than an exhaustive or permanent census [36].

CONCLUSION

Polygenic pharmacotherapy extends pharmacogenomic reasoning beyond isolated variant rules by considering distributed genomic effects alongside pharmacokinetics, pharmacodynamics, interactions, population context, and clinical predictors. The evidence landscape shows substantial methodological development but more limited progression to treatment-specific, externally transferable, interaction-aware, and prospectively evaluated decision strategies. Predictive performance, mechanistic plausibility, treatment interaction, implementation, and patient benefit remain distinct evidentiary stages. Future translation depends on representative validation, reliable drug-response phenotypes, transparent score provenance, comparison with existing clinical information, prospective evaluation of treatment decisions, and explicit assessment of uncertainty and equity. The mapped evidence supports continued development and testing, not universal clinical adoption or automated dose selection.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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