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International Journal of Pharmaceutical Research & Allied Sciences, 2025, 14(3):11-21
https://doi.org/10.51847/hBsJHV5cVf

Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Precision Pharmacotherapy without Exclusion: An Equity-by-Design Framework for Ancestry Diversity, Access, Interpretability, and Clinical Implementation across Health Systems

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ABSTRACT

Pharmacogenomics can improve medicine selection and dose individualization, but greater biological precision does not automatically produce equitable care. Exclusion may arise when evidence is derived from narrowly represented populations, genomic associations are transferred without adequate validation, ancestry is replaced by racial or geographic proxies, uncertain variants are treated as definitive, testing is inaccessible, or recommended alternatives cannot be obtained. This article proposes an original Equity-by-Design Framework that treats equity as a property of the complete research-to-care pathway. The architecture links six gates: evidence representation and provenance; assay and interpretation; ancestry-related transferability and dynamic clinical state; access to testing and treatment alternatives; interpretability and shared decision-making; and health-system implementation, monitoring, and governance. An uncertainty record accompanies each decision object, while stop-or-escalate rules prevent progression when evidence coverage, access, interpretability, or monitoring capacity is insufficient. The framework also proposes subgroup-sensitive predeployment evaluation, lifecycle monitoring, and corrective-action authority. Its contribution is the integration of biological transferability, social access, communication, and institutional accountability within one conceptual architecture. Validation would require computational, analytical, clinical, usability, implementation, economic, equity, and governance studies. The framework does not establish the clinical utility of any gene–drug pair, justify ancestry-based prescribing, define universal fairness thresholds, or constitute a validated clinical, regulatory, or deployment pathway.

Key words: *Pharmacogenomics, Precision pharmacotherapy, Genotype, Phenoconversion, Clinical Implementation, Dose individualization*
Received: 30 March 2025; **Revised:** 18 July 2025; **Accepted:** 21 July 2025

INTRODUCTION

Pharmacogenomics examines how genomic variation may influence pharmacokinetics, pharmacodynamics, treatment response, and adverse effects. Precision pharmacotherapy is broader because it combines genomic information with clinical phenotype, comorbidities, organ function, concomitant medicines, environmental exposures, patient preferences, and available treatments. Genotype-guided therapy is therefore one strategy within precision pharmacotherapy rather than a synonym for the field [1].

The evidentiary maturity of pharmacogenomic applications varies across genes, drugs, phenotypes, and clinical settings. Some applications support established recommendations, whereas others remain limited by incomplete functional evidence, uncertain associations, weak transferability, or insufficient proof that testing changes decisions or outcomes. Phenoconversion further shows that interacting medicines, disease, inflammation, and organ dysfunction may alter the relationship between inherited genotype and current functional phenotype [2].

An equity problem emerges when precision is judged only by analytical accuracy or average performance. Race, ethnicity, ancestry, geography, and social position describe different constructs and cannot be substituted without justification. A technically accurate result may still contribute to inequity when evidence is population-skewed, interpretation is less certain for some groups, testing is inaccessible, or treatment alternatives are unavailable [3].

This article develops an original, non-empirical Equity-by-Design Framework. It organizes representation, assay validity, transferability, dynamic clinical state, access, interpretability, implementation, monitoring, and governance as linked conditions of equitable decision use. Its gates, uncertainty record, and corrective-action pathways are proposed constructs requiring empirical validation and do not constitute clinical recommendations or regulatory criteria.

How precision pharmacotherapy can reproduce inequity

Precision pharmacotherapy can reproduce inequity when prediction or treatment rules are transported beyond the populations in which they were developed. Polygenic models derived mainly from European-ancestry data may perform less well in other populations because allele frequencies, linkage disequilibrium, and genetic architecture differ [4]. Although polygenic scores and pharmacogenomic rules are not identical, both show that higher average precision can coexist with unequal transferability.

Exclusion can also begin in databases used to identify and interpret variation. Underrepresentation reduces opportunities to detect population-enriched variants, estimate frequencies, characterize linkage patterns, and establish confident genotype–phenotype relationships. Database imbalance may therefore produce unequal interpretability, with well-represented populations receiving more informative results and underrepresented populations receiving greater uncertainty [5].

Apparently neutral variables can encode structural inequality. A health-management algorithm that used expenditure as a proxy for need underestimated illness burden among Black patients because unequal prior spending distorted the label [6]. This mechanism should not be generalized mechanically to every pharmacogenomic tool, but it shows why testing eligibility, benefit prediction, alert prioritization, and follow-up rules must be audited for access-dependent proxies.

These mechanisms interact. Population imbalance can weaken evidence; weak evidence can increase interpretive uncertainty; proxy-based rules can influence who is tested; and financial, geographic, linguistic, or institutional barriers can determine who can act on a result. Equity is therefore not achieved merely by offering the same test to everyone or deleting race from an algorithm. It requires examination of the complete pathway and its consequences.

Population representation and ancestry-related transferability

Population representation concerns who contributes data, whose variants can be interpreted confidently, and which communities share in governance and benefit. Ancestry-related transferability is narrower: it asks whether an association, phenotype translation, predictive model, or treatment rule remains sufficiently valid beyond its development population. Allele frequency, linkage disequilibrium, allelic heterogeneity, and environmental context can affect cross-population inference [7].

Diversity alone does not guarantee transferability. Studies must address population structure, imputation quality, sample-size imbalance, local ancestry, heterogeneous linkage patterns, and context-specific effects. Methods that perform well in a large homogeneous cohort may not produce balanced inference in smaller or more heterogeneous populations [8]. Evaluation must therefore examine how populations contribute to discovery, estimation, calibration, interpretation, and uncertainty.

Terminology also matters. Race is primarily a social classification; ethnicity may reflect cultural or national affiliation; geography indicates location; and genetic ancestry estimates inherited similarity relative to reference populations. Biogeographic groupings can help annotate pharmacogenetic evidence, but they are not discrete biological types and remain sensitive to admixture, within-group diversity, and reference-panel choice [9].

The framework defines transferability as decision-specific. An assay may transfer analytically while a phenotype rule does not; a phenotype label may remain valid while a dosing recommendation lacks evidence in the receiving

population or health system. Ancestry should be used only when it adds justified information beyond measured genotype, phenotype, and clinical state. It should never substitute silently for missing data or individual assessment.

Proposed equity-by-design framework

Equity by design means evaluating exclusion while evidence, assays, interpretive rules, access pathways, communication processes, and implementation systems are being built. This differs from assessing subgroup disparities only after deployment. Diversity roadmaps emphasize participation, leadership, infrastructure, analysis, interpretation, and benefit sharing across the genomic research lifecycle [10]. The present framework adapts that lifecycle principle to precision pharmacotherapy.

The architecture contains six proposed gates. Gate 1 examines evidence representation and provenance. Gate 2 evaluates assay content, analytical validity, variant calling, and phenotype translation. Gate 3 examines ancestry-related transferability together with phenoconversion and current clinical state. Gate 4 evaluates access to testing and clinically reasonable alternatives. Gate 5 addresses interpretability and shared decision-making. Gate 6 evaluates implementation, monitoring, and governance.

Ancestry is not prohibited, but its role must be explicit, methodologically justified, and decision-specific. Population-specific pharmacogenomic implementation shows that ancestry estimates may support bounded interpretation or service design in some settings [11]. Such examples do not justify race-based prescribing or universal portability. Their relevance depends on the population, reference data, assay, gene–drug relationship, workflow, and treatment environment.

Figure 1 presents the original conceptual synthesis for equity-by-design architecture for precision pharmacotherapy, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

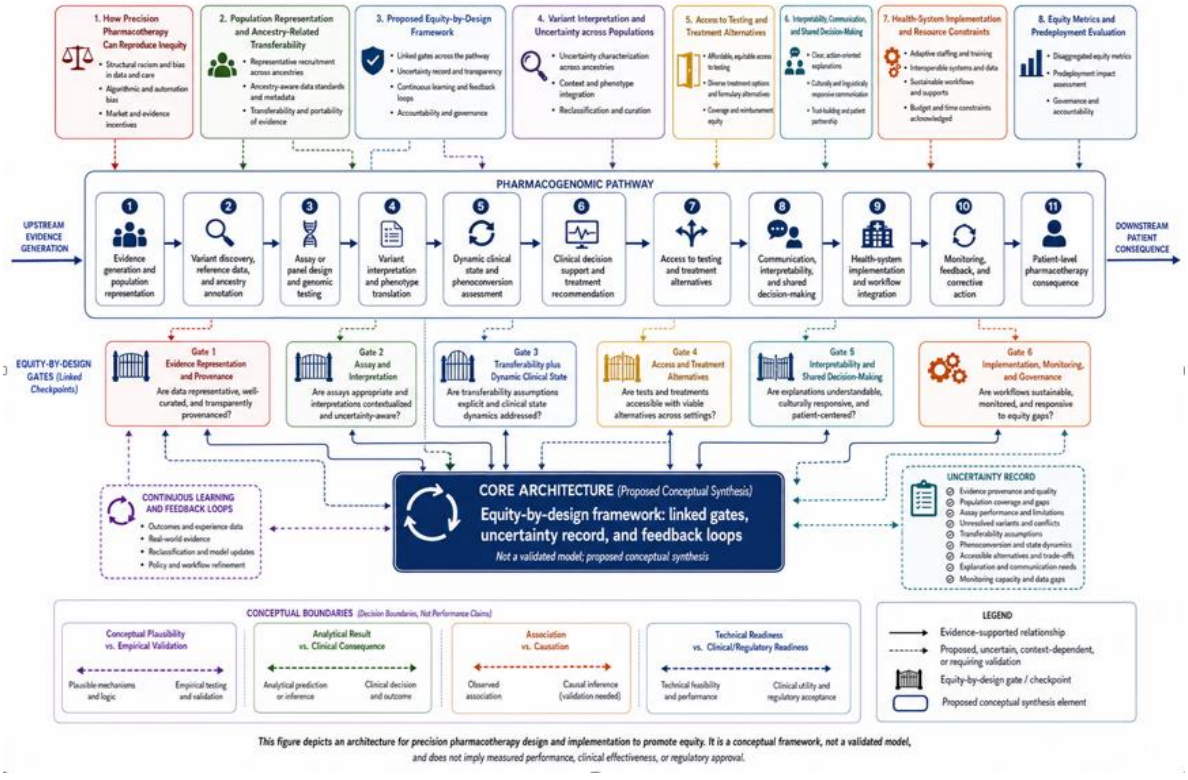

Figure 1. Equity-by-Design Architecture for Precision Pharmacotherapy

A pharmacogenomic digital twin is proposed only as an updateable patient-state representation that may combine genotype, translated phenotype, current medicines, drug interactions, organ function, relevant exposures, and prior treatment response. Digital-twin concepts support the broader possibility of models updated as patient state changes [12]. Here, the construct is an organizing device, not an autonomous prescriber or a claim of complete biological simulation.

An uncertainty record accompanies each decision object. It documents evidence provenance, population coverage, assay limitations, unresolved variants, transferability assumptions, possible phenoconversion, accessible alternatives, explanation needs, and monitoring capacity. A stop-or-escalate rule applies when material uncertainty cannot be bounded, when no accessible alternative exists, or when subgroup outcomes cannot be monitored. Passing a gate permits further evaluation; it does not certify equity or clinical readiness.

Variant interpretation and uncertainty across populations

Variant interpretation begins with what an assay can detect. Pharmacogenomic alleles vary among populations, so a panel optimized around variants common in one group may provide incomplete characterization elsewhere [13]. Equity-sensitive interpretation must disclose tested alleles, undetectable variation, and the relationship between panel content and the population in which the result will be used.

Standard terminology improves communication of genotype, diplotype, predicted phenotype, and recommendation status across laboratories and health systems [14]. Yet a standardized metabolizer label is not a direct measurement of current function. Its reliability depends on correct variant detection, accurate allele-function assignment, appropriate diplotype translation, relevant gene–drug evidence, and the clinical setting.

Phenoconversion shows why genotype-predicted phenotype and current functional phenotype must remain distinct. Inhibitors, inducers, inflammation, disease, and organ dysfunction may produce clinically important discordance [15]. The framework therefore proposes a dynamic-state assessment recording interacting medicines, disease-related modifiers, organ function, prior response, and the time at which context was evaluated.

The uncertainty record combines evidentiary coverage, analytical coverage, interpretive confidence, and dynamic-state uncertainty. It should state whether relevant variants may be missing, whether functional assignments remain unresolved, and whether transferability or phenoconversion assumptions are material. Population frequencies can identify possible gaps but cannot replace individual assessment or justify deterministic ancestry-based inference. **Table 1** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for definitions, components, relationships, and intended uses in precision pharmacotherapy without exclusion.

Table 1. Definitions, components, relationships, and intended uses in Precision Pharmacotherapy without Exclusion

Component or scientific dimension	Problem addressed	Inputs or determinants	Proposed mechanism or relationship	Expected contribution	Evidence required	Failure or uncertainty risk	Boundary statement
Population representation	Unequal evidentiary confidence	Recruitment, provenance, variant and phenotype data	Analytically meaningful representation improves coverage	Transparent evidence gaps	Population-specific evidence [5]	Token inclusion or weak subgroup data	Representation does not guarantee equal outcomes
Transferability	Uncertain portability	Allele frequencies, linkage structure, environment	Decision-specific validation replaces blanket portability	Bounded cross-population use	External validation and calibration [7]	Essentialism or proxy misuse	Ancestry does not determine individual response
Assay coverage	Missed relevant variation	Tested loci, structural variation, sequencing depth	Panel content is compared with relevant variation	Identification of blind spots	Analytical validation [13]	False reassurance from negative results	Negative panels do not exclude all variation
Interpretation	Inconsistent translation	Allele function, diplotype, terminology	Standardized terms plus uncertainty annotation	Traceable interpretation	Reproducible translation [14]	Outdated or ambiguous assignments	Standard labels do not remove uncertainty
Dynamic clinical state	Genotype–phenotype discordance	Medicines, inflammation, disease, organ function	Current modifiers update the decision object	Context-sensitive inference	Modifier validation [15]	Unrecognized phenoconversion	No drug-specific action follows automatically

Access	Results cannot be obtained or acted upon	Cost, geography, laboratory and formulary access	Testing and alternatives are evaluated together	Practical actionability	Access studies [16]	Testing without treatment access	Equal offer is not equal benefit
Interpretability	Results are not understandable	Explanation, language, preferences	Dual clinician and patient interpretability	Better-informed decisions	Comprehension testing [17]	Opaque communication	Explanation alone does not establish benefit
Equity architecture	Fragmented treatment of exclusion	Outputs from preceding dimensions	**Original synthesis:** linked gates, uncertainty record, and feedback loops	Testable lifecycle framework	Multidomain validation	False assurance from isolated gates	The framework is conceptual

Access to testing and treatment alternatives

Access begins before an order is placed. Eligibility rules, referral pathways, reimbursement, sample logistics, specialist distribution, and turnaround time determine who can obtain a useful result. Population-wide availability may reduce some barriers, but equitable implementation still depends on utility, financing, and service capacity [16]. Availability must therefore be distinguished from practical accessibility.

Geographic disadvantage can intersect with medication exposure. Patients living farther from services may receive pharmacogenetically relevant medicines while having less access to testing, specialist interpretation, or follow-up [18]. This supports location-sensitive access audits but does not prove that testing alone will correct geographic disparities.

Economic evaluation must include more than assay price. Value depends on the gene–drug pair, actionable-variant prevalence, comparator strategy, testing timing, clinical consequences, implementation costs, and availability of alternatives. Existing economic evaluations are strongly context-dependent [19]. Guideline inclusion or analytical validity therefore does not establish affordability or cost-effectiveness in every system.

The framework proposes an accessible-alternatives safeguard. A recommendation cannot be considered practically actionable unless the patient can obtain at least one clinically reasonable option without disproportionate burden. When no accessible alternative exists, the system should disclose the mismatch, preserve non-genetic options, and escalate the barrier to an accountable service. This is an evaluation principle, not a treatment or financing mandate.

Interpretability, communication, and shared decision-making

Interpretability has technical and relational dimensions. Clinicians need the result, evidence basis, uncertainty, action logic, and conditions limiting use. Patients need to know what was tested, what the result may mean, what remains uncertain, and which alternatives are available. Receipt of a result does not ensure understanding [17].

Communication is therefore part of the intervention. Direct patient–provider discussion of pharmacogenomic results has been associated with better recall of medication changes [20]. Recall is not equivalent to adherence or clinical benefit, but it is a necessary intermediate outcome and supports explanation pathways that allow questions and document rationale.

Trust and perceived value should not be inferred from uptake alone. Underrepresented patients may recognize benefits while also expressing concerns about privacy, discrimination, misunderstanding, and unequal access [21]. These concerns should not be treated as fixed group traits; they depend on institutional history, communication quality, prior experience, and practical consequences.

The framework proposes dual interpretability: a clinician-facing decision trace and a patient-facing explanation. Validation should assess comprehension, usability, decisional conflict, accessibility, language, and workload. One interface or explanation model should not be assumed suitable for every population.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for testable propositions, evidence requirements, and validation criteria for precision pharmacotherapy without exclusion.

Table 2. Testable propositions, evidence requirements, and validation criteria for Precision Pharmacotherapy without Exclusion

Architecture layer or process stage	Core function	Information or material flow	Interaction with other components	Validation criterion	Potential failure mode	Human or experimental responsibility	Readiness boundary
Representation	Define evidentiary scope	Participant and provenance data	Shapes coverage and transferability	Subgroup evidence assessment [5]	Nominal diversity	Investigators and data stewards	No broad claim when material groups remain unevaluated
Assay and interpretation	Produce a bounded genomic result	Sample to variant to phenotype	Supplies dynamic-state and decision layers	Analytical accuracy and version control [13]	Missed variants or hidden ambiguity	Laboratories and curators	Uncertainty requires annotation or escalation
Dynamic state	Detect current modifiers	Medicines, disease, organ function	May alter phenotype relevance	Prospective modifier validation [15]	Stale clinical data	Clinicians and investigators	Genotype alone is insufficient when modifiers matter
Access	Establish practical usability	Referral, payment, logistics, alternatives	Constrains utility and choice	Completion, affordability, and availability [16]	Unfunded follow-up	Systems, payers, laboratories	No readiness when only advantaged groups can benefit
Communication	Support informed choice	Decision trace to patient explanation	Connects recommendation to action	Comprehension and usability [17]	Deterministic messaging	Clinicians, patients, researchers	Delivery is not informed understanding
Decision support	Deliver current guidance	Knowledge to trigger to response	Depends on governance and workflow	Fit, maintenance, uptake, auditability [22]	Alert fatigue or stale rules	Informatics and clinical teams	Activation is not equitable implementation
Monitoring and governance	Detect and correct unequal effects	Subgroup signals to corrective action	Feeds redesign or restricted use	Prespecified monitoring and response [23]	Monitoring without authority	Analysts and governance bodies	Average benefit cannot establish equity

10. Health-system implementation and resource constraints

Clinical decision support is the operational bridge between pharmacogenomic evidence and a medication decision. Its performance depends on computable knowledge, appropriate triggering, timing, interface design, maintenance, override handling, and clear ownership [22]. A correct rule may fail if it appears too late, lacks an available alternative, or cannot retrieve relevant clinical context.

Implementation is not equivalent to ordering a test. Multisite programs have used different testing models, services, information systems, professional roles, and return-of-results strategies [24]. This variation shows that the health system is part of intervention performance. A model functioning in an integrated center may not transfer to a fragmented or resource-limited setting.

A multicentre panel-based implementation study found fewer adverse drug reactions when actionable recommendations were delivered within a functioning clinical pathway [25]. The finding supports the importance of delivery and uptake but should not be generalized beyond the studied panel, populations, medicines, settings, or outcomes.

The proposed minimum-readiness domains are laboratory capability, validated interpretation, maintained knowledge, workflow integration, accessible alternatives, trained responsibility, patient communication, follow-up, subgroup monitoring, and corrective authority. Missing material domains should trigger redesign or restricted use. These are proposed criteria, not universal regulatory thresholds.

Equity metrics and predeployment evaluation

Equity evaluation requires more than average accuracy, alert acceptance, or clinical benefit. Developers must specify the groups examined, the outcome compared, the fairness concept selected, and the mechanisms

generating the data. Fairness criteria may conflict when baseline risks, labels, access, or measurement differ [26]. The framework therefore rejects a single universal equity score.

Race, ethnicity, and ancestry variables require explicit scrutiny before inclusion in a prediction rule, dose equation, or implementation pathway. Race corrections have sometimes embedded weak biological assumptions and altered access to care [27]. This does not make all ancestry information invalid; it requires construct definition, causal justification, incremental value, and external validation.

Predeployment stress tests should examine underrepresented evidence, panel mismatch, uncertain variants, transferred rules, phenoconversion, cost, geography, unavailable alternatives, proxy-based prioritization, language barriers, workflow failure, and missing subgroup outcomes. Thresholds for acceptable disparity must be justified prospectively; none can be inferred from this framework.

The framework yields testable propositions: average performance will not ensure subgroup equity; ancestry variables will add value only when explicitly justified; inaccessible alternatives will reduce practical utility; communication and workflow will mediate use; and monitoring without corrective authority will fail to prevent recurrent exclusion. These remain hypotheses.

Table 3 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for failure modes, boundary conditions, governance needs, and implementation priorities for precision pharmacotherapy without exclusion.

Table 3. Failure modes, boundary conditions, governance needs, and implementation priorities for Precision Pharmacotherapy without Exclusion

Decision scenario or design trade-off	Trigger or context	Competing objective	Evidence threshold	Uncertainty treatment	Corrective or escalation action	Expected implication	What cannot be concluded
Broad use despite unequal coverage	Acceptable aggregate performance	Scale versus subgroup confidence	External subgroup evaluation [4]	Label unresolved populations and contexts	Expand evidence, restrict claims, or defer use	Reduces silent overtransport	That diversity alone proves equal benefit
Use of ancestry or race	Variable appears predictive	Performance versus proxy risk	Construct definition and validation [27]	Record reference dependence and missingness	Remove, replace, recalibrate, or restrict	Makes variable use auditable	That every ancestry variable is valid or invalid
Negative panel result	No recognized actionable allele	Simplicity versus incomplete coverage	Demonstrated variant coverage [13]	State untested regions and residual risk	Additional testing or non-genetic management	Prevents false reassurance	That a negative result excludes all variation
Genotype–state discordance	Interactions or disease alter function	Stable genotype versus dynamic phenotype	Context-specific modifier evidence [15]	Record timing and confidence	Reassess or seek specialist input	Makes phenoconversion visible	That a dose change follows automatically
Testing or alternatives are inaccessible	Cost, geography, formulary, or referral barriers	Universal offer versus practical participation	Documented completion and accessibility [16]	Treat non-completion as a system signal	Fund, decentralize, redesign, or restrict claims	Aligns access with utility	That offering a test proves equitable access
Proxy-biased decision support	Access-dependent label drives prioritization	Efficiency versus clinical need	Audit of labels and proxies [6]	Assess missingness and measurement differences	Replace outcome, redesign, or restrict	Reduces encoded historical inequity	That every group difference is discriminatory
Subgroup drift	Performance or access changes after use	Stability versus updating	Prospective monitoring [23]	Treat drift and missing outcomes as material	Investigate, recalibrate, restrict, or suspend	Enables lifecycle correction	That monitoring alone proves safety or equity

Governance, monitoring, and corrective action

Predeployment evaluation cannot anticipate every change in population, evidence, laboratory practice, formulary, workflow, or prescribing behavior. Responsible use therefore requires monitoring for drift, unequal access, subgroup harm, alert overrides, inaccessible alternatives, delayed follow-up, and changes in the data-generating process [23].

Governance must also control how race, ethnicity, and ancestry are defined, measured, analyzed, and reported. Genomic research recommendations emphasize explicit definitions, justification, harmonization, and transparent reporting [28]. The framework extends these principles into laboratory interpretation, decision support, patient communication, and monitoring.

Corrective action should be linked to trigger–action pairs. Signals may include deteriorating subgroup performance, disproportionate non-completion, repeated uncertain interpretations, inaccessible alternatives, unexplained overrides, or new evidence changing allele function. Responses may include investigation, panel revision, recalibration, workflow redesign, restricted use, suspension, or withdrawal.

Accountability should be distributed but not diffuse. Evidence stewards, laboratories, curators, decision-support owners, clinicians, pharmacists, health-system leaders, and equity oversight bodies require defined responsibilities. Local allocation must remain consistent with law, professional scope, resources, and organizational structure.

Limitations and research priorities

The framework cannot eliminate the heterogeneity it is designed to expose. Populations differ in ancestry, linkage structure, environment, migration history, healthcare access, treatment patterns, and outcome measurement. Greater diversity improves evidence while creating more complex analytic and interpretive requirements [29]. The architecture should therefore organize decision-specific questions rather than convert populations into uniform categories.

Figure 2 presents the original conceptual synthesis for points at which exclusion can enter the pharmacogenomic pathway, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

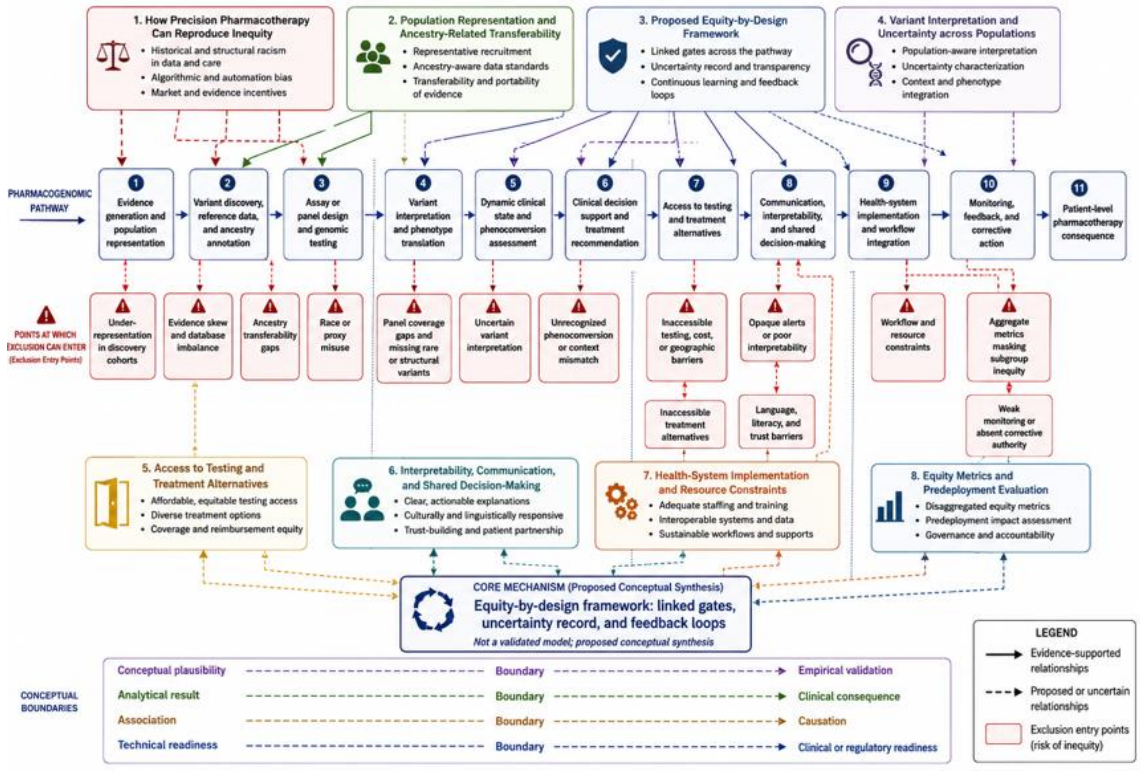

Figure 2. Points at Which Exclusion Can Enter the Pharmacogenomic Pathway.

A second limitation is the incompleteness of single-common-variant models. Rare variants, structural variants, copy-number changes, haplotypes, polygenic effects, epigenetic regulation, and dynamic non-genetic influences

may contribute to variability that current panels do not capture [30]. Greater model complexity may improve explanation while increasing data requirements and unequal-performance risks.

Validation should proceed in stages. Computational evaluation should test provenance, transportability, calibration, missingness, and subgroup performance. Analytical evaluation should assess variant detection and translation. Clinical evaluation should compare decision consequences with relevant alternatives. Implementation research should examine workflow, communication, access, resource use, and governance response.

Research priorities include globally diverse evidence generation, functional characterization of rare and structural variation, ancestry-aware but non-essentialist methods, dynamic phenoconversion models, accessible testing and alternatives, interpretable decision support, multilingual communication, and governance experiments. The framework remains conditional on the drug, gene, population, assay, health system, decision context, available alternatives, and consequences of error.

CONCLUSION

Precision pharmacotherapy without exclusion requires more than accurate genotyping or increasingly detailed prediction. The proposed Equity-by-Design Framework links representation, assay coverage, interpretation, ancestry-related transferability, phenoconversion, access, alternatives, communication, implementation, monitoring, and corrective authority across the research-to-care lifecycle. Its six gates, uncertainty record, stop-or-escalate rules, dual interpretability requirement, accessible-alternatives safeguard, equity metrics, and governance loops are conceptual constructs intended for testing and revision. The framework does not establish clinical utility, justify race-based prescribing, define universal fairness thresholds, or constitute a clinical, regulatory, or deployment standard.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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