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Pharmacogenomic Actionability Depends on the Drug, the Phenotype, and the Clinical Decision Point

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ABSTRACT

Pharmacogenomic evidence is often summarized by asking whether a gene–drug pair is actionable. That formulation is useful for cataloguing knowledge but too coarse for many prescribing decisions. The same gene can support different recommendations across drugs, a pharmacokinetic association can remain clinically nonactionable, a genotype–predicted phenotype can be altered by assay limitations or phenoconversion, and the value of genetic information can change according to whether the immediate task is drug selection, initial dosing, titration, monitoring, or avoidance. This Perspective argues that actionability should therefore be indexed to three coordinates: the drug actually being considered, the clinically current phenotype that can be defended from the available genotype and contextual information, and the decision point at which information could alter management. Evidence from antidepressants, beta-blockers, methadone, antiplatelet therapy, statins, aminoglycosides, thiopurines, and fluoropyrimidines illustrates why biological relevance, prescribing relevance, and outcome relevance should not be collapsed. Genotype-to-phenotype translation and phenoconversion further show that phenotype is an inferential and sometimes dynamic intermediate rather than a fixed synonym for genotype. The article consequently develops a proposed Drug–Phenotype–Decision view of pharmacogenomic actionability. Its purpose is not to replace existing prescribing guidelines, but to make explicit the boundaries that determine when a genomic result can reasonably change a specific pharmaceutical decision.

Keywords: Pharmacogenomics, Precision pharmacotherapy, Genotype-to-phenotype translation, Phenoconversion, Clinical decision support, Therapeutic individualization

INTRODUCTION

Pharmacogenomics has moved from the demonstration of inherited variation in drug response toward guideline-based prescribing and health-system implementation, but translation remains highly heterogeneous across genes, medicines, outcomes, and clinical settings [1]. That heterogeneity is not evidence that pharmacogenomics is intrinsically weak; it is evidence that “actionability” is being asked to carry several different meanings. In the PREPARE study, a structured multigene implementation strategy reduced clinically relevant adverse drug reactions among patients with actionable genotypes, showing that pharmacogenomic information can contribute to measurable safety gains when testing, prescribing recommendations, and workflow are linked [2]. Yet PRIME Care demonstrated a different pattern: pharmacogenomic testing clearly shifted antidepressant prescribing away from predicted drug–gene interactions, whereas the advantage in remission was modest and not persistent across

follow-up [3]. A prescribing decision can therefore change even when a downstream clinical endpoint changes less, later, or not at all.

A second problem is exposure. The prevalence of an actionable genotype in a population does not identify how often that genotype is relevant to an actual treatment decision. Hospital-based data show that clinically consequential opportunities emerge at the intersection of genotype and relevant drug prescribing, not from variant carriage alone [4]. Actionability is thus better treated as a conditional relation than as a stable property attached to a gene name. This Perspective develops that proposition by separating gene–drug evidence, genotype-to-phenotype translation, dynamic enzyme activity, and the clinical decision itself. The central claim is deliberately narrower than a universal model of precision medicine: a pharmacogenomic result becomes clinically actionable only when its evidence is specific enough to support a defined action for a particular drug, a defensible phenotype, and a relevant decision point.

Defining pharmacogenomic actionability

A practical definition of actionability must specify what clinicians are being asked to do. The 2023 CPIC guideline for serotonin reuptake inhibitor antidepressants illustrates why a broad category such as “antidepressant pharmacogenomics” is insufficient. CYP2D6, CYP2C19, and CYP2B6 evidence can support prescribing recommendations for specified drugs, whereas the evidence reviewed for SLC6A4 and HTR2A does not support their use for antidepressant prescribing [5]. The evidential state therefore differs within a single therapeutic area: a result may be biologically interesting, associated with treatment variation, or available on a test panel without reaching the threshold for a prescribing recommendation.

Drug identity also matters within a pharmacological class. The CPIC beta-blocker guideline supports CYP2D6-based recommendations for metoprolol while finding insufficient evidence for comparable prescribing recommendations across the other beta-blockers and pharmacogenes evaluated [6]. The converse problem is illustrated by methadone. CYP2B6 variation contributes to methadone pharmacokinetics, yet the available downstream evidence does not support routine genotype-based alteration of methadone prescribing [7]. These examples separate three levels that are often conflated: a gene may affect a molecular or pharmacokinetic process; that effect may or may not translate into a clinically meaningful phenotype; and even a credible phenotype may or may not justify changing therapy.

The phenotype itself is not enough to determine the action. In G6PD deficiency, medication-specific evidence leads to different risk classifications rather than a single rule that every potentially oxidant drug must be handled identically [8]. Clinical necessity, exposure, alternative treatments, and the severity of the consequence remain relevant. For this Perspective, pharmacogenomic actionability is therefore defined as a decision-indexed state: evidence must support a particular management change for a particular drug in a patient whose relevant phenotype and clinical context are sufficiently resolved. This is a proposed analytical definition, not a replacement for CPIC or other established guideline terminology.

Gene–drug evidence is not uniform

The most visible evidence against binary actionability is that established pharmacogenomic relationships produce different kinds of clinical action. CYP2C19–clopidogrel guidance can change antiplatelet selection in defined phenotype and indication contexts; statin recommendations depend on the specific statin, dose, and implicated transporter or metabolic gene; and high-risk MT-RNR1 variants primarily alter the acceptability of aminoglycoside exposure when safer alternatives are available [9–11]. These are not interchangeable manifestations of a single “positive PGx” category. They differ in mechanism, clinical consequence, reversibility, available alternatives, and the point in therapy at which genomic information can still change management.

Dose modification is similarly heterogeneous. TPMT and NUDT15 phenotypes can alter thiopurine starting-dose strategy, but genotype does not eliminate the need for subsequent clinical and laboratory titration [12]. For fluoropyrimidines, prospective DPYD-guided dose individualization supports reduced initial dosing for selected decreased-function variants, while the tested variants do not exhaust all possible DPD-related risk [13]. The relevant unit of actionability is therefore not a “dose gene” or a “selection gene.” It is the specific decision that the evidence can support at a defined moment in treatment.

This distinction matters because a pharmacogenomic relationship can fail at several different points. Evidence may be insufficient for any prescribing change; it may justify avoiding a drug but not define a dose; it may guide an initial dose while leaving maintenance dosing to observed tolerance or exposure; or it may justify a different drug only in a particular indication. Because the analytical problem is not whether each pair is simply positive or

negative, but which action becomes defensible and where that inference stops, the contrasts require a matrix that keeps observation, interpretation, alternative action, and contextual boundaries visibly separate.

Table 1. Mechanism-discrimination matrix for why gene–drug evidence does not imply a single actionability state

Decision family	Row-defining gene–drug case	What is directly established	Inference that remains bounded	Alternative clinical action	Population or clinical boundary that can change the action	Proposed article-level actionability test
Evidence boundary	CYP2D6 with metoprolol versus other evaluated beta-blockers	Actionable prescribing evidence is molecule-specific within the class	A pharmacogene associated with one class member does not confer class-wide actionability	Apply the drug-specific recommendation on rather than extrapolating across the class	Beta-blocker selected; phenotype; indication; available evidence	Does the recommendation attach to the actual molecule under consideration?
Evidence boundary	CYP2B6 with methadone	Genotype can alter pharmacokinetics	Exposure differences alone do not establish a beneficial genotype-based dose change	Continue clinically guided methadone prescribing when genotype-specific action is unsupported	Clinical outcome evidence; indication; concomitant factors	Does the phenotype change a clinical decision, or only explain exposure variability?
Drug-selection discrimination	CYP2C19 with clopidogrel	Reduced-function phenotypes affect clopidogrel activation and can support alternative therapy in defined settings	One recommendation does not automatically extend across all clopidogrel indications	Select an alternative antiplatelet strategy when the guideline-supported context applies	Indication; phenotype; competing antiplatelet options	Is the action supported for this phenotype in this therapeutic indication?
Exposure-specific safety management	SLCO1B1, ABCG2, or CYP2C9 with statins	Variant effects and recommendations differ across statins and doses	A generic statin pharmacogenomic rule is not justified	Modify statin choice or dose according to the specific gene–drug context	Statin molecule; dose; patient risk; therapeutic alternatives	Is risk interpretation specific to the prescribed statin and exposure?
Toxicity avoidance	MT-RNR1 with aminoglycosides	High-risk variants support avoidance where alternatives are feasible	Genotype does not make aminoglycoside use absolutely impossible in every clinical circumstance	Prefer a non-aminoglycoside option when clinically reasonable	Infection severity; urgency; efficacy of alternatives	Does the consequence justify changing drug choice before exposure?
Dose initialization	TPMT or NUDT15 with thiopurines	Reduced-function phenotypes support graded starting-dose modification	Genotype does not determine the complete maintenance dose	Start with phenotype-informed dosing and continue response- or toxicity-guided adjustment	Drug; phenotype; disease context; subsequent monitoring	Which part of the dosing sequence is actually informed by genotype?
Dose initialization	DPYD with fluoropyrimidines	Selected variants support prospective initial-dose reduction	A limited variant panel does not exclude all DPD-related toxicity risk	Reduce the initial dose for supported variants while retaining	Variant coverage; regimen; treatment tolerance	Is the actionable claim limited to the variants and regimen

	clinical vigilance	actually supported?
Note: The final column is a proposed synthesis used in this Perspective to test whether evidence supports a defined drug–phenotype–decision relation. It is not an externally validated scoring system.		

Genotype-to-phenotype translation

Before a clinical decision can be indexed to phenotype, genotype must be translated through an explicit functional interpretation. CYP2D6 demonstrates the problem particularly well. CPIC and the Dutch Pharmacogenetics Working Group developed consensus recommendations to standardize activity-score-to-phenotype translation because inconsistent mappings could make the same genotype appear to imply different metabolizer categories across systems [14]. Standardization improves interpretive consistency, but it does not transform phenotype assignment into a direct clinical outcome claim; drug-specific evidence is still required downstream.

The upstream genotype may also be incompletely resolved. CYP2D6 contains deletions, duplications, hybrids, and other structural configurations that can complicate allele assignment and copy-number interpretation [15]. In a large psychiatric pharmacogenomic cohort, more detailed CYP2D6 copy-number characterization and incorporation of phenoconversion information altered inferred potential actionability for subsets of tested patients [16]. The relevant inference is not that more complex testing is always clinically superior. Rather, analytical resolution can change the phenotype that enters a prescribing algorithm, so assay content is part of the actionability chain.

Methodological comparison of CYP2D6 and CYP2C19 genotyping further reinforces this point: different clinical genotyping approaches vary in coverage and practical performance [17]. Consequently, “the genotype” should not be treated as a method-free fact. A clinically useful phenotype depends on what variants and structures were assayed, how allele function was assigned, and how translation rules were applied. These steps create an interpretation boundary between molecular measurement and pharmaceutical decision making. The boundary is especially important when rare or structurally complex alleles or incomplete test coverage make an apparently precise phenotype less certain than its categorical label suggests.

Phenoconversion and dynamic enzyme activity

Even a technically correct germline genotype may not describe current enzyme activity. CYP2D6 phenoconversion provides the clearest clinical example: concomitant inhibitors can reduce functional enzyme activity such that the clinically relevant phenotype differs from the genotype-predicted phenotype [18]. This makes phenotype temporally conditional. A patient can retain the same genotype while moving into a different functional state as comedications are started, stopped, or changed.

Real-world psychiatric testing illustrates the practical importance of that distinction. Incorporating phenoconversion alongside more detailed CYP2D6 copy-number assessment can change inferred potential actionability in a subset of patients [16]. Such reclassification should not be equated with demonstrated improvement in outcomes, but it shows why a static genotype-to-phenotype label can be insufficient for decision support.

The broader interpretation advanced here is proposed: pharmacogenomic actionability may be time-dependent whenever the phenotype relevant to drug disposition or response is itself dynamic. Phenoconversion is directly established for defined drug–enzyme contexts; extending the idea to organ dysfunction, disease-state effects, treatment phase, or other modifiers requires mechanism- and drug-specific evidence rather than analogy alone. Thus, “current phenotype” should mean the best defensible functional state at the clinical decision point, not an assumption that germline genotype permanently fixes enzyme activity.

Dose selection, drug selection, and monitoring as distinct decisions

Clinical trials of genotype-guided antiplatelet therapy show why the decision point and comparator must be specified. In TAILOR-PCI, genotype-guided selection among patients undergoing PCI did not meet the prespecified primary superiority threshold for the ischemic endpoint, despite a direction of effect favoring the genotype-guided strategy [19]. That result should not be rewritten as either proof that CYP2C19 is irrelevant or proof that genotype-guided therapy is superior. It answers a particular comparative question under a particular endpoint and trial design.

POPular Genetics addressed a different clinical comparison and supported a genotype-guided strategy that balanced thrombotic protection and bleeding risk relative to routine use of more potent P2Y₁₂ inhibition after primary PCI [20]. Taken together, the trials illustrate that “drug selection” is not a single intervention. Its value

depends on what the genotype-guided arm is being compared with, which outcome is prioritized, and whether the goal is greater efficacy, lower toxicity, de-escalation, or preservation of net clinical benefit.

Dose decisions are equally divisible. Genotype can help initialize therapy for selected drugs, but precision dosing may subsequently require observed concentrations, clinical response, organ function, adherence, interacting drugs, or model-informed updating [21]. Thiopurine dosing distinguishes phenotype-informed starting dose from subsequent titration [12]. Prospective DPYD-guided fluoropyrimidine dosing similarly supports genotype-informed initialization without eliminating later clinical observation [13].

The proposed decision decomposition in this Perspective therefore separates at least four questions: Which drug should be used? What starting dose is justified? What subsequent adjustment is required as patient state and exposure become observable? What monitoring is needed because uncertainty or toxicity cannot be resolved genomically? Under this proposed view, a gene–drug association becomes actionable only to the extent that evidence answers one of these questions for the relevant phenotype and treatment context; it should not be stretched to answer the others.

Clinical consequence and therapeutic index

Pharmacogenomic actionability becomes clinically consequential only when the predicted difference matters enough to alter management. The relevant threshold is therefore not determined by genetic effect alone. A phenotype associated with a serious, difficult-to-reverse toxicity creates a different decision problem from one associated with a modest exposure shift that can be observed and corrected during therapy. The G6PD guideline illustrates this dependence on the medication-specific probability and severity of hemolysis rather than on G6PD status in isolation [8]. Similarly, high-risk MT-RNR1 variants can justify avoiding aminoglycosides when effective alternatives exist because the consequence under consideration is potentially severe ototoxicity, while urgent infection may constrain the available choice [11].

Therapeutic index adds another dimension. For thiopurines, reduced TPMT or NUDT15 function changes the safety of conventional starting doses, but subsequent management still depends on tolerance and therapeutic response [12]. DPYD-guided fluoropyrimidine dosing likewise shows why pre-treatment genotype can be most useful at a particular transition: before an initial exposure capable of producing substantial toxicity [13]. These examples do not establish a universal numerical threshold at which genetic information becomes actionable. They instead show that the evidential burden for changing therapy is inseparable from what could happen if treatment is left unchanged and from whether later observation can safely correct an imperfect initial choice.

The comparator also changes the consequence of acting. TAILOR-PCI did not meet its prespecified primary superiority threshold for genotype-guided P2Y12 selection [19], whereas POPular Genetics evaluated a different comparison and supported genotype-guided selection as a strategy for balancing thrombotic protection against bleeding associated with broader potent antiplatelet use [20]. A pharmacogenomic result can therefore be clinically useful for avoiding one type of harm without proving superiority on every efficacy endpoint.

The interpretation advanced here is proposed: therapeutic consequence acts as a decision-pressure modifier rather than as another genomic variable. Severity, reversibility, availability of alternatives, ability to monitor, and the consequences of delayed correction determine how much uncertainty can reasonably be tolerated at the decision point. These features cannot be reduced to a single therapeutic-index score because the selected evidence does not validate such a scale. They can, however, be organized as a sequence of clinical transitions, which makes clear where genomic information acts, where monitoring takes over, and where an alternative treatment interrupts the sequence.

The resulting sequence is summarized in **Table 2** because prose obscures whether pharmacogenomic information governs the same therapeutic transition in every case.

Table 2. Sequence of clinical transitions that determine whether a pharmacogenomic signal warrants action

Treatment transition	Governing clinical consequence	Trigger for changing the default course	Observable state after the transition	Monitoring requirement	Alternative action if risk remains unacceptable	Condition that can interrupt or reverse the sequence	Population or treatment boundary	Proposed article-level test
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Before drug selection	A serious exposure-related harm is avoidable by choosing another effective medicine	A sufficiently supported high-risk phenotype is known before exposure	Patient remains unexposed to the implicated drug	Confirm that the alternative remains clinically effective and appropriate	Select a therapeutically suitable nonimplicated medicine	Urgency or lack of an effective alternative can constrain avoidance	Indication, infection severity, available therapies	Does genotype change which drug should be given before exposure occurs?
Before first dose	Conventional starting exposure may be excessive for a reduced-function phenotype	Phenotype-specific dosing evidence is available before therapy	Treatment begins from an altered initial exposure	Early toxicity and response remain clinically relevant	Start lower or use a different regimen where supported	Incomplete variant coverage or changing clinical state preserves residual risk	Genotype coverage, regimen, disease setting	Does the evidence support initialization of dose , rather than permanent dose determination?
Early treatment	Initial genotype-informed dosing does not fully resolve individual exposure or response	Measured tolerance, response, concentration, or changing covariates becomes available	Patient-specific treatment information accumulates	Active reassessment is required	Titrate, pause, switch, or intensify observation according to clinical evidence	New organ dysfunction, interacting therapy, or unexpected toxicity can supersede the initial estimate	Drug, monitoring feasibility, treatment phase	Has the decision moved from genotype-informed initialization to observed-patient adjustment ?
During continuing therapy	Functional phenotype can change while germline genotype remains constant	A relevant inhibitor or other supported phenotype modifier appears	Current enzyme activity may differ from the original genotype-predicted state	Medication reconciliation and phenotype reassessment become necessary	Reconsider dose, drug, or monitoring if the current functional state changes	Removal of the modifier can restore the prior functional state	Modifier, timing, enzyme-drug relationship	Is the phenotype used for the decision still clinically current ?
When several reasonable therapies remain	Benefit and harm depend on the comparator rather than on genotype alone	Genotype identifies a treatment distinction but competing strategies remain viable	Different therapeutic trade-offs become possible	Outcomes relevant to both efficacy and toxicity must remain visible	Choose the option matching the clinical objective and evidence base	A different endpoint or comparator can alter the apparent value of acting	Indication, endpoint, comparator, therapeutic alternatives	What specific decision objective does the pharmacogenomic result improve?

Note: The sequence and article-level tests are proposed synthesis. They organize evidence-supported forms of drug selection, dose initialization, monitoring, phenotype reassessment, and comparator-dependent choice without assigning an unvalidated score or clinical threshold.

The same reasoning is difficult to represent as a simple genotype-to-prescription pathway. **Figure 1** therefore places therapeutic consequence at the central decision boundary and reconciles discordant evidence before a result is allowed to cross into a clinical action.

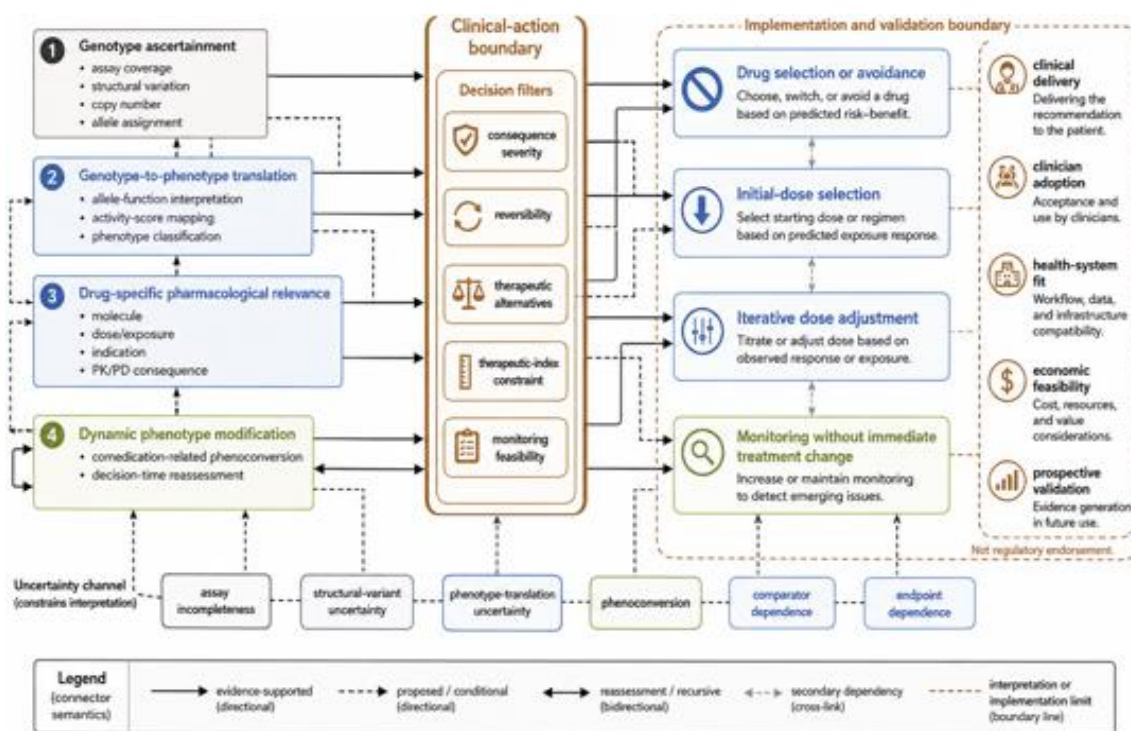


Figure 1. Where pharmacogenomic evidence crosses—or fails to cross—the clinical action boundary

A drug–phenotype–decision actionability matrix

The preceding sections support a narrower representation of actionability than the customary question of whether a gene–drug association exists. The proposed Drug–Phenotype–Decision Actionability Matrix treats actionability as the intersection of three coordinates. The first is the actual drug or exposure under consideration. The second is the phenotype that can be defended at that moment from genotype, assay coverage, translation rules, and supported contextual modifiers. The third is the clinical decision that remains open: selection, avoidance, starting dose, subsequent adjustment, or monitoring.

Each coordinate prevents a different type of overreach. The drug coordinate prevents extrapolation from metoprolol to all beta-blockers or from one statin–gene relationship to an entire class [6]. The phenotype coordinate prevents a CYP2D6 genotype category from being treated as a permanently fixed functional state when relevant inhibition can produce phenoconversion [18]. The decision coordinate prevents an exposure association such as CYP2B6–methadone from being transformed automatically into a dose recommendation [7]. It also prevents evidence supporting an initial dose from being stretched into a claim that genotype determines the complete treatment trajectory.

The matrix is intentionally not a scoring tool. It does not assign numerical weights to evidence, therapeutic index, phenotype certainty, or implementation readiness. Instead, it asks whether all three coordinates are specified strongly enough for the proposed clinical action. A relationship may therefore be actionable for drug selection but not for dose, actionable for starting dose but not maintenance dose, or informative for monitoring while insufficient to justify an immediate medication change. Model-informed precision dosing reinforces this separation because later adjustment can incorporate concentrations, response, and changing covariates that were unavailable at the initial genomic decision [21].

The framework also leaves an explicit unresolved state. If assay coverage is inadequate, phenotype translation is uncertain, the patient's current functional phenotype is altered, the comparator is unclear, or the relevant clinical endpoint has not been established, the appropriate classification is not automatically “nonactionable.” It is **action** unresolved for the specified decision. This distinction preserves potentially meaningful biology without overstating clinical utility.

Implementation and validation

A decision architecture is clinically useful only if it survives implementation. Economic evidence provides one boundary: a systematic review of pharmacogenetic testing for drugs with CPIC guidance found many favorable economic evaluations, but conclusions remained heterogeneous and dependent on drug, testing strategy,

assumptions, and health-system context [22]. Clinical evidence and economic actionability should therefore remain separate questions.

Clinical decision support introduces a second boundary. Published pharmacogenomic CDS approaches vary substantially, and useful implementation depends on presenting information to the appropriate clinician, through an appropriate channel and format, at the time the decision can still be changed [23–25]. Those implementation principles are directly compatible with the Drug–Phenotype–Decision view because a recommendation delivered after the relevant decision point may be scientifically valid but operationally inert.

Implementation metrics also require discrimination. Clinician acceptance of a pharmacogenomic alert does not necessarily correspond to the medication action that the alert intended, and adoption of genotype-guided simvastatin recommendations has not been automatic even within an established clinical pharmacogenetics program [26]. A system should therefore distinguish alert firing, alert acceptance, medication change, persistence of that change, and relevant patient outcomes rather than treating any single interface event as proof of successful actionability.

Transfer across institutions is another unresolved problem. Multisite evaluation of antidepressant pharmacogenomic implementation demonstrates substantial variation in institutional processes and determinants [27]. A decade of PREDICT experience likewise shows the importance of structured genomic data, durable informatics, and end-to-end decision support for maintaining pharmacogenomic knowledge in clinical workflow [28]. These reports support the need for implementation infrastructure but do not prospectively validate the proposed matrix.

Validation of the framework should consequently occur at several levels. Analytical validation must establish that the relevant genotype is reliably captured. Interpretive validation must show that genotype-to-phenotype translation remains appropriate for the locus and current clinical context. Decision validation must test whether the proposed action is superior, noninferior, safer, more efficient, or otherwise advantageous against the clinically relevant comparator for the specified endpoint. Implementation validation must then determine whether the information is delivered and used correctly in the intended setting. Until those levels are tested prospectively, the matrix should be regarded as an organizing device for specifying pharmacogenomic claims, not as a validated clinical algorithm.

CONCLUSION

Pharmacogenomic actionability is more precise when framed as a property of a drug–phenotype–decision relation rather than of a gene or gene–drug pair alone. Drug identity determines whether a molecular or pharmacokinetic effect is relevant to the therapy being considered. Phenotype translation determines whether the patient's current functional state is sufficiently resolved. The clinical decision point determines what the evidence is actually being asked to change.

This view also clarifies why apparently discordant pharmacogenomic findings can coexist. Biological relevance can be present without prescribing utility; an established prescribing recommendation can affect drug selection without fixing dose; an initial dose recommendation can coexist with later phenotype-, exposure-, or response-guided adjustment; and a scientifically defensible recommendation can still fail to become useful if it reaches clinicians at the wrong time or through an ineffective workflow.

The proposed Drug–Phenotype–Decision Actionability Matrix is therefore a framework for disciplined inference, not a validated scoring system or universal treatment algorithm. Its value lies in forcing every actionability claim to identify the drug, defend the phenotype, specify the clinical decision, and expose the evidential and implementation boundaries that remain. Pharmacogenomics becomes most clinically interpretable when those boundaries are made explicit rather than compressed into a binary label.

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