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# *When Does Pharmacogenomics Improve Routine Therapeutics? A Realist Review of Contexts, Mechanisms, Implementation Conditions, and Patient Outcomes*

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## ABSTRACT

*Pharmacogenomics is increasingly used to guide medication selection and dose individualization, yet routine implementation produces inconsistent clinical and patient outcomes. This realist review examines how pharmacogenomic programmes operate, for whom, and under which conditions they generate therapeutic benefit, limited uptake, or unintended consequences. The initial programme theory proposed that benefit becomes more likely when a clinically consequential drug–gene relationship is translated into a timely, understandable, and feasible recommendation; incorporated into prescribing workflows; supported by laboratory, informatics, professional, and reimbursement infrastructure; and accepted by clinicians and patients. Evidence was identified through iterative, purposive searching and appraised for explanatory relevance, richness, and rigour. Contexts, programme resources, actor responses, proposed mechanisms, outcomes, negative cases, and rival explanations were compared across therapeutic and implementation settings. The synthesis indicates that testing does not act independently. Pharmacogenomic resources must reduce uncertainty, create perceived actionability, strengthen prescriber confidence, support patient trust, and coordinate responsibility before they can alter treatment. Even then, prescribing change produces patient benefit only when it materially affects a credible pathway to toxicity prevention or improved response. Delayed results, ambiguous recommendations, alert fatigue, phenoconversion, uncertain ancestry transferability, weak reimbursement, and unequal access can interrupt this pathway. The refined programme theory therefore treats pharmacogenomic utility as an emergent property of evidence validity, therapeutic consequence, timing, interpretation, behavioural response, organizational capability, population relevance, and access. Pharmacogenomics may improve routine therapeutics when these conditions align, but implementation activity alone cannot establish clinical utility.*

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

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## INTRODUCTION

Pharmacogenomics uses inherited genomic variation to inform medication selection, dosing, or monitoring. Its rationale is that genetic differences can alter drug metabolism, transport, target interaction, immune response, and susceptibility to adverse effects. However, genomic information becomes therapeutically relevant only when it is

connected to a clinical decision that can be changed. An analytically accurate genotype or statistically credible association is therefore not equivalent to improved treatment. Utility depends on whether the result applies to the drug, population, and decision; is available at the appropriate time; and supports a feasible alternative action [1].

Asking whether pharmacogenomics "works" often treats testing as a uniform intervention. In practice, pre-emptive panel testing differs from reactive single-gene testing, transparent guideline recommendations differ from proprietary algorithms, and interruptive alerts differ from pharmacist-mediated consultation. Therapeutic consequences also vary, from prevention of severe toxicity to modest changes in medication selection. The evidence therefore supports heterogeneous readiness across gene–drug pairs, populations, outcomes, and healthcare systems rather than universal implementation or rejection [2].

Patient-outcome evidence demonstrates the potential of coordinated pharmacogenomic care. A multicentre programme combining pre-emptive panel testing with prescribing guidance and implementation support reduced clinically relevant adverse drug reactions in its evaluated configuration [3]. The intervention nevertheless included interpretation, workflow integration, professional education, and mechanisms for returning information during prescribing. Its outcome cannot be attributed to genotype generation alone.

A realist review is appropriate because it asks how, why, for whom, and under what conditions a complex programme generates outcomes. Realist appraisal emphasizes explanatory relevance, richness, and rigour rather than relying only on a conventional evidence hierarchy [4]. This review develops and refines a programme theory explaining when pharmacogenomic implementation improves routine therapeutics. It separates resources from mechanisms, implementation from patient benefit, genotype from current functional phenotype, and technical availability from clinical utility.

*Realist-review questions and initial programme theory*

The review addressed six questions: What initial theory explains how pharmacogenomic implementation is expected to improve treatment? In which clinical, organizational, technological, population, and patient contexts does it operate? Which resources trigger changes in reasoning, behaviour, or system response? Which proximal and patient-level outcomes follow? Why do similar programmes succeed, fail, or produce mixed effects? How should the programme theory be refined after comparing positive and negative cases?

Pharmacogenomics was treated as a family of programmes rather than a single intervention. A genotype, report, guideline, decision-support alert, specialist consultation, or patient explanation was classified as a programme resource. A mechanism was defined as the reasoning or response activated when an actor or system encountered that resource, including reduced uncertainty, perceived actionability, confidence, trust, coordinated responsibility, or alert fatigue [4].

The initial programme theory proposed that benefit becomes more likely when the drug–gene relationship is sufficiently robust for the intended decision, the result is available before or during prescribing, and the recommendation identifies an understandable and feasible action. Persistent records, accessible guidance, specialist support, appropriate communication, and organizational ownership may then activate clinician confidence, patient acceptance, and coordinated action. Failure becomes more likely when results are delayed, ambiguous, nontransferable, poorly integrated, or disconnected from a patient-relevant outcome pathway. This theory is provisional and explanatory rather than a validated clinical rule.

*Search, selection, appraisal, and evidence extraction*

Evidence identification followed an iterative and purposive realist strategy. Searches combined pharmacogenomics and precision-pharmacotherapy concepts with genotype-guided treatment, dose individualization, clinical utility, adverse reactions, phenoconversion, ancestry transferability, decision support, patient perspectives, reimbursement, and equity. Reference-list examination and citation tracing were used to identify evidence that could support, challenge, or refine emerging explanations.

Eligible sources informed at least one component of the programme theory: context, implementation resource, actor response, proposed mechanism, proximal outcome, patient outcome, negative case, or boundary condition. Primary trials and implementation studies were prioritized for prescribing and patient-outcome claims. Reviews, tutorials, consensus papers, and methodological studies were used where appropriate for terminology, implementation architecture, or realist reasoning. Sources that mentioned pharmacogenomics without contributing to a specific explanatory proposition were excluded.

Appraisal considered relevance to programme theory, richness of contextual and explanatory detail, and rigour sufficient for the assigned inference [4]. Evidence was not converted into a numerical quality score. Extraction

distinguished contexts, resources, actor or system responses, proposed mechanisms, outcomes, positive or negative cases, and rival explanations. Synthesis used cross-case comparison, identification of demi-regularities, and retroductive reasoning. Mechanisms remained provisional where mediation was not directly tested.

*Clinical and organizational contexts*

Pharmacogenomic programmes operate within systems whose laboratory capacity, information architecture, professional roles, financing, and governance differ. The Ubiquitous Pharmacogenomics initiative showed that cross-country implementation requires coordinated testing, standardized interpretation, education, decision support, and adaptation to national healthcare structures [5]. A guideline may reduce uncertainty where clinicians trust it and can act, yet remain ineffective when turnaround, reimbursement, treatment availability, or prescribing authority is misaligned.

Role clarity is similarly important. A multidisciplinary point-of-care model connected laboratory medicine, pharmacy, clinical pharmacology, genetics, informatics, prescribing teams, and institutional governance [6]. This configuration may strengthen confidence and coordinated responsibility. Conversely, genomic information may remain unused when laboratories regard prescribing as outside their role, clinicians view interpretation as a specialist task, and technical teams deploy alerts without clinical ownership.

Long-term implementation experience indicates that decision support is an end-to-end knowledge system rather than a single alert. The PREDICT programme connected patient identification, testing, interpretation, phenotype assignment, result storage, prescribing logic, recommendations, maintenance, and consultation [7]. Failure at any stage can interrupt use. A correct result may arrive too late, remain unstructured, fail to trigger guidance, or generate an alert without a practical action.

Large-scale pre-emptive sequencing can make results available before prescribing. The RIGHT 10K programme demonstrated that genomic variation could be generated, interpreted, returned, and incorporated across a large academic centre [8]. However, scale creates requirements for durable storage, current interpretation, patient communication, and governance. Such feasibility does not establish patient benefit, economic value, or transferability to less-resourced systems.

*Mechanisms influencing prescriber and patient behaviour*

Pharmacogenomic information changes treatment only when it changes clinical reasoning. Point-of-care decision support has altered prescribing toward recommended actions, showing that a timely result can make a drug–gene interaction more salient and reduce interpretation burden [9]. Prescribing change remains a proximal outcome, not proof of improved safety or effectiveness.

Adherence depends on recommendation design and institutional credibility. Clinicians were more likely to follow alerts that provided specific, actionable recommendations within an established programme [10]. These resources may activate perceived actionability and confidence. The same result may be ignored when the recommendation is vague, conflicts with other priorities, or proposes an unavailable treatment.

Patient mechanisms differ from prescriber mechanisms. Participants receiving pre-emptive results reported variable understanding and perceptions of future relevance [11]. Communication may support engagement when results are explained as durable resources for future prescribing, but technical language and probabilistic implications may create confusion.

Trust, representation, privacy, and perceived benefit also influence acceptance. Underrepresented patients expressed interest in personalized medication while raising concerns about data use, discrimination, evidence relevance, and unequal access [12]. These findings support trust and representational legitimacy as mechanisms, but stated preferences do not establish adherence or therapeutic benefit.

**Table 1** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for initial programme theory, contexts, mechanisms, and outcome categories for when does pharmacogenomics improve routine therapeutics?

**Table 1.** Initial programme theory, contexts, mechanisms, and outcome categories for When Does Pharmacogenomics Improve Routine Therapeutics ?

| Evidence domain or review construct | Review question | Eligible evidence type | Key extraction fields | Appraisal or relevance criterion | Synthesis role | Main limitation | Interpretation boundary |
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|---|---|---|---|---|---|---|---|
| **Drug–gene actionability** | Under which clinical conditions can a genomic result change treatment? | Clinical trials, prospective safety studies, implementation studies | Drug, gene, decision, timing, alternative action, patient outcome | Direct connection between the result and a feasible clinical action | Tests the proposition that actionability precedes benefit | Actionable guidance may still be ignored or arrive too late | Biological association is not equivalent to clinical utility [1] |
| **Initial programme theory** | Which resources are expected to trigger which actor or system responses? | Realist-method sources and explanatory clinical evidence | Context, resource, actor, response, mechanism, outcome, rival explanation | Explanatory relevance, richness, and rigour | Structures theory testing and refinement | Mechanisms are often inferred rather than directly measured | A test, report, or alert is a resource rather than a mechanism [4] |
| **Organizational readiness** | Which institutional conditions make results usable? | Multisite implementation studies, programme descriptions, informatics tutorials | Laboratory capacity, role allocation, governance, result storage, specialist support | Sufficient operational detail to identify dependencies | Explains variation between settings | Successful academic programmes may not transfer to other systems | Feasibility does not establish patient benefit [6] |
| **Prescriber reasoning** | How does information change medication decisions? | Alert-level studies, prescribing analyses, qualitative studies | Alert timing, recommendation specificity, acceptance, override, reason for response | Direct observation of clinician action or reported reasoning | Identifies confidence, actionability, and uncertainty reduction as proposed mechanisms | Behavioural change may be produced by institutional authority rather than genomic evidence alone | Prescribing change is a proximal outcome, not proof of improved therapeutics [9] |
| **Alert adherence** | When do clinicians follow pharmacogenomic recommendations? | Clinical decision-support evaluations | Alert type, recommended action, adherence, workflow context | Clear link between alert configuration and clinician response | Tests whether specificity and institutional endorsement support uptake | Single-system findings may overestimate wider adherence | High alert adherence cannot be generalized across platforms or institutions [10] |
| **Patient understanding** | How do patients interpret returned results? | Surveys, interviews, participant-perspective studies | Perceived understanding, relevance, recall, communication preferences | Direct patient-reported explanatory data | Examines comprehension as a mechanism supporting future use | Self-report may not reflect objective understanding | Result disclosure does not ensure comprehension or future action [11] |
| **Patient trust and equity** | Why might patients accept or resist testing? | Studies involving underrepresented populations and equity-focused analyses | Trust, privacy, representation, perceived benefit, access concerns | Attention to population context and alternative explanations | Adds trust and representational legitimacy to the programme theory | Attitudes do not establish actual medication use or outcomes | Personalized framing does not remove structural inequity [12] |
| **Decision-support configuration** | Which technical features connect results with action? | Informatics reviews, tutorials, implementation studies | Structured result, phenotype translation, alert timing, recommendation, maintenance | Adequate description of the full information pathway | Explains how technical resources reduce or increase cognitive burden | Interface performance may be inseparable from local workflow | Technical integration is necessary in some settings but is not sufficient for clinical utility [7] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Outcome categories** | Which outcomes indicate implementation, behaviour, or therapeutic consequence? | Trials, observational studies, implementation evaluations | Result availability, prescribing change, adverse reaction, effectiveness, access, equity | Outcome must match the claimed stage in the programme pathway | Prevents conflation of deployment with benefit | Distal outcomes are less commonly and less consistently measured | Implementation activity, clinician response, and patient benefit must remain analytically distinct [3] |

*Testing models and decision-support configurations*

Reactive testing is initiated for a current prescribing decision and may increase immediate relevance but delay treatment. Pre-emptive testing creates reusable information before prescribing but requires durable storage and updating. Single-gene testing offers a focused answer, whereas panels create a broader resource with greater interpretation and governance demands.

Standardized phenotype terminology can reduce ambiguity across laboratories, guidelines, records, and clinical services [13]. Shared terminology supports consistent communication, but it cannot correct differences in allele coverage, phenotype assignment, or population relevance.

Decision support must present results at the right time and with a clear action. Effective configurations require structured data, concise recommendations, accessible evidence, feasible alternatives, and knowledge maintenance [14]. Excessive interruption can produce fatigue, whereas passive information may never influence care.

Genotype may not represent current metabolic function. Co-medications can inhibit or induce enzymes and create phenoconversion, making genotype-only interpretation misleading [15]. Context-aware guidance may improve relevance, although adherence, organ function, disease, and unrecorded medicines remain alternative explanations.

Native electronic-record genomic modules can support persistent results and automated guidance. Implementation within the Epic Genomics Module illustrates how structured results, phenotype logic, alerts, and recommendations can be linked [16]. Performance nevertheless depends on local governance, laboratory interfaces, maintenance, and clinician trust.

*Context–mechanism–outcome configurations*

The GIFT trial represents a positive configuration in which genotype-guided warfarin dosing was used during a high-risk initiation period after hip or knee arthroplasty. Guidance may have reduced dosing uncertainty and improved anticoagulation control, contributing to the evaluated composite outcome [17]. The finding is bounded by the population, algorithm, comparator, and perioperative pathway.

In primary percutaneous coronary intervention, rapid CYP2C19 testing guided P2Y12 inhibitor selection. The POPular Genetics strategy maintained thrombotic protection while reducing bleeding relative to more intensive treatment [18]. Rapid testing, a clear treatment contrast, and clinician confidence in de-escalation were integral to this configuration.

TAILOR-PCI used related CYP2C19-guided reasoning but did not produce an unequivocally positive primary result [19]. Event rates, timing, adherence, comparator choice, and endpoint design may have influenced the result. Nonsignificance is neither proof of no effect nor evidence of established benefit.

PRIME Care showed that pharmacogenomic testing reduced prescribing of medications with predicted drug–gene interactions, but symptom-remission effects were limited and not sustained [20]. The configuration distinguishes process improvement from durable patient benefit.

Cardiovascular trials differed in population, timing, comparator strategy, action contrast, and endpoints and should not be treated as replications of one uniform intervention [17–19]. Benefit appears more plausible when testing occurs during a consequential decision, identifies a clear action, and materially changes a pathway to harm or benefit.

*Conditions associated with therapeutic benefit*

Therapeutic benefit is most credible when a variant identifies serious preventable risk and a feasible adjustment exists. DPYD-guided fluoropyrimidine dosing linked genotype information to reduced starting doses for patients at increased toxicity risk [21]. The clear exposure–toxicity pathway supports a bounded safety proposition.

Multisite CYP2C19-guided antiplatelet implementation suggests that timely results can support treatment selection after percutaneous coronary intervention [22]. Because the evidence was observational, site practices, adherence, patient selection, and clinician behaviour remain possible explanations.

Psychiatric pharmacogenomics presents a less consistent configuration. In the GUIDED trial, selected response and remission outcomes improved although the primary symptom endpoint was not clearly improved [23]. Endpoint choice therefore substantially affects interpretation.

Another randomized study reported improved outcomes with targeted pharmacogenetic guidance in depression and anxiety [24]. However, assay specificity, algorithm transparency, sponsorship, and population differences constrain generalization. Psychiatric trials report mixed patterns across medication selection, symptoms, response, and remission [20, 23, 24].

**Table 2** organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for context–mechanism–outcome configurations supported by the selected evidence.

**Table 2**. Context–mechanism–outcome configurations supported by the selected evidence.

| Method, platform, or evidence category | Representative application | Reported strength | Validation context | Generalization concern | Contradictory evidence | Evidence gap | Review interpretation |
|---|---|---|---|---|---|---|---|
| **Pre-emptive multigene panel** | Multicountry prevention of adverse drug reactions | Patient-relevant safety outcome within a structured implementation programme | Coordinated testing, guidance, education, and workflow integration | The programme effect cannot be attributed to genotyping alone | Benefit may be reduced where treatment alternatives or implementation support are absent | Which programme components mediate benefit | A positive configuration in which genomic and implementation resources acted together [3] |
| **Genotype-guided warfarin dosing** | Perioperative anticoagulation initiation | Randomized evidence of improvement in the evaluated composite outcome | Defined surgical population and dosing algorithm | Limited transferability to other indications and care pathways | Different anticoagulation contexts may have lower baseline risk or weaker action contrast | Comparative evidence outside the studied setting | Benefit was context specific rather than a class-wide warfarin effect [17] |
| **Rapid CYP2C19-guided de-escalation** | Primary PCI antiplatelet selection | Noninferior thrombotic protection with lower bleeding exposure | Rapid testing and clear treatment alternatives | Dependent on comparator strategy and result timing | Other CYP2C19-guided strategies have not produced identical primary outcomes | Which decision window and comparator maximize utility | Result timing and action contrast appear central to the CMO pathway [18] |
| **CYP2C19-guided escalation** | Post-PCI treatment selection | Biologically coherent strategy with an inconclusive primary result | Randomized cardiovascular trial | Event rates, adherence, timing, and endpoint structure affect interpretation | A related de-escalation strategy produced a more favorable configuration | Identification of mediating implementation factors | A negative or conditional case that narrows universal benefit claims [19] |
| **Pragmatic psychiatric PGx** | Depression medication selection | Reduced prescribing of medications with predicted drug–gene interactions | Routine clinical care | Process improvement did not yield persistent remission benefit | Positive psychiatric trials used different assays and study designs | Durable patient outcomes and independent algorithm evaluation | Prescribing improvement and therapeutic benefit are separate outcomes [20] |
| **DPYD-guided dose** | Fluoropyrimidine toxicity prevention | Prospective evidence supporting | Pre-treatment testing linked | Does not generalize to variants or | Intensive monitoring may | Optimization across ancestry | Strong benefit configuration where risk, |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **individualizatio n** | | reduced severe toxicity | to a clear dose modification | drugs with weaker exposure–toxicity relationships | contribute to observed safety | groups and uncommon variants | action, and outcome pathway are closely linked [21] |
| **Multisite CYP2C19 implementation** | Antiplatelet therapy after PCI | Favorable observed outcomes when results informed treatment | Real-world multisite implementatio n | Residual confounding and site differences | Randomized evidence remains mixed across strategies | Prospective evaluation of implementatio n fidelity | Supports timely use but cannot isolate genotype guidance from implementatio n context [22] |
| **Combinatorial psychiatric testing** | Major depressive disorder | Improvement in selected secondary outcomes | Patient- and rater-blinded randomized design | Primary and secondary outcomes differ in interpretive weight | Pragmatic evidence found limited durable remission benefit | Transparent comparison of algorithms and clinically meaningful endpoints | Evidence suggests conditional rather than uniform benefit [23] |
| **Targeted psychiatric PGx** | Depression and anxiety treatment | Positive randomized clinical outcome | Specific assay, population, and treatment setting | Commercial and study-specific factors constrain transferability | Other psychiatric trials show mixed effects | Independent replication and assay-to-assay comparison | Positive evidence remains configuration specific [24] |
| **Actionable point-of-care CDS** | Prescribing recommendatio n during medication ordering | Demonstrated prescribing change | Integrated institutional clinical workflow | Prescribing change may not affect a patient-relevant pathway | Alert burden or weak recommendation s may lead to override | Direct linkage between alert response and patient outcomes | CDS supports action only when it activates confidence and feasible response [9] |

*Conditions associated with failure or limited uptake*

Payer uncertainty about utility, eligible populations, budget impact, and pre-emptive testing can restrict coverage even where testing is clinically available [25]. This may reduce institutional investment and concentrate access in well-resourced systems.

International evidence identifies recurring barriers involving professional knowledge, reimbursement, guidelines, laboratory resources, and organizational infrastructure [26]. These factors can reinforce one another: limited demand weakens investment, while weak infrastructure limits experience and confidence.

Poor decision-support design can inhibit use. Ambiguous, poorly timed, or excessively disruptive alerts may trigger confusion, resistance, or fatigue [27]. A recommendation that ignores patient context or offers no practical alternative may appear irrelevant despite credible gene–drug evidence.

Testing remains uneven across drugs and populations in managed care [28]. Utilization patterns cannot identify whether low use reflects absent indication, weak coverage, limited knowledge, patient preference, or evidence uncertainty. Technical availability therefore does not ensure routine implementation.

*Refined programme theory*

Population representation modifies evidence validity. Limited ancestral diversity restricts knowledge of allele frequencies, variants, and phenotype relationships and can reduce confidence in transferability [29]. Representation is therefore both an evidentiary and equity condition.

Functional phenotype is also dynamic. CYP2D6 alleles and interacting medicines can jointly alter metabolic activity, producing phenoconversion [30]. The relevant context is the patient's current medication environment, not genotype alone.

Polygenic prediction illustrates a broader transferability hazard. Scores developed predominantly in European-ancestry datasets may perform less reliably in underrepresented populations and widen disparities [31]. Polygenic scores are not equivalent to pharmacogenomic recommendations, but they demonstrate that genomic utility depends on population validation.

Race should not substitute for measured genetic variation, ancestry, environment, or social context. Equity-focused analysis warns that racial categories can conceal heterogeneity and reproduce structural assumptions [32]. Trust may also decline when programmes essentialize race or overlook unequal access.

The refined programme theory proposes that benefit requires sufficient alignment among evidence validity, population relevance, therapeutic consequence, timing, dynamic phenotype, decision-support quality, prescriber reasoning, patient trust, organizational capability, and access. These conditions are neither individually sufficient nor stable across settings.

**Figure 1** presents the original conceptual synthesis for context–mechanism–outcome configurations for pharmacogenomic implementation, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

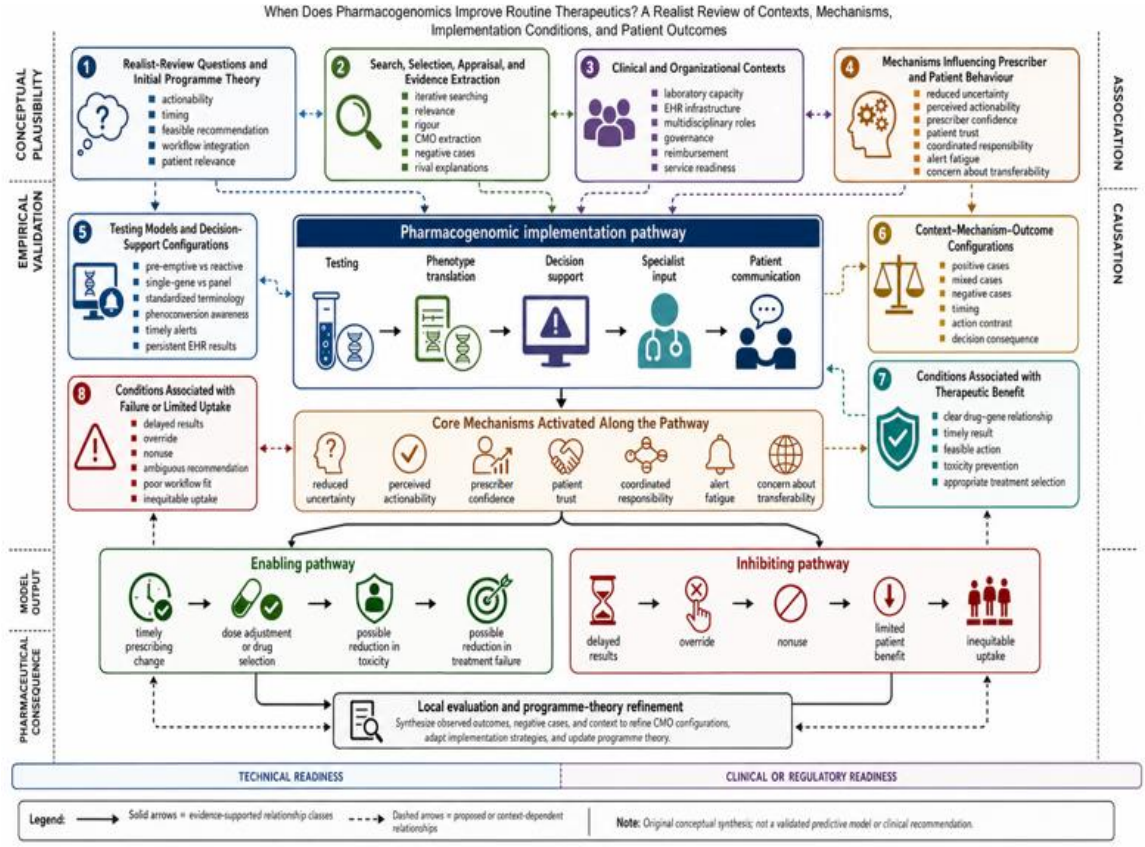


**Figure 1.** Context–Mechanism–Outcome Configurations for Pharmacogenomic Implementation.

The figure is an original conceptual synthesis developed for "When Does Pharmacogenomics Improve Routine Therapeutics? A Realist Review of Contexts, Mechanisms, Implementation Conditions, and Patient Outcomes." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

*Implementation implications and evidence gaps*

Economic evidence is configuration dependent. Cardiovascular cost-effectiveness studies vary according to test cost, baseline risk, treatment effect, uptake, and care-pathway assumptions [33]. Favorable modeling may support organizational confidence but does not establish realized savings elsewhere.

Implementation capability has increased through guidelines, electronic records, laboratory methods, and institutional experience. Reimbursement, interoperability, education, evidence expectations, scalability, and responsibility nevertheless remain uneven [34]. Progress therefore reflects partial barrier erosion rather than completed readiness.

International guideline infrastructure can reduce interpretive uncertainty. The Clinical Pharmacogenetics Implementation Consortium supports evidence evaluation, terminology, and accessible recommendations [35].

Guideline availability, however, does not establish local affordability, population validity, feasibility, or clinical utility.

Future studies should specify the complete programme: decision, population, timing, assay, phenotype translation, co-medication assessment, recommendation, interface, professional ownership, patient communication, treatment action, and outcome pathway. Negative cases, diverse populations, phenoconversion, override reasons, trust, access, and durable patient outcomes require greater attention.

## CONCLUSION

Pharmacogenomics improves routine therapeutics not simply when a genetic association exists, but when clinically relevant evidence is converted into a timely, understandable, trusted, equitable, and feasible treatment action. Benefit emerges from configurations linking therapeutic consequence, result timing, dynamic phenotype, decision support, prescriber reasoning, patient acceptance, organizational capability, and access. Positive cases are most persuasive when a clear action prevents a serious and plausible harm. Limited outcomes commonly arise when implementation changes prescribing without materially changing the patient-level outcome pathway. The refined programme theory therefore provides an explanatory framework for local evaluation and adaptation, not a validated predictive model, universal recommendation, regulatory determination, or deployment-ready system.

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