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*Review Article*

# The Polygenic Risk Score in Clinical Pharmacy: From Genomic Architecture to Precision Drug Therapy: A Narrative Review

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## ABSTRACT

Background: Precision medicine increasingly relies on polygenic risk scores (PRS) to predict drug efficacy, safety, and therapeutic variability. Traditional monogenic pharmacogenetics, focused on individual gene variants, explains only 20-40% of drug response variation, leaving substantial "missing heritability." Polygenic models aggregating thousands of genome-wide variants offer improved prediction, yet clinical implementation in pharmacy practice remains inconsistent and incomplete. Objective: This narrative review synthesizes evidence on PRS methodologies, clinical applications across therapeutic domains, the pharmacist's role in precision drug therapy, barriers to adoption, and emerging technologies, to provide a comprehensive synthesis for pharmacy educators, practitioners, and health system leaders. Methods: A targeted literature search of PubMed, Google Scholar, and bioRxiv (2010-2025) identified 90 peer-reviewed articles addressing PRS genomic principles, calculation and validation methodologies, clinical applications in cardiovascular (statins, clopidogrel), psychiatric (antidepressants, antipsychotics), and endocrine (metformin) pharmacotherapy, pharmacy implementation frameworks, and ethical and regulatory considerations. Articles were selected based on methodological rigor, applicability to clinical pharmacy practice, and contribution to understanding of PRS mechanisms, validation, or implementation. Results: Polygenic models capture cumulative genetic burden and demonstrate moderate to good predictive accuracy across therapeutic domains (AUC 0.60-0.75), exceeding monogenic approaches. Clinical applications are emerging but largely research-stage; few pragmatic trials assess PRS-guided pharmacotherapy effectiveness versus standard care. Pharmacists' competencies as genomic consultants are well-articulated conceptually but underdeveloped operationally. Major barriers include economic constraints (cost of testing, lack of reimbursement), educational gaps (insufficient pharmacist training), methodological concerns (ancestry bias, limited population-specific models), and incomplete regulatory frameworks and implementation infrastructure. Literature distribution shows emphasis on clinical applications (31%) and PRS methodology (24%), with limited evidence on pharmacy implementation (20%) or health economic impact. Conclusion: PRS represent a paradigm shift toward precision pharmacotherapy but require systematic workforce development, health system investment, policy reform, and implementation science evidence to realize clinical and equitable impact. Keywords: polygenic risk score; pharmacogenomics; precision medicine; clinical pharmacy; implementation barriers; ancestry bias; drug efficacy; personalized medicine.

## INTRODUCTION

Clinical pharmacy is undergoing a paradigm shift from monogenic pharmacogenetics to polygenic approaches for predicting drug response and optimizing therapeutic outcomes. Historically, pharmacogenetics focused on single-gene variants affecting drug metabolism particularly cytochrome P450 polymorphisms that directly influence clinical efficacy and toxicity (1). While this monogenic approach has yielded clinically actionable findings, it explains only a fraction of interindividual variability in drug response (2). A substantial portion of therapeutic outcome variation remains unexplained despite widespread adoption of single-gene pharmacogenetic testing, a phenomenon termed "missing heritability" (3). This gap reflects the biological reality that most drug responses are polygenic, resulting from the cumulative effects of hundreds or thousands of genetic variants distributed across the genome, each with small individual effect sizes (4).

Polygenic Risk Scores (PRS) represent an emerging solution to this complexity. PRS are composite mathematical measures that aggregate the weighted contributions of multiple genetic variants to predict individual predisposition to a specific phenotype, including drug efficacy, adverse drug reactions, and disease susceptibility (5). Unlike categorical monogenic predictions (e.g., "poor metabolizer" versus "extensive metabolizer"), PRS generate continuous risk estimates that capture cumulative genetic burden and provide more granular risk stratification (6). Recent advances in genome-wide association studies (GWAS) have generated vast datasets of genetic variants associated with complex traits, enabling the calculation and clinical application of increasingly sophisticated PRS models (7).

Despite growing scientific momentum, PRS implementation in clinical pharmacy practice remains inconsistent and fragmented. Several formidable barriers limit adoption: most published PRS models derive from predominantly European ancestry populations, restricting their validity and applicability to non-European populations including South Asians (8); the high cost of genomic sequencing and variant analysis exceeds current funding models in many healthcare systems (9); and pharmacists and clinicians lack standardized education and training in PRS interpretation, integration into electronic health records, and patient risk communication (10). Additionally, ethical and regulatory frameworks governing PRS data use, informed consent, and genetic discrimination remain underdeveloped (11). The emergence of artificial intelligence–enhanced and dynamic PRS models that integrate epigenetic and real-world lifestyle data presents further opportunities but also methodological complexity not yet reflected in clinical training or infrastructure (12).

To date, reviews of pharmacogenomics have focused primarily on monogenic applications or narrow therapeutic domains. A comprehensive, practice-focused synthesis examining the methodological foundations of PRS, their clinical applications across multiple therapeutic specialties, the pharmacist's central role as a genomic consultant, and the multifaceted barriers to clinical adoption has not been systematically synthesized. Such a synthesis is timely given the rapid evolution of PRS science, the urgent need for pharmacist upskilling, and the imperative to address ancestry bias and equitable implementation in diverse populations.

This narrative review synthesizes current evidence on polygenic risk scores in clinical pharmacy. Specifically, we examine (i) the genomic architecture of drug response and the distinction between monogenic and polygenic models; (ii) PRS methodologies, including calculation algorithms, validation approaches, and ancestry considerations; (iii) clinical applications of PRS in cardiovascular, psychiatric, and endocrine pharmacotherapy; (iv) the evolving role of pharmacists as genomic consultants, including data interpretation, electronic health record integration, and patient counseling; (v) major barriers to PRS adoption including economic, educational, ethical, and regulatory obstacles; and (vi) emerging AI-enhanced and dynamic PRS models and their potential to advance precision medicine. Through this synthesis, we aim to provide clinical pharmacists, pharmacy educators, and health system leaders with an evidence-informed roadmap for integrating PRS into contemporary precision pharmacy practice.

# MATERIAL AND METHODS

### *Review Design and Scope*

This narrative review synthesizes evidence on polygenic risk scores in clinical pharmacy practice. A narrative review approach was selected over a systematic review methodology to allow comprehensive integration of mechanistic genomic concepts, clinical trial and observational evidence, implementation science, and expert interpretation across multiple therapeutic domains and methodological perspectives. This approach is appropriate given the breadth of the review scope, the heterogeneous nature of the evidence base (spanning basic pharmacogenomics, GWAS methodology, clinical applications, and health systems implementation), and the need for interpretive synthesis that connects technical pharmacogenomic principles to pharmacy practice guidance (13). The review was not prospectively registered because narrative reviews are not typically registered with PROSPERO; however, the scope, eligibility criteria, and organizational framework were defined before literature retrieval began.

### *Information Sources and Search Strategy*

A targeted literature search was conducted in PubMed, Google Scholar, and bioRxiv using a combination of keywords and MeSH terms including "polygenic risk score," "PRS," "polygenic," "genome-wide association," "GWAS," "pharmacogenomics," "precision medicine pharmacy," "drug efficacy," "ancestry bias genetics," "pharmacogenetic load," "epigenetics drug response," and "machine learning pharmacogenomics." The search was deliberately broad and iterative, designed to capture publications spanning foundational genomic concepts, PRS methodology, clinical applications across therapeutic domains, implementation frameworks, and emerging technologies including artificial intelligence. Articles published from 2010-2025 were included, with preference given to recent systematic reviews, landmark GWAS studies, clinical guidelines from professional organizations, and high-impact implementation or health equity research. No language restrictions were applied, though the majority of relevant literature was in English.

### *Study Selection and Eligibility Criteria*

Given the narrative design, formal dual-screening was not performed. Instead, articles were selected based on explicit relevance criteria: (i) direct focus on polygenic risk scores, pharmacogenomic prediction, or genome-wide genetic variation in drug response; (ii) methodological rigor (peer-reviewed publications prioritized; preprints included only when methodologically sound and addressing underrepresented topics); (iii) applicability to clinical pharmacy practice, patient care, or health system implementation; and (iv) contribution to understanding of PRS mechanisms, validation, clinical application, barriers, or future directions. Articles addressing historical monogenic pharmacogenetics were included selectively only when essential for establishing the contrast with polygenic approaches. Reviews, consensus statements, and editorial commentaries were included alongside primary research when they synthesized evidence or provided expert guidance. This selection approach prioritizes relevance and quality over exhaustive enumeration, consistent with narrative review methodology.

### *Data Extraction and Organization Framework*

Literature was organized thematically rather than by study type or population. The review is structured around six conceptual domains: (i) genomic architecture of drug response, including the distinction between monogenic and polygenic inheritance and the concept of missing heritability; (ii) PRS methodologies, encompassing variant selection algorithms (pruning and thresholding versus Bayesian methods), validation strategies (reproducibility, accuracy, robustness), and the challenge of ancestry bias; (iii) clinical applications across cardiovascular (statins, clopidogrel), psychiatric (antidepressants, antipsychotics), and endocrine (metformin) pharmacotherapy; (iv) the pharmacist's role as a genomic consultant, including competencies in data interpretation, electronic health record integration, and patient counseling on probabilistic risk; (v) barriers to adoption spanning economic constraints,

educational disparities, ethical concerns, and regulatory gaps; and (vi) emerging technologies and future directions, including AI-enhanced models and dynamic PRS incorporating epigenetic and real-world data. For each domain, evidence was synthesized to present current state, evidentiary gaps, and practice implications.

### *Quality Appraisal and Evidence Synthesis*

Formal risk-of-bias assessment tools were not applied systematically, as is appropriate for a narrative review; however, methodological quality was considered informally during synthesis. Preference was given to evidence from well-conducted prospective cohort studies, randomized controlled trials, systematic reviews, and health economic analyses over narrative case reports or opinion pieces. GWAS studies were evaluated for sample size, ancestry diversity, and replication in independent populations. Clinical validation studies were prioritized when assessing PRS clinical utility. Implementation and health equity research were evaluated for clarity of outcome measures and representativeness of populations studied. Where major discrepancies or contradictions were identified in the literature (e.g., regarding optimal PRS calculation methods or generalizability across populations), these were noted explicitly in the synthesis rather than resolved through meta-analytic pooling.

### *Limitations and Potential Selection Bias*

This narrative approach carries inherent limitations in comprehensiveness and reproducibility. The search was broad but not exhaustive; some relevant articles may have been missed, particularly grey literature, preprints not yet indexed, or studies in languages other than English. Selection of articles for inclusion reflected the authors' judgment of relevance, and another reviewer might weight evidence differently or emphasize other aspects of the field. The review prioritizes recent literature (2010-2025) and English-language sources, which may inadvertently underrepresent geographic perspectives or earlier foundational work. No formal assessment of publication bias was undertaken. The thematic organization allows for conceptual synthesis but may obscure quantitative patterns (e.g., temporal trends in PRS adoption rates or cost-effectiveness data) that would emerge from more structured evidence mapping. Finally, the expertise and perspective of the authors grounded in clinical pharmacy and precision medicine may influence interpretation toward pharmacy-specific applications and implementation barriers. Despite these limitations, the narrative approach allows for nuanced integration of mechanistic, clinical, and implementation evidence in a way suited to educating a diverse audience of pharmacists, educators, and health system leaders navigating the transition toward PRS-informed precision pharmacy.

## RESULTS / EVIDENCE SYNTHESIS

### *Literature Overview and Scope of Evidence*

The targeted literature search identified over 200 peer-reviewed articles, reports, and guidelines relevant to polygenic risk scores in clinical pharmacy. From this pool, 90 publications were selected for detailed review based on explicit relevance criteria and methodological quality considerations. The evidence base spans foundational genomic theory (15 articles on GWAS methodology and missing heritability), PRS calculation and validation frameworks (22 articles on algorithms, ancestry considerations, and clinical validation), clinical applications across therapeutic domains (28 articles on cardiovascular, psychiatric, and endocrine pharmacotherapy), pharmacy practice and implementation (18 articles on pharmacist competencies, electronic health record integration, and barriers to adoption), and emerging technologies (12 articles on artificial intelligence, dynamic PRS, and epigenetic integration). The included literature comprises landmark peer-reviewed studies, systematic reviews, clinical guidelines from professional organizations, health services research, and implementation science publications. Notable gaps in the evidence base include limited health economic analyses specific to pharmacy-delivered PRS services, sparse implementation pilot data from real-world clinical pharmacy settings, and underrepresentation of studies from non-European ancestry populations.

### *Genomic Architecture of Drug Response: Monogenic Versus Polygenic Models*

Traditional pharmacogenetics has established that single-gene variants in cytochrome P450 enzymes (CYP2D6, CYP2C19, CYP3A4) and other drug-metabolizing proteins directly influence drug exposure and toxicity (14). These monogenic variants classify individuals into discrete metabolizer phenotypes poor, intermediate, extensive, or ultra-rapid with well-documented clinical consequences for drug dosing and efficacy (15). However, the explanatory power of monogenic testing is limited. Studies comparing predicted versus observed drug response in cohorts with known CYP genotypes consistently demonstrate that single-gene variants explain 20-40% of interindividual variation in drug response for most drugs, leaving 60–80% unexplained (16). This "missing heritability" reflects the reality that drug response is a complex, multifactorial phenotype determined by multiple biological pathways: drug absorption and distribution, target receptor sensitivity and signaling cascades, downstream physiological response, and interactions with environmental and lifestyle factors (17).

Evidence indicates that the majority of genetic variants influencing drug response have small individual effect sizes (odds ratios or beta coefficients <1.2) and are distributed across the entire genome rather than concentrated in known pharmacogene regions (18). For example, in antihypertensive response, genetic variation in genes controlling vascular tone, renal sodium handling, sympathetic nervous system activity, and immune regulation all contribute to treatment outcomes, yet no single variant dominates (19). In psychiatric pharmacotherapy, response to antidepressants depends on variants in genes affecting serotonin, noradrenaline, and dopamine pathways, as well as neuroplasticity and stress response mechanisms processes involving dozens of genes with distributed effects (20). Polygenic models, by contrast, aggregate these multiple small-effect variants into a single composite score that captures cumulative genetic burden. Unlike categorical monogenic predictions, PRS generate continuous risk estimates reflecting a spectrum of genetic predisposition, with the potential to improve prediction accuracy over single-gene testing (21).

The concept of "pharmacogenic load" the cumulative adverse effect of multiple small-effect variants on drug efficacy or safety provides a mechanistic framework for understanding why polygenic approaches are necessary. A patient may harbor multiple variants, each slightly reducing drug absorption, modifying receptor sensitivity, or impairing downstream signaling. Individually, each variant may have negligible clinical consequence, but their combined effect can substantially impair therapeutic response or increase toxicity risk, necessitating dose escalation, alternative agents, or combination therapy (22). This cumulative model is consistent with precision medicine principles and explains why fixed dosing regimens often fail to produce consistent outcomes across populations (23).

### *PRS Methodologies: Calculation, Validation, and Population Considerations*

The calculation of polygenic risk scores requires several methodological decisions that directly impact accuracy, reproducibility, and generalizability (24). Two primary algorithmic approaches have been widely adopted: pruning and thresholding (P+T) and Bayesian methods (Table 2). The P+T method is conceptually straightforward and computationally efficient: single nucleotide polymorphisms (SNPs) are selected based on p-value thresholds derived from GWAS summary statistics, correlated variants are removed via linkage disequilibrium (LD) pruning, and retained SNPs are weighted by their effect size and summed (25). The advantages of P+T include simplicity, rapid computation, and interpretability; the disadvantages include potential loss of informative variants below the p-value threshold and inability to account for complex LD patterns across the genome (26).

Bayesian methods represent a more sophisticated approach. These algorithms model all available SNPs simultaneously using prior distributions of effect sizes and take into account linkage disequilibrium structure across the genome (27). Advanced implementations, including LDpred and PRS-CS, adjust SNP effect sizes conditional on LD patterns, improving prediction accuracy for highly polygenic traits where thousands of variants each contribute small effects (28). Bayesian methods are particularly beneficial when PRS comprise 10,000 or more SNPs and individual effect sizes are very small, as is typical for

complex drug response and disease susceptibility phenotypes (29). However, Bayesian approaches are computationally intensive, require careful tuning of hyperparameters, and demand statistical expertise not universally available in clinical settings (30). The choice of algorithm involves a trade-off between statistical sophistication and practical implementation feasibility.

Validation of PRS is essential before clinical deployment and involves three interconnected components: reproducibility, accuracy, and robustness (Table 2). Reproducibility is assessed through external validation, in which a PRS model developed in one population is applied to independent cohorts to determine whether similar predictive performance is achieved (31). High reproducibility indicates that the score captures generalizable genetic signal rather than overfitting to derivation data. Accuracy refers to the predictive power of the PRS its ability to correctly classify risk or predict the outcome of interest. Common accuracy metrics include area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and calibration plots (32). In clinical pharmacy, PRS must achieve accuracy sufficient to inform meaningful therapeutic decisions, such as dose adjustment or agent selection; however, statistical accuracy alone does not guarantee clinical utility, which requires demonstration that PRS-guided decisions improve patient outcomes compared to standard care (33).

Robustness addresses the stability of PRS performance across different genotyping platforms, imputation strategies, and analytical pipelines (34). Standardization of preprocessing, quality control, and reporting is necessary to ensure consistency across laboratories and clinical settings. Professional and regulatory bodies, including the American College of Medical Genetics and the Genetic Testing Regulatory Coalition, have begun issuing guidelines emphasizing the importance of transparent reporting of PRS construction, validation metrics, and performance characteristics (35).

Ancestry bias represents a critical and underaddressed limitation of contemporary PRS. The vast majority of GWAS studies have been conducted in populations of European ancestry, resulting in PRS models derived from European-centric genetic data (36). When such PRS are applied to non-European populations, prediction accuracy often deteriorates substantially because allele frequencies, effect sizes, and linkage disequilibrium patterns differ across populations (37). For example, a PRS developed from a European cohort may misclassify risk in South Asian, African, or Latin American individuals, potentially leading to inappropriate therapeutic decisions and deepening health disparities (38). This is not merely a statistical problem but an ethical imperative: fair and equitable implementation of precision medicine requires that PRS be validated in diverse populations and that research infrastructure and funding support the generation of population-specific models (39). Efforts to address ancestry bias include multi-ancestry meta-analyses, transfer learning approaches, and ancestry-specific calibration; however, these require adequate representation of underrepresented groups in genomic research, which remains limited due to funding constraints, infrastructure gaps, and historical underinvestment in non-European populations (40).

### *Clinical Applications of PRS Across Therapeutic Domains*

Evidence for PRS application in clinical practice is emerging across three major therapeutic domains: cardiovascular, psychiatric, and endocrine. In cardiovascular medicine, statin response demonstrates substantial inter-individual variability: approximately 40-50% of patients do not achieve target lipid goals on standard doses, yet genetic factors explain only a small fraction of this variation (41). While individual variants in SLCO1B1 and other genes influence statin-induced myopathy risk, monogenic testing cannot predict overall treatment efficacy (42). PRS combining variants in lipid metabolism, inflammation, and muscle function pathways show promise for stratifying patients likely to benefit from intensive statin therapy versus those at elevated risk of adverse effects, potentially enabling more personalized dosing or agent selection (43). Similarly, response to the antiplatelet agent clopidogrel is highly variable;

CYP2C19 loss-of-function variants explain approximately 10–15% of the variability in platelet inhibition and adverse event risk (44). PRS incorporating variants in platelet activation pathways, drug transporters, and vascular biology genes show improved prediction of responder versus non-responder phenotypes, offering the potential for individualized antiplatelet therapy and thrombotic risk reduction (45).

In psychiatric medicine, the unpredictability of antidepressant and antipsychotic response is a major clinical challenge. Current monogenic approaches focus on CYP2D6 and CYP2C19 polymorphisms, which determine drug metabolism but provide limited insight into pharmacodynamic mechanisms (46). Evidence indicates that antidepressant response depends on variants affecting serotonin transporter, serotonin receptors, brain-derived neurotrophic factor, and neuroplasticity pathways, processes involving dozens of genes (47). PRS combining variants in these domains show moderate to good prediction of treatment response in major depressive disorder, with some studies demonstrating that PRS-guided treatment selection reduces trial-and-error prescribing and accelerates achievement of remission (48). In schizophrenia, PRS for antipsychotic response show promise for predicting not only efficacy but also metabolic side effects such as weight gain and metabolic syndrome risk, information that could guide choice of agent and enable preventive interventions (49).

In endocrine medicine, metformin represents the first-line agent for type 2 diabetes, yet glycemic response shows high variability. Known transporters such as SLC22A1 explain limited variance (50). PRS incorporating variants in insulin resistance, beta-cell function, glucose metabolism, and mitochondrial pathways show improved prediction of metformin efficacy (51). A distinctive feature of PRS in endocrinology is its intersection with nutritional science and nutrigenomics: genetic predisposition to insulin resistance or obesity is modified by dietary composition (carbohydrate quality, fat profile, overall caloric balance), enabling the potential for genotype-informed personalized nutrition recommendations alongside pharmacological therapy (52). Evidence from observational studies suggests that patients receiving genotype-informed dietary counseling combined with pharmacotherapy achieve superior long-term metabolic control compared to pharmacotherapy alone, though randomized controlled trial evidence is limited (53).

Across these domains, the clinical utility of PRS depends on several factors: (i) the availability of well-validated, ancestry-diverse PRS models; (ii) accessibility and affordability of genomic testing in clinical settings; (iii) integration of PRS results into electronic health records with clinical decision support; (iv) pharmacist or clinician competency in interpreting continuous risk scores in clinical context; and (v) demonstration through implementation science research that PRS-guided therapeutic decisions improve patient outcomes beyond standard care. Current evidence indicates that these enabling conditions are inconsistently met across healthcare systems (54).

### *The Pharmacist as Genomic Consultant: Competencies and Integration Pathways*

Evidence from implementation science and pharmacy practice research identifies several competencies essential for pharmacists to effectively use PRS: (i) understanding PRS methodology, including effect sizes, confidence intervals, and interpretation of continuous risk scores; (ii) integrating PRS with clinical variables (age, comorbidities, medication interactions, adherence) to inform personalized therapeutic recommendations; (iii) communicating probabilistic risk to patients in clear, non-alarmist language without overstating genetic determinism; (iv) documenting PRS-informed interventions in electronic health records and clinical decision support systems; and (v) collaborating with physicians, nurses, geneticists, and other team members to implement evidence-based, precision-guided treatment plans (55).

Integration of PRS into clinical workflows requires systematic incorporation into electronic health records and decision support systems. Successful examples from research settings include automated alerts that flag patients with high PRS for cardiovascular disease who are not on statin therapy, or prompts suggesting antipsychotic selection based on predicted metabolic risk (56). Pharmacists are

uniquely positioned to design and refine these decision support tools, ensuring that PRS data are presented in actionable, clinically interpretable formats and that alerts avoid alarm fatigue (57). Additionally, pharmacists must manage the ethical dimension of PRS counseling: explaining that high PRS does not equate to certainty of poor response, that drug response is influenced by modifiable factors (lifestyle, adherence, drug interactions), and that PRS represents one input among many in shared decision-making (58).

The evidence base on pharmacist-led PRS implementation is nascent. Pilot programs in academic medical centers and integrated health systems demonstrate feasibility of pharmacist consultation on PRS-guided therapy, but data on sustainability, cost-effectiveness, and patient outcomes are limited (59). No large-scale randomized controlled trials comparing PRS-guided pharmacist intervention to standard care have been completed, creating an evidence gap regarding the clinical and economic impact of this emerging role (60).

### *Barriers to Adoption and Implementation Infrastructure*

The identified barriers to PRS adoption in clinical pharmacy span economic, educational, ethical, and regulatory domains. Economically, whole-genome sequencing, which provides the most comprehensive data for PRS calculation, costs $300-$1,000 per patient, and targeted genotyping panels, while cheaper ($50-$200), may not capture all relevant variants (61). For health systems and individual patients, the cost-benefit analysis remains unclear: investment in PRS testing must be justified by documented improvements in clinical outcomes, reduced hospitalizations, or cost savings from avoided adverse drug reactions (62). Health economic evidence is sparse; only a handful of studies have examined cost-effectiveness of PRS-guided pharmacotherapy, and results are mixed (63). Furthermore, reimbursement frameworks in most healthcare systems do not yet recognize pharmacist consultation on genomic data as a billable service, limiting financial incentives for implementation (64).

Educationally, pharmacists and other healthcare providers lack standardized training in genomic science, PRS interpretation, and precision medicine. Traditional PharmD curricula emphasize pharmacology and therapeutics but allocate minimal time to statistical genetics, GWAS methodology, or interpretation of probabilistic risk (65). Practicing pharmacists often lack competency in genomic literacy and require substantial continuing education to confidently interpret PRS results and communicate risk to patients (66). This educational gap is recognized by pharmacy organizations, but systemic curriculum reform has been slow (67).

Ethically, PRS raises concerns about genetic discrimination (employment, insurance), data privacy, informed consent, and the "duty to recontact" patients when new genetic evidence emerges (68). While genetic non-discrimination laws (e.g., the Genetic Information Nondiscrimination Act in the United States) provide some protection, enforcement is limited and international variation in legal protections is substantial (69). Data privacy and secure storage of genomic information is essential, yet breaches and unauthorized secondary use of genetic data occur (70). Additionally, the question of whether healthcare providers have an obligation to recontact patients and inform them of updated risk assessments based on new PRS models or evidence is unresolved ethically and legally (71).

Regulatorily, there is no unified framework for PRS validation, reporting, and clinical deployment. Regulatory bodies including the FDA, EMA, and international organizations have begun issuing guidance, but standardized requirements for analytical validity, clinical validity, and clinical utility remain underdeveloped (72). The absence of standards creates uncertainty about what level of evidence is sufficient before PRS can be recommended for clinical use, potentially slowing adoption while also risking premature or inappropriate implementation of inadequately validated scores (73).

*Table 1: Comparison of Monogenic Pharmacogenetics and Polygenic Risk Scores (PRS) in Clinical Pharmacy*

| Feature | Monogenic Pharmacogenetics (PGx) | Polygenic Risk Score (PRS) | REFERENCES |
|---|---|---|---|
| **Genetic Basis** | Single gene or limited variants (typically 1–5) | Multiple genes across the genome (100–100,000+) | (14), (15) |

| Feature | Monogenic Pharmacogenetics (PGx) | Polygenic Risk Score (PRS) | REFERENCES |
|---|---|---|---|
| **Effect Size Per Variant** | Large, clinically significant (OR 2–10+) | Small individual effects, cumulative impact (OR 1.05–1.2 per SNP) | (16), (18) |
| **Scope of Analysis** | Focused on drug-metabolizing enzymes or single targets | Genome-wide integration across diverse biological pathways | (17), (19) |
| **Prediction Output** | Categorical (e.g., poor, intermediate, extensive metabolizer) | Continuous risk score (percentile or standard deviation units) | (21), (32) |
| **Variance Explained** | Limited; explains 20–40% of drug response variation in most contexts | Higher; captures cumulative genetic burden and "missing heritability" | (16), (21) |
| **Clinical Applications** | Drug metabolism, toxicity prediction (well-defined gene–drug interactions) | Efficacy, disease risk, treatment response (complex, polygenic traits) | (14), (43) |
| **Data Requirements** | Low to moderate (single or few genes; genotyping cost $50–$300) | High (requires large genomic datasets; sequencing cost $300–$1,000) | (61) |
| **Population Sensitivity** | Moderate; effect sizes relatively stable across populations | High; requires population-specific calibration due to allele frequency and LD differences | (36), (37) |
| **Interpretation Complexity** | Relatively simple; binary or categorical assignment | Complex; requires statistical training and integration of multiple clinical variables | (32), (55) |
| **Current Integration into Practice** | Implemented in many settings; CPIC guidelines available | Emerging; limited but growing adoption; few standardized clinical workflows | (54), (59) |

*Table 2: Key Methodological Considerations in PRS Development and Validation*

| Component | Description | Strengths | Limitations | Evidence Status |
|---|---|---|---|---|
| **Pruning & Thresholding (P+T)** | Selects SNPs based on p-value threshold; removes correlated variants via LD pruning; weights and sums remaining variants | Simple, fast, interpretable; computationally efficient | May miss rare or sub-threshold variants; cannot account for complex LD patterns; less accurate for highly polygenic traits | Established; widely adopted (25), (26) |
| **Bayesian Methods (LDpred, PRS-CS)** | Models all SNPs simultaneously using prior distributions; conditions on genome-wide LD structure | Higher predictive accuracy; captures complex variant interactions; accounts for LD patterns | Computationally intensive (hours to days per model); requires hyperparameter tuning and statistical expertise; not yet standardized across platforms | Emerging; increasingly used in research; limited clinical deployment (27), (28) |
| **Reproducibility Testing** | Validates PRS in independent cohorts not used in model development; measures consistency of prediction across settings | Ensures reliability and detects overfitting; essential for clinical utility | Requires large external datasets; sparse in underrepresented populations | Standard required (31), (33) |
| **Accuracy Assessment** | Evaluates predictive performance using AUC, sensitivity, specificity, calibration plots, and clinical validity | Quantifies predictive ability; enables comparison across PRS models | Statistical accuracy alone does not guarantee clinical utility; threshold for "acceptable" accuracy varies by clinical context | Standard required (32), (33) |
| **Robustness & Standardization** | Tests PRS stability across different genotyping platforms, imputation strategies, and analytical pipelines | Enhances consistency across laboratories; critical for standardized clinical implementation | Requires extensive validation work; standardization efforts are ongoing but incomplete | Emerging; professional guidelines being developed (34), (35) |
| **Ancestry Considerations & Cross-Population Validation** | Evaluates PRS performance in diverse populations; develops ancestry-specific models; uses transfer learning or calibration approaches | Addresses equity; improves generalizability; recognizes population genetic differences | Limited by underrepresentation of non-European populations in GWAS; requires population-specific research infrastructure and funding | Critical gap; active research focus (36)–(40) |

*Table 3: PRS Clinical Applications Across Therapeutic Domains*

| Therapeutic Domain & Drug | Current Monogenic Approach | Key Genetic Pathways in PRS | Primary Outcome | Prediction Accuracy (AUC) | Clinical Evidence Level | Implementation Status |
|---|---|---|---|---|---|---|
| **Cardiovascular** | | | | | | |
| **Statins (atorvastatin, pravastatin)** | SLCO1B1 polymorphisms (myopathy risk) | Lipid metabolism, inflammation, muscle function | LDL reduction; statin-induced myopathy | 0.62–0.70 | Observational cohort studies | Research setting; limited clinical deployment |
| **Clopidogrel (Plavix)** | CYP2C19 loss-of-function (poor activation) | Platelet activation, drug transport, vascular biology | Platelet inhibition; thrombotic event prevention | 0.65–0.75 | RCT, observational | Pilot implementation in cardiology |
| **Psychiatric** | | | | | | |
| **Antidepressants (sertraline, fluoxetine, escitalopram)** | CYP2D6, CYP2C19 (metabolism only) | Serotonin pathways, neuroplasticity, stress response, BDNF | Treatment response (symptom reduction ≥50%); remission | 0.60–0.68 | RCT, observational cohort | Research trials; limited clinical use |
| **Antipsychotics (risperidone, olanzapine, aripiprazole)** | CYP3A4, CYP2D6 (metabolism) | Dopamine, serotonin receptors; metabolic regulation; weight gain pathways | Response to antipsychotic; metabolic side effects (weight gain, metabolic syndrome) | 0.58–0.72 | Observational, case-control | Research studies; not yet clinically integrated |
| **Endocrine** | | | | | | |
| **Metformin (first-line T2DM)** | SLC22A1 transporter variants | Insulin resistance, beta-cell function, glucose metabolism, mitochondrial pathways | Glycemic control (HbA1c reduction); efficacy classification | 0.63–0.71 | Observational, small RCT | Research; integrated with nutrigenomics pilots |

AUC = Area under the receiver operating characteristic curve (ranges 0.5–1.0; >0.7 considered clinically useful). RCT = Randomized controlled trial.

*Table 4: Barriers to PRS Adoption in Clinical Pharmacy: Domains, Specific Barriers, and Evidence*

| Barrier Domain | Specific Barriers | Impact on Adoption | Evidence / Documentation |
|---|---|---|---|
| **Economic** | High cost of WGS ($300–$1,000/patient); targeted panels cheaper but potentially incomplete | Limits accessibility; unclear ROI for health systems; no reimbursement for pharmacist PRS consultation in most systems | Limited health economic analyses; sparse cost-effectiveness studies (61)–(63) |
| **Educational** | PharmD curricula lack genomics training (<10% dedicate ≥20 hours); practicing pharmacists lack genomic literacy | Pharmacists unprepared to interpret PRS, counsel patients, or integrate into EHR; continuing education fragmented | Pharmacy education gap documented; no standardized genomic competency framework (65)–(67) |
| **Ethical & Legal** | Genetic discrimination risk (employment, insurance); data privacy breaches; unresolved "duty to recontact"; informed consent complexity | Deters patients and providers; limits data sharing for research; creates legal uncertainty | Genetic non-discrimination laws variable; ethical frameworks underdeveloped (68)–(71) |
| **Regulatory & Standardization** | No unified validation framework; FDA/EMA guidance nascent; PRS reporting standards not standardized; unclear clinical utility requirements | Uncertainty about evidence bar for clinical deployment; risk of premature or inadequate implementation | Regulatory landscape evolving; SEQC, GA4GH developing standards (72), (73) |
| **Methodological** | Ancestry bias in existing PRS (majority European-derived); limited population-specific models; LD and allele frequency differences across populations | PRS poorly predictive in non-European populations; deepens health disparities; reduces generalizability | Ancestry bias extensively documented; infrastructure for diverse GWAS underfunded (36)–(40) |
| **Implementation Infrastructure** | Limited clinical decision support integration; no standardized EHR workflows; few implementation pilots in pharmacy settings | PRS results not easily accessible to pharmacists; unclear how to operationalize recommendations; evidence gap on outcomes | Implementation science evidence sparse; no large RCTs of PRS-guided pharmacist intervention (59), (60) |

The evidence synthesis identified substantial literature on PRS genomic architecture, methodological frameworks, and emerging clinical applications, though implementation evidence in pharmacy is nascent. Monogenic approaches explain only 20-40% of drug response variation; polygenic models capturing thousands of genome-wide variants show promise for improved prediction across cardiovascular, psychiatric, and endocrine domains (AUC 0.60–0.75). However, methodological concerns-particularly ancestry bias, cost, and lack of clinical validation studies-limit clinical deployment. The pharmacist's role as a genomic consultant is well-articulated conceptually but operationally underdeveloped. Major barriers span economic (funding, reimbursement), educational (curriculum gaps), ethical (privacy, discrimination), regulatory (no unified standards), and implementation domains. Emerging AI-enhanced and dynamic PRS models integrating epigenetic and real-world data show theoretical promise but remain research-stage technologies.

## DISCUSSION

This narrative review synthesizes evidence on polygenic risk scores in clinical pharmacy, spanning genomic architecture, PRS methodologies, clinical applications across therapeutic domains, implementation frameworks, and emerging technologies. The evidence base reveals a field in transition: robust scientific foundation for PRS as a superior predictor of drug response variance compared to monogenic approaches, coupled with emerging clinical applications in cardiovascular, psychiatric, and endocrine pharmacotherapy, yet marked by substantial implementation gaps and underdeveloped pharmacy-specific infrastructure.

The distinction between monogenic and polygenic models represents a conceptual pivot in precision medicine. Our synthesis confirms that traditional pharmacogenetics, while clinically valuable for drugs with well-characterized gene–drug interactions, explains only 20-40% of observed interindividual variation in drug response across most therapeutic contexts (14-16). Polygenic models address this "missing heritability" by aggregating thousands of genome-wide variants into composite risk scores that capture cumulative genetic burden (17-19). The mechanistic foundation is sound: drug response results from multiple biological pathways absorption, distribution, metabolism, elimination, target binding, signal transduction, and downstream physiological response each governed by multiple genes with small individual effects (20). The concept of "pharmacogenic load" provides an intuitive clinical framework: patients accumulating adverse genetic variants may require dose escalation, alternative

agents, or combination therapy despite normal metabolism of the drug itself (21-22). This paradigm shift from single-gene to systems-based thinking is aligned with contemporary precision medicine philosophy and reflects the biological complexity of therapeutic outcomes.

However, the clinical translational evidence for PRS is nascent and geographically concentrated. Across cardiovascular, psychiatric, and endocrine domains, PRS demonstrate moderate to good predictive accuracy (AUC 0.60-0.75), meeting or approaching the AUC >0.70 threshold often cited as clinically useful (41-55). Most of this evidence derives from observational cohort studies and small randomized trials conducted in research settings, often in populations of European ancestry. Few large-scale, pragmatic implementation trials have examined whether PRS-guided pharmacist or physician decision-making improves patient outcomes beyond standard care. This evidence gap is critical: statistical accuracy does not automatically translate to clinical utility, which requires demonstration that PRS-informed interventions result in superior drug efficacy, reduced adverse events, or cost savings (32-33). The limited health economic literature is particularly striking—only a handful of studies have modeled the cost-effectiveness of PRS testing and intervention in pharmacy practice, creating uncertainty about the financial case for health system investment (61-63).

The ancestry bias challenge identified in this review is not merely a methodological limitation but an ethical imperative and a barrier to equitable implementation. The overwhelming majority of GWAS studies and resulting PRS models derive from European ancestry populations, resulting in prediction models that perform poorly when applied to non-European groups (36-40). This creates a vicious cycle: underrepresentation of non-European populations in genomic research leads to poor PRS performance in those populations, discouraging their clinical use and perpetuating health disparities. The South Asian population burden of complex diseases and the high genetic diversity within South Asia make it particularly urgent to develop population-specific PRS models; however, research infrastructure, funding, and political will remain inadequate (74). Recent efforts in multi-ancestry meta-analyses and transfer learning show promise but require sustained investment and equitable partnership with researchers and health systems in underrepresented regions (40, 75).

The pharmacist's role as a genomic consultant is conceptually compelling but operationally underdeveloped. Our review identified multiple core competencies: interpreting continuous risk scores, integrating PRS with clinical variables and medication history, communicating probabilistic risk to patients without genetic determinism, and implementing PRS-informed recommendations in electronic health records and clinical decision support systems (55-58). However, pharmacy education has not systematically evolved to prepare students and practicing pharmacists for these roles. PharmD curricula traditionally emphasize pharmacology and therapeutics, with genomic content comprising <10% of formal instruction in most programs (65-67). The result is a workforce unequipped to operationalize PRS in clinical practice. Professional organizations including the American Pharmacists Association and the American Association of Colleges of Pharmacy have begun developing competency frameworks, but implementation and accreditation alignment remain nascent (76). Continuing education and competency-based training programs are fragmented and not universally accessible. Without systematic educational reform, even where PRS testing is available and accurate, pharmacists will lack the competency to interpret results and counsel patients effectively.

Integration into clinical workflows is another critical barrier. PRS results must be incorporated into electronic health records in actionable formats, with decision support alerts designed for point-of-care use by pharmacists and physicians (56-57). Successful examples from research settings exist automated recommendations for antipsychotic choice based on predicted metabolic risk, or alerts flagging patients with high cardiovascular disease PRS not on statin therapy but these remain largely research prototypes (77). Deployment in operational healthcare settings requires standardized data architectures, validated clinical decision rules, workflow redesign, and careful attention to alert fatigue and user acceptance (78). Pharmacists must be involved in designing these systems to ensure that PRS data are presented in

clinically intelligible formats and that recommended actions align with actual prescribing authority and pharmacy practice models (79). The evidence base on implementation effectiveness is sparse; few pragmatic trials have examined how different EHR integration strategies affect pharmacist behavior, prescribing patterns, or patient outcomes (59), (60).

The economic landscape for PRS in pharmacy is uncertain. Whole-genome sequencing costs $300-$1,000 per patient; targeted genotyping panels cost $50-$200 but may miss important variants (61). For health systems and individual patients, the cost-benefit must be justified by demonstrated improvements in drug efficacy, reduced hospitalizations, or avoided adverse events. Yet the health economic literature on PRS-guided pharmacotherapy is minimal (62-63). Without clear evidence of cost-effectiveness, health system adoption is understandably cautious. Additionally, reimbursement frameworks in most countries do not recognize pharmacist consultation on genomic data as a billable clinical service, removing financial incentive for implementation (64). Changing this landscape requires parallel actions: generating robust health economic evidence, advocating for reimbursement policy change, and demonstrating sustained improvement in patient outcomes through implementation science research.

The ethical and regulatory framework for PRS remains underdeveloped. Genetic discrimination (employment, insurance), data privacy, informed consent complexity, and the "duty to recontact" patients when new genetic evidence emerges are substantive concerns that pharmacists and health systems must address (68-71). While genetic non-discrimination laws exist in some jurisdictions (e.g., the U.S. Genetic Information Nondiscrimination Act), enforcement is limited and international variation is substantial. Data governance and cybersecurity standards for genomic information must be strengthened. Informed consent for PRS testing must communicate both benefits and limitations, including the probabilistic (not deterministic) nature of risk, the potential for incidental findings, and data use and privacy protections (80). Regulatory bodies including the FDA and EMA have begun issuing guidance on PRS validation and reporting, but unified, internationally harmonized standards remain absent (72-73). This regulatory uncertainty creates barriers to innovation while potentially risking inadequately validated PRS entering clinical use without oversight. Professional organizations must work with regulatory bodies to establish transparent, evidence-based standards for PRS clinical validation and deployment (81).

Emerging technologies present both promise and complexity. Artificial intelligence and machine learning enable integration of multidimensional data genetic, epigenetic, environmental, behavioral, and microbiome into dynamic PRS models that evolve with new information and individual circumstances (82-84). Dynamic PRS incorporating epigenetic changes and real-world data could provide more accurate, personalized risk assessments and more adaptive therapeutic recommendations (85-87). However, these approaches introduce additional interpretability challenges, require substantial computational resources, and demand new regulatory frameworks for validation and deployment. Clinical pharmacists will need even more sophisticated training to understand and confidently use AI-enhanced PRS tools (88). Additionally, the potential for bias in machine learning algorithms including perpetuation of ancestry bias, algorithmic discrimination, and unintended consequences of algorithmic decision-making must be carefully monitored and mitigated (89).

### Limitations of This Review

This narrative review carries inherent methodological limitations. The search strategy, while targeted and systematic, was not exhaustive; some relevant articles, particularly grey literature and non-English publications, may have been omitted. Selection of articles for detailed review reflected the authors' judgment of relevance, introducing potential selection bias toward topics aligned with the authors' expertise and interests. The thematic organization prioritizes conceptual synthesis over quantitative evidence mapping, potentially obscuring temporal trends or epidemiological patterns that would emerge from more structured evidence synthesis. No formal quality appraisal tool was applied systematically, though methodological quality was considered informally during synthesis. The review

emphasizes English-language, published peer-reviewed literature, which may underrepresent geographic perspectives, indigenous knowledge, or alternative approaches. Finally, the authors' expertise in clinical pharmacy and precision medicine may reflect a pharmacy-centric perspective that emphasizes implementation barriers and opportunities specific to pharmacy practice while potentially underweighting perspectives from physicians, geneticists, or patients themselves.

### Clinical and Policy Implications

For clinical pharmacists, this review demonstrates that PRS represent a scientifically valid and increasingly available tool for precision drug therapy, but successful implementation requires substantial preparation. Pharmacists should advocate for and participate in health system initiatives to integrate genomic testing and PRS interpretation into clinical workflows, ensure that electronic health records include decision support tools, and develop clinical consultation services for PRS-guided pharmacotherapy. Individual pharmacists should pursue continuing education in genomic science and PRS interpretation to build competency. Pharmacy organizations should accelerate curriculum reform, develop standardized competency frameworks aligned with board examination content, and establish credentialing or specialization pathways for pharmacists with advanced genomic expertise.

For health system leaders, this review underscores that PRS implementation requires multifaceted investment: (i) funding and infrastructure for genomic testing and laboratory validation; (ii) electronic health record systems capable of storing and presenting PRS data with actionable clinical decision support; (iii) educational programs to upskill existing pharmacists and integrate genomic content into pharmacy training; (iv) clear reimbursement policies recognizing pharmacist consultation on genomic data; and (v) implementation science research to evaluate the real-world effectiveness, feasibility, and cost-effectiveness of PRS-guided pharmacy services. Early adopters should document implementation processes, barriers encountered, and outcomes to generate evidence that informs system-wide deployment.

For policy makers and regulatory bodies, this review identifies critical needs: (i) standardized frameworks for PRS analytical validity, clinical validity, and clinical utility assessment, with transparent reporting requirements; (ii) investment in GWAS and PRS research in underrepresented populations to address ancestry bias and enable equitable implementation; (iii) reimbursement policy reform to recognize and compensate pharmacist consultation on genomic data; (iv) regulatory clarity regarding data governance, consent, and privacy protections for genomic information; (v) educational standards and accreditation for health professional training in genomics and precision medicine. International coordination on regulatory standards would reduce fragmentation and facilitate global evidence generation.

For researchers, this review highlights critical evidence gaps: (i) large-scale pragmatic randomized trials comparing PRS-guided versus standard pharmacotherapy on patient outcomes; (ii) health economic analyses examining cost-effectiveness of PRS testing and pharmacist consultation; (iii) implementation science research on barriers, facilitators, and strategies for successful PRS deployment in diverse healthcare settings; (iv) studies examining ancestry-specific PRS performance and approaches to address bias; (v) research on pharmacist competencies, training needs, and factors influencing confidence and competence in genomic data interpretation; (vi) patient-centered research on understanding, acceptability, and preferences regarding probabilistic genetic risk communication.

## CONCLUSION

Polygenic Risk Scores represent a scientifically grounded evolution in precision pharmacotherapy, moving beyond the limitations of monogenic approaches to integrate genome-wide genetic variation and predict drug response with moderate to good accuracy across cardiovascular, psychiatric, and endocrine therapeutic domains. However, translation of this scientific promise into routine clinical

pharmacy practice remains underdeveloped, constrained by economic barriers (cost of genomic testing and lack of reimbursement), educational gaps (insufficient pharmacist training in genomic interpretation), methodological concerns (ancestry bias limiting generalizability), and incomplete regulatory and implementation infrastructure. Pharmacists are uniquely positioned to serve as genomic consultants, integrating PRS data into clinical workflows, interpreting probabilistic risk, counseling patients, and optimizing therapeutic decisions; however, systematic workforce development, health system investment, policy reform, and implementation science evidence are necessary preconditions. Future advancement requires parallel efforts across funding (diverse GWAS and implementation research), education (curriculum reform and competency development), infrastructure (EHR integration and decision support), regulation (harmonized standards for PRS validation and deployment), and health equity (ancestry-specific models and fair access). Emerging AI-enhanced dynamic PRS models show promise for further precision gains but demand ongoing attention to methodological validity and ethical governance. With coordinated action across academia, health systems, professional organizations, and policy makers, PRS can fulfill its potential to advance equitable, evidence-based, truly personalized pharmacotherapy.

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