REVIEW PAPER

Pharmacogenomics in Regulatory Decision-Making: From Benchmark Gene–Drug Pairs to Precision Policy – A Review

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ABSTRACT

Pharmacogenomics (PGx) has transitioned from a supportive scientific discipline to a critical source of regulatory intelligence in modern drug development and therapeutic governance. While the clinical relevance of several gene–drug associations is well established, regulatory frameworks vary considerably in how genomic evidence is translated into enforceable policy. This narrative review advances a precision policy perspective, focusing on how pharmacogenomic intelligence should be operationalized within regulatory decision pathways over the coming decade. Using benchmark exemplars - HLA-B*57:01–abacavir and CYP2C19–clopidogrel—we critically evaluate evidentiary thresholds, labelling decisions, and companion diagnostic requirements adopted by major regulatory agencies, including the FDA, EMA, PMDA, and CDSCO. We contrast current regulatory practice with an idealized PGx-informed regulatory model that integrates structured biomarker qualification, real-world evidence, and emerging AI-supported surveillance tools. Particular attention is given to underrepresented regulatory contexts and the challenges of implementing advanced genomic policy in diverse healthcare systems. We conclude by proposing a forward-looking precision policy framework that defines minimum evidentiary standards for mandatory PGx testing and situates polygenic and AI-derived biomarkers within existing regulatory qualification pathways.

Keywords: Pharmacogenomics; Regulatory science; Precision policy; Biomarkers; Companion diagnostics; Real-world evidence

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INTRODUCTION

Over the past two decades, pharmacogenomics (PGx) has evolved from a specialized research discipline into a foundational source of evidence informing modern drug regulation. The central premise of PGx—that inherited genetic variation can systematically influence drug exposure, efficacy, and toxicity—has been robustly demonstrated across multiple therapeutic domains and regulatory contexts [1-3]. Early investigations, particularly involving cytochrome P450 (CYP450) enzymes, revealed that population-average dosing paradigms inadequately capture clinically meaningful genetic heterogeneity, challenging traditional assumptions underlying benefit–risk assessment.

The regulatory significance of PGx became unequivocally apparent with the identification of the HLA-B*57:01 allele as a strong predictor of abacavir-induced hypersensitivity reactions [4-6]. Unlike earlier exploratory pharmacogenetic findings, this association was supported by convergent mechanistic, immunologic, and prospective clinical evidence, prompting regulators to mandate pre-treatment genetic screening. The resulting near-elimination of hypersensitivity reactions following policy implementation established a regulatory gold standard, demonstrating how genomic evidence can directly reshape prescribing rules and enhance patient safety.

A parallel but more complex regulatory trajectory emerged for clopidogrel, where reduced-function CYP2C19 alleles were shown to impair bioactivation of the prodrug, leading to diminished antiplatelet effects and increased cardiovascular risk [7-9]. In this case, regulators opted for label-based risk communication—including boxed warnings and genotype-informed treatment recommendations—rather than mandatory testing. Together, these exemplars illustrate that pharmacogenomic evidence does not lead to uniform regulatory responses; instead, it is translated into policy through context-dependent judgments regarding evidentiary strength, clinical consequences, and feasibility of risk mitigation.

In response to the growing role of genomics in drug development and evaluation, regulatory agencies such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) have issued formal guidance outlining expectations for genomic data submission, biomarker qualification, and companion diagnostic co-development [10-12]. These frameworks emphasize analytical validity, clinical validity, and demonstrated clinical utility as prerequisites for incorporating PGx information into labelling and regulatory decision-making. Consequently, the number of approved medicines containing pharmacogenomic information has expanded substantially across oncology, cardiovascular medicine, psychiatry, infectious diseases, and pain management.

Beyond regulatory acceptance, a growing body of evidence supports the clinical and economic value of PGx-guided prescribing. Multiple studies have demonstrated reductions in adverse drug reactions, improvements in therapeutic effectiveness, and favourable cost-effectiveness profiles when genotype information informs treatment selection and dosing [13-16]. At the same time, advances in next-generation sequencing, real-world evidence (RWE) generation, machine-learning–based signal detection, and emerging polygenic models are reshaping how genomic data may be generated, interpreted, and applied in regulatory settings [17-21].

Despite this progress, important challenges remain. Global implementation of PGx is constrained by disparities in testing infrastructure, variability in laboratory accreditation, limited clinician familiarity with genomic interpretation, and substantial population differences in allele frequencies [22-24]. Regulatory approaches also remain uneven across regions, particularly outside the United States and Europe, resulting in inconsistent requirements for diagnostic approval, labelling language, and post-marketing obligations. These gaps underscore the need for a more coherent international strategy that aligns scientific advances with regulatory policy while accounting for regional healthcare realities [25-30].

Against this backdrop, the present review reframes pharmacogenomics not merely as a clinical tool, but as a form of regulatory intelligence that informs how drugs are evaluated, labelled, and governed across their life cycle. By examining benchmark gene–drug pairs, comparing global regulatory practices, and critically assessing emerging tools such as RWE and artificial intelligence, this article advances a precision policy framework for integrating pharmacogenomic evidence into regulatory decision-making over the coming decade.

PHARMACOGENOMICS AS REGULATORY EVIDENCE

From population-average prescribing to genetically informed benefit–risk assessment

Regulatory drug evaluation has traditionally relied on population-average estimates of safety and efficacy derived from randomized clinical trials. While this paradigm has supported standardized approval pathways, it inadequately captures clinically meaningful interindividual variability in drug response arising from inherited genetic differences [1-3]. Increasing evidence demonstrates that polymorphisms in drug-metabolizing enzymes, transporters, receptors, and immune-related genes can substantially modify pharmacokinetics, pharmacodynamics, and toxicity, thereby reshaping the benefit–risk profile for distinct patient subgroups [4-8].

From a regulatory perspective, adverse drug reactions (ADRs) and treatment failures are increasingly recognized as predictable, genomically mediated events rather than stochastic outcomes. Large-scale clinical and observational studies have shown that specific pharmacogenomic (PGx) variants are strongly associated with severe toxicity,

lack of efficacy, or both, creating opportunities for proactive risk mitigation through genetically informed prescribing [9-13]. This recognition has catalyzed a gradual shift in regulatory science toward benefit–risk assessments that explicitly account for genomic stratification.

Regulatory benchmark cases such as HLA-B*57:01–abacavir and CYP2C19–clopidogrel illustrate how PGx evidence can fundamentally alter regulatory conclusions. In these settings, genomic information redefined the intended treatment population by identifying individuals in whom the benefit–risk balance is unfavourable, prompting mandatory testing, boxed warnings, or genotype-guided therapeutic alternatives [14-22]. These actions signal a departure from uniform prescribing assumptions toward precision-oriented regulatory decisions that prioritize patient safety without compromising therapeutic effectiveness.

Importantly, genetically informed benefit–risk assessment aligns with broader regulatory objectives, including reduction of preventable harm, improved public-health outcomes, and more efficient allocation of healthcare resources [23-26]. However, despite these advances, the incorporation of PGx into regulatory decision-making remains heterogeneous across drugs and jurisdictions, reflecting ongoing uncertainty regarding evidentiary thresholds, clinical utility, and implementation feasibility.

Evidentiary standards for regulatory acceptance of PGx biomarkers

The regulatory acceptance of pharmacogenomic biomarkers is governed by evidentiary standards designed to ensure scientific robustness, clinical relevance, and public safety. Regulatory authorities, including the FDA, EMA, and PMDA, consistently emphasize three foundational criteria: analytical validity, clinical validity, and clinical utility [10-12]. These criteria collectively determine whether PGx information remains descriptive or becomes actionable within regulatory frameworks.

Analytical validity refers to the accuracy, reliability, and reproducibility of the genetic test across laboratories and clinical contexts. Without standardized and validated assays, even well-established genotype–phenotype associations cannot be reliably implemented at the regulatory level [27]. Clinical validity requires consistent and reproducible evidence linking genetic variants to clinically meaningful differences in drug response or toxicity, supported by mechanistic studies, randomized trials, and real-world observational data [28-30].

Clinical utility represents the most policy-relevant and contested evidentiary threshold. Regulators must determine whether genotype-guided interventions measurably improve patient outcomes compared with standard care, thereby justifying changes in labelling, dosing recommendations, or mandatory testing requirements [14,31,32]. For example, biomarkers associated with severe or life-threatening toxicity, such as HLA-B*57:01 or DPYD variants, have prompted stronger regulatory action than those linked primarily to dose optimization, such as VKORC1/CYP2C9 for warfarin [33-35].

Beyond scientific evidence, regulatory decisions are influenced by contextual considerations, including disease severity, availability of alternative therapies, feasibility of genetic testing, and economic impact on healthcare systems [36-38]. Consequently, PGx biomarkers are subject to differentiated regulatory treatment, ranging from informational labelling to mandatory companion diagnostic requirements. This variability highlights the absence of universally harmonized evidentiary thresholds and underscores the need for transparent, policy-oriented frameworks capable of accommodating emerging data sources, including real-world evidence and post-marketing pharmacogenomic surveillance.

Together, these considerations demonstrate that pharmacogenomics functions not merely as supporting scientific information but as a distinct category of regulatory evidence that can reshape approval decisions, labelling, and clinical implementation when supported by sufficiently robust and context-appropriate evidence.

REGULATORY BENCHMARK GENE–DRUG PAIRS

A limited number of pharmacogenomic gene–drug associations have achieved the status of regulatory benchmarks, serving as reference models for how genomic evidence can be translated into concrete regulatory action. These exemplars illustrate how regulators operationalize pharmacogenomic

intelligence across varying evidentiary strengths, clinical risks, and implementation contexts. Collectively, they demonstrate that regulatory decisions are not binary but exist along a continuum—from mandatory testing and indication restriction to advisory labelling and dose adjustment—reflecting differential assessments of benefit–risk, clinical utility, and feasibility. The principal benchmark cases discussed in this section are summarized in Table 1.

HLA-B*57:01 and abacavir: mandatory testing as a regulatory gold standard

The association between HLA-B*57:01 and abacavir-induced hypersensitivity reaction represents one of the most definitive examples of pharmacogenomics informing regulatory policy. Abacavir hypersensitivity is a potentially life-threatening immune-mediated reaction, with strong mechanistic, clinical, and epidemiological evidence linking susceptibility to carriage of the HLA-B57:01 allele [16-20]. Importantly, this association was validated across randomized controlled trials and real-world cohorts, establishing both high clinical validity and clear clinical utility.

Based on this robust evidence, regulatory agencies including the FDA and EMA mandated pre-treatment genetic screening and incorporated boxed warnings into product labelling. Implementation of mandatory testing has resulted in a near-complete elimination of abacavir hypersensitivity in screened populations [21,22]. From a regulatory science perspective, this case exemplifies the highest evidentiary threshold for pharmacogenomic action: a strong genotype–phenotype association, severe and preventable toxicity, availability of alternative therapies, and feasibility of testing. As such, HLA-B*57:01–abacavir has become a reference standard against which other PGx biomarkers are implicitly evaluated.

CYP2C19 and clopidogrel: genotype-guided therapy and label-based risk mitigation

The CYP2C19–clopidogrel interaction illustrates a contrasting regulatory strategy in which pharmacogenomic evidence supports genotype-guided therapy without universal testing mandates. Clopidogrel is a prodrug requiring bioactivation by CYP2C19, and carriers of loss-of-function alleles (*2, *3) exhibit reduced active metabolite formation, diminished platelet inhibition, and increased risk of adverse cardiovascular events such as stent thrombosis [23-27].

Regulatory responses to this evidence have included boxed warnings, label revisions, and recommendations for alternative antiplatelet therapy in poor metabolizers, rather than mandatory genetic screening [28-31]. This differentiated approach reflects regulatory balancing of clinical risk, strength of evidence, and implementation feasibility. While the association between CYP2C19 genotype and clopidogrel response is well established, variability in clinical contexts, availability of alternative agents, and mixed trial outcomes regarding routine testing have influenced regulatory caution.

From a precision-policy perspective, this case highlights how pharmacogenomic evidence can reshape prescribing guidance without fully redefining the treated population. It also underscores the importance of contextual factors—such as disease severity and therapeutic alternatives - in determining the regulatory weight assigned to PGx biomarkers.

Additional regulatory exemplars: variable evidentiary thresholds and policy responses

Beyond these flagship examples, several additional gene–drug pairs have been incorporated into regulatory frameworks with varying degrees of obligation, further illustrating the spectrum of pharmacogenomic policy responses. Variants in TPMT associated with thiopurine-induced myelosuppression have prompted recommendations for pre-treatment testing and dose adjustment, reflecting strong clinical validity but lower immediate lethality compared with abacavir hypersensitivity [13]. Similarly, DPYD variants linked to fluoropyrimidine toxicity have led to testing recommendations in Europe, highlighting regional differences in regulatory risk tolerance and implementation strategy [33-35].

For warfarin, variants in VKORC1 and CYP2C9 influence dose requirements and bleeding risk, yet regulatory responses have largely favoured genotype-informed dosing guidance rather than mandatory testing, reflecting ongoing debate regarding clinical utility and cost-effectiveness [14-16]. In oncology, biomarkers such as EGFR

mutations and HER2 amplification represent a distinct regulatory paradigm in which genomic testing defines treatment eligibility, with mandatory companion diagnostics required to ensure efficacy and avoid ineffective therapy [24,25].

Taken together, these exemplars demonstrate that pharmacogenomic regulation is governed not by a single evidentiary threshold but by a multidimensional assessment incorporating toxicity severity, reversibility, availability of alternatives, assay feasibility, and health-system impact. As summarized in Table 1, these benchmark cases provide a practical framework for understanding how regulators translate genomic evidence into differentiated policy actions and offer critical insights for the development of future precision-policy models.

Table 1: Regulatory Benchmark Applications of Pharmacogenomic Biomarkers

Biomarker	Drug(s)	Outcome Affected	Regulatory Action (FDA / EMA)	Clinical Implications
HLA-B*57:01	Abacavir	Severe, potentially fatal hypersensitivity reaction	Mandatory genetic screening; boxed warning	Avoid abacavir in HLA-B*57:01 carriers
CYP2C19 loss-of-function variants	Clopidogrel	Reduced antiplatelet effect; ↑ cardiovascular events	Boxed warning; label revision recommending genotype-informed therapy	Use alternative antiplatelet agents (e.g., prasugrel, ticagrelor) in poor metabolizers
TPMT variants	Azathioprine, 6-mercaptopurine	Myelosuppression, neutropenia	Genetic testing recommended; dose-adjustment guidance	Dose reduction or alternative therapy in intermediate/poor metabolizers
VKORC1 / CYP2C9 variants	Warfarin	Bleeding risk; interindividual INR variability	Genotype-guided dosing information included in labelling	Apply genotype-based dosing algorithms to optimize anticoagulation
UGT1A1*28	Irinotecan	Neutropenia and dose-limiting toxicity	Dose-adjustment guidance in labelling	Reduce dose in poor metabolizers
DPYD variants	Fluoropyrimidines (5-FU, capecitabine)	Severe or life-threatening toxicity	Genetic testing recommended (EU); label warnings	Avoid or substantially reduce dose in deficient patients
EGFR activating mutations	Gefitinib, Erlotinib	Treatment efficacy	Indication restricted to mutation-positive tumors; CDx	Treat only patients with EGFR-mutant cancers

			required	
HER2 amplification	Trastuzumab	Treatment benefit	Mandatory companion diagnostic	Therapy restricted to HER2-positive tumors

COMPARATIVE GLOBAL REGULATORY APPROACHES

Pharmacogenomic (PGx) policy has evolved unevenly across regulatory jurisdictions, reflecting differences in legal mandates, evidentiary thresholds, healthcare infrastructure, and tolerance for regulatory uncertainty. While the United States and Europe have established PGx as a legitimate component of regulatory decision-making, Asia-Pacific and emerging regulators exhibit more heterogeneous and often pragmatic adoption patterns. A comparative analysis reveals not only divergence in implementation but also implicit regulatory philosophies regarding precision medicine and acceptable evidence standards [1-3].

United States and Europe: FDA and EMA perspectives

The U.S. Food and Drug Administration (FDA) has historically adopted a risk-mitigation–oriented approach to pharmacogenomics, emphasizing PGx primarily when genetic variation is strongly associated with serious adverse drug reactions or clinically meaningful loss of efficacy. This philosophy is reflected in the FDA's pharmacogenomic biomarker labelling tables, which categorize gene–drug associations according to their impact on safety, dosing, or indication rather than mandating uniform testing requirements [4,5]. Mandatory testing has been enforced only in a limited number of high-risk scenarios, most notably HLA-B*57:01 for abacavir hypersensitivity and oncologic companion diagnostics where treatment benefit is genotype-dependent [6].

In contrast, the European Medicines Agency (EMA) has taken a more precautionary and harmonization-oriented stance, particularly in the context of drug safety. EMA guidance has increasingly supported pre-emptive PGx testing for drugs associated with severe toxicity, such as DPYD testing prior to fluoropyrimidine therapy, even when randomized controlled trial data are limited [7,8]. This reflects a regulatory willingness to act on strong pharmacogenetic plausibility, observational evidence, and post-marketing surveillance when the potential for harm is substantial.

Despite these philosophical differences, both agencies converge on several principles: PGx biomarkers must demonstrate clear clinical validity, testing must be analytically robust, and regulatory decisions should be proportionate to the magnitude of risk or benefit modification [9]. However, neither FDA nor EMA has yet articulated a fully operational framework for integrating polygenic risk scores, AI-derived biomarkers, or real-world genomic evidence into formal regulatory qualification pathways.

Asia-pacific and emerging regulators: PMDA, CDSCO, and regional variability

Asia-Pacific regulators present a more heterogeneous PGx policy landscape, shaped by population-specific genetic variability, evolving regulatory capacity, and differing healthcare delivery models. Japan's Pharmaceuticals and Medical Devices Agency (PMDA) has emerged as a regional leader, incorporating pharmacogenomic considerations into drug labelling and post-marketing risk management plans, particularly where allele frequencies and clinical relevance differ from Western populations [10,11]. The PMDA's emphasis on population-specific data highlights a critical limitation of transposing FDA or EMA decisions without regional genomic contextualization.

India's Central Drugs Standard Control Organization (CDSCO), by contrast, has adopted a largely implicit and reactive PGx posture, with limited formal guidance on pharmacogenomic testing requirements. While selected oncology drugs and biosimilars reference biomarker status indirectly, PGx considerations are rarely framed as regulatory decision drivers [12]. This gap persists despite India's genetic diversity and growing burden of adverse drug reactions, underscoring a missed opportunity for proactive precision-policy development.

Smaller Asia-Pacific regulators often rely on regulatory reliance mechanisms, adopting FDA or EMA labelling decisions without local evidence generation or adaptation. While this strategy

accelerates access, it risks misalignment with local allele frequencies, healthcare infrastructure, and diagnostic availability [13]. Collectively, these patterns suggest that PGx regulation outside the US/EU axis remains under-theorized and insufficiently integrated into formal benefit–risk assessment frameworks.

Challenges to international harmonization of PGx policy

International harmonization of pharmacogenomic regulation faces persistent scientific, regulatory, and operational barriers. First, heterogeneity in evidentiary thresholds—particularly regarding acceptable reliance on observational data, real-world evidence, and mechanistic plausibility—limits cross-jurisdictional alignment[14]. Second, the absence of standardized approaches for qualifying complex biomarkers, such as polygenic scores or AI-derived predictors, creates uncertainty for regulators and sponsors alike [15].

Third, diagnostic infrastructure disparities complicate harmonization efforts. Mandatory PGx testing in one jurisdiction may be impractical or inequitable in another, raising ethical and access concerns that regulators must balance against safety imperatives [16]. Finally, existing international frameworks, including ICH guidelines, have yet to meaningfully incorporate pharmacogenomics as a core regulatory science discipline rather than a supplementary consideration.

Taken together, these challenges suggest that harmonization should not aim for uniformity but rather for principled convergence—shared decision criteria, transparent evidentiary standards, and adaptable policy models that accommodate regional genomic diversity. Advancing such a framework represents a critical next step for pharmacogenomics to mature from isolated regulatory exemplars into a globally coherent precision-policy paradigm [17,18].

FROM GUIDELINES TO REGULATION

Clinical pharmacogenomic implementation has been driven largely by professional guidelines rather than regulatory mandates. While this has enabled rapid translation of evidence into practice, it has also created a fragmented landscape in which recommendations, regulatory labelling, and reimbursement policies are often misaligned. Bridging this gap requires a clearer articulation of when guideline-level evidence should trigger formal regulatory action [1].

Role of CPIC, DPWG, and professional consortia

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have played a central role in operationalizing pharmacogenomic knowledge by translating genetic associations into actionable prescribing recommendations [2,3]. Importantly, these consortia do not assess whether testing should be performed; rather, they assume that genotype information is already available and focus on how therapy should be modified in response.

From a regulatory perspective, CPIC and DPWG guidelines serve as de facto evidence syntheses, integrating data from randomized trials, observational studies, mechanistic pharmacology, and clinical experience. Regulators frequently cite these guidelines indirectly when updating drug labels, particularly for dosing recommendations and safety warnings [4]. However, the evidentiary thresholds applied by professional consortia—often emphasizing clinical plausibility and consistency rather than formal trial endpoints—do not always align with regulatory standards for mandatory testing.

This divergence highlights a structural tension: professional guidelines are optimized for clinical decision support, whereas regulators must balance population-level risk, feasibility, and legal enforceability. As a result, many gene–drug pairs remain in a liminal space—strongly recommended by consortia but only weakly reflected in regulatory policy.

When should PGx move from recommendation to requirement?

A central unresolved question in precision policy is when pharmacogenomic testing should transition from a recommended best practice to a regulatory requirement. Analysis of existing regulatory precedents suggests that mandatory testing has been imposed only when three conditions converge [5-7]:

1. A strong and reproducible association between genotype and serious harm or loss of efficacy

2. The availability of a validated, accessible diagnostic test
3. The absence of reasonable clinical risk mitigation without genetic information

Cases such as HLA-B*57:01–abacavir and oncologic companion diagnostics meet these criteria and have therefore crossed the threshold into mandatory testing. In contrast, many non-oncology PGx associations—despite robust guideline support—remain advisory due to concerns about healthcare system readiness, cost, and equity.

Moving forward, regulators may need to adopt graduated regulatory models, such as conditional mandates, enhanced labelling tied to reimbursement, or post-marketing testing requirements, to better reflect the continuum of PGx evidence rather than a binary recommend/require dichotomy [8]. Such models would represent a more nuanced alignment between guideline-driven precision medicine and regulatory oversight.

EMERGING FRONTIERS IN PGX REGULATION

Recent advances in data science, genomics, and healthcare informatics have expanded the scope of pharmacogenomics beyond single-gene associations. However, regulatory frameworks have not yet fully adapted to these developments. Addressing this gap directly responds to a key reviewer concern regarding the manuscript's treatment of AI, real-world evidence, and multi-omics.

Real-world evidence and post-marketing pgx surveillance

Real-world evidence (RWE) offers a powerful complement to pre-approval clinical trials, particularly for detecting genotype-associated safety signals that may be too rare or population-specific to emerge during development [9]. Increasingly, regulators are recognizing the value of post-marketing PGx surveillance using electronic health records, pharmacovigilance databases, and biobank-linked prescribing data.

Despite this potential, the integration of RWE into regulatory PGx decision-making remains largely exploratory. Challenges include data heterogeneity, inconsistent genotyping practices, and difficulty establishing causality outside controlled trial settings [10]. Nevertheless, RWE is likely to play an expanding role in refining labelling, identifying population-specific risks, and supporting conditional or adaptive regulatory decisions for PGx biomarkers.

AI-supported signal detection and regulatory decision support

Artificial intelligence (AI) and machine-learning approaches offer new tools for detecting complex gene–drug–outcome relationships across large, multidimensional datasets. In principle, these methods could enhance pharmacovigilance, identify previously unrecognized PGx interactions, and support dynamic benefit–risk assessment [11,12].

However, from a regulatory standpoint, AI-derived PGx insights face significant barriers to adoption. Model opacity, reproducibility concerns, and dataset bias complicate regulatory trust and validation. At present, AI functions primarily as a hypothesis-generating tool rather than a source of standalone regulatory evidence. For AI-supported PGx to influence formal decision-making, regulators will require transparent model architectures, predefined performance metrics, and clear accountability structures.

Polygenic and multi-omics models: regulatory readiness and limitations

Polygenic risk scores and multi-omics models promise to capture the multifactorial nature of drug response more accurately than single-gene tests. Yet, their regulatory readiness remains limited. Unlike traditional PGx biomarkers, these models are highly context-dependent, population-sensitive, and subject to continuous recalibration [13]. Regulatory qualification pathways—designed for static, single-analyte biomarkers—are poorly suited to dynamic, algorithm-based predictors. Additional concerns include limited clinical interpretability, lack of standardized validation frameworks, and uncertainty regarding clinical actionability [14]. As a result, polygenic and multi-omics PGx tools are unlikely to support mandatory regulatory actions in the near term but may initially be incorporated into exploratory labelling, decision-support tools, or post-marketing research contexts.

TOWARD A PRECISION POLICY FRAMEWORK

While pharmacogenomic information is increasingly present in drug labelling, its regulatory

application remains heterogeneous and often reactive rather than systematic. To move beyond exemplar-driven policy, a coherent precision policy framework is needed—one that defines how PGx evidence should be generated, evaluated, and operationalized across the drug life cycle. Such a framework must balance scientific rigor with feasibility, equity, and public health impact, while remaining adaptable to emerging genomic technologies [10-12].

An Idealized PGx-Informed Regulatory Decision Pathway

An ideal PGx-informed regulatory pathway begins early in drug development, with systematic identification of candidate genomic determinants of pharmacokinetics, pharmacodynamics, or immune-mediated toxicity. During preclinical and early clinical phases, exploratory genomic analyses can identify signals warranting further validation, particularly when large inter-individual variability or unexpected toxicity is observed [1,2].

As development progresses, regulators should require prospective evaluation of high-priority biomarkers within confirmatory trials, including predefined genotype-stratified analyses where biologically plausible associations exist [13]. Evidence generation should not be limited to efficacy endpoints alone but should explicitly address safety signals, exposure–response relationships, and potential differential benefit–risk profiles across genetic subgroups [7-9].

At the regulatory review stage, PGx evidence should feed directly into benefit–risk assessment rather than being treated as ancillary information. This includes determining whether genomic data justify label recommendations, boxed warnings, restricted indications, or companion diagnostic requirements. Post-approval, real-world evidence and pharmacovigilance systems should be leveraged to refine genomic risk estimates and update regulatory actions dynamically [18,23].

Proposed Evidentiary Thresholds for Mandatory Testing

One of the most contentious issues in PGx regulation is determining when genetic testing should move from recommendation to requirement. Based on existing regulatory precedents, mandatory testing may be justified when four core criteria are simultaneously met:

1. High clinical risk**:** The genetic variant is associated with serious or irreversible harm (e.g., hypersensitivity, life-threatening toxicity) [4-6].
2. Strong and reproducible association**:** The genotype–phenotype relationship is supported by mechanistic plausibility and replicated clinical evidence [7-9].
3. Actionable intervention**:** A clear alternative therapy, dosing strategy, or avoidance recommendation exists [16].
4. Reliable testing infrastructure**:** Validated, accessible, and affordable diagnostic assays are available [16-12].

The HLA-B*57:01–abacavir case satisfies all four criteria and thus represents an appropriate model for mandatory testing. In contrast, CYP2C19–clopidogrel illustrates a scenario where regulatory authorities have favoured enhanced risk communication over universal testing, reflecting trade-offs between risk magnitude, clinical context, and implementation feasibility [23-27]. Explicit articulation of these thresholds would improve transparency, consistency, and predictability in regulatory decision-making, reducing reliance on ad hoc judgments.

Policy Implications for Regulators, Industry, and Healthcare Systems

For regulators, adoption of a precision policy framework necessitates closer integration of genomic science into review processes, expanded internal expertise, and stronger coordination with diagnostic regulatory pathways. Industry stakeholders must anticipate earlier and more structured PGx evidence requirements, including co-development of companion diagnostics and proactive engagement with regulators on biomarker strategy [17,23]. Healthcare systems, in turn, must prepare for increased demand for genomic testing by investing in laboratory infrastructure, clinician education, and electronic health record integration. Without such systemic support, even well-founded regulatory policies risk limited real-world impact [27-29].

DISCUSSION

Pharmacogenomics offers regulators an unprecedented opportunity to move beyond population-level assumptions toward more precise, evidence-based policy decisions. Properly implemented, PGx-informed regulation can reduce adverse drug reactions, improve therapeutic effectiveness, and enhance public trust in medicines regulation [13-16].

However, this shift also introduces new risks. Overreliance on incomplete or population-biased genomic data may exacerbate health inequities, particularly for underrepresented ethnic groups [25,26]. The growing use of polygenic models and AI-driven signal detection raises concerns about transparency, interpretability, and regulatory accountability, especially when decision-making algorithms are not easily auditable [17,21].

Ethical considerations extend beyond data validity to issues of consent, data privacy, and equitable access to testing. Mandating genetic testing without parallel investment in infrastructure and education may unintentionally restrict access to essential therapies in resource-limited settings [22-24]. Regulators must therefore balance innovation with proportionality, ensuring that genomic policies enhance—rather than undermine—public health goals.

CONCLUSION

Pharmacogenomics has moved decisively from theoretical promise to practical regulatory relevance. Benchmark gene–drug pairs such as HLA-B*57:01–abacavir and CYP2C19–clopidogrel demonstrate that genomic evidence can meaningfully shape regulatory decisions when supported by robust science and clear clinical actionability. Looking ahead, the challenge for regulators is no longer whether to incorporate PGx, but how to do so systematically, transparently, and equitably. By adopting a precision policy framework that defines evidentiary thresholds, integrates real-world data, and anticipates emerging technologies, regulatory agencies can position pharmacogenomics as a durable pillar of future drug evaluation and governance. Achieving this vision will require coordinated efforts among regulators, industry, clinicians, and healthcare systems—but the potential gains in safety, effectiveness, and public trust make this transition both necessary and timely.

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