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# CLINICAL PHARMACOLOGY OF PERSONALIZED DRUG THERAPY: CURRENT APPROACHES AND FUTURE PERSPECTIVES

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**Abstract.**

Personalized drug therapy seeks to optimize medication selection and dosing by integrating patient-specific determinants of pharmacokinetics, pharmacodynamics, efficacy and toxicity. This structured literature-based review summarizes current clinical pharmacology approaches that support individualized treatment and evaluates their practical convergence. A targeted review of international peer-reviewed literature and major pharmacogenetic guidance was performed, emphasizing pharmacogenomics, therapeutic drug monitoring (TDM), model-informed precision dosing (MIPD), organ-function-based dose adjustment, biomarkers, drug-interaction assessment and clinical decision support. Evidence synthesis shows that clinically actionable personalization is strongest when a measurable source of variability is linked to a specific prescribing action. Pharmacogenetic guidance is established for several high-impact gene-drug pairs, while TDM and MIPD are particularly valuable for medicines with narrow therapeutic indices or marked exposure variability. Multimodal approaches that combine genotype, phenotype, laboratory data and longitudinal response provide a more robust basis for dose adaptation than any single data stream. Important barriers include unequal access to testing, population diversity, data interoperability, model validation and clinician workflow. The future of personalized pharmacotherapy will likely depend on validated decision-support systems that integrate pharmacogenomics, real-time monitoring and explainable predictive models while retaining clinician oversight.

**Keywords:** personalized medicine; clinical pharmacology; pharmacogenomics; therapeutic drug monitoring; model-informed precision dosing; biomarkers; clinical decision support.

## 1. INTRODUCTION

Interindividual variability in drug response is a central problem in clinical pharmacology. Patients receiving the same nominal dose may experience insufficient efficacy, excessive toxicity or substantially different drug exposure because of variation in genetics, age, body size, organ function, disease state, concomitant medicines, adherence and environmental factors. Precision medicine reframes this variability as clinically useful

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information: rather than treating the population mean as the optimal choice for every patient, clinicians seek to identify the variables that can predict response and convert them into an actionable therapeutic plan (1,2).

Clinical pharmacology is particularly well positioned to operationalize personalized medicine because it links drug disposition, target response and patient characteristics. The modern framework extends beyond pharmacogenomics. It includes conventional pharmacokinetic and pharmacodynamic principles, renal and hepatic dose adjustment, therapeutic drug monitoring (TDM), disease and safety biomarkers, pharmacogenetic testing, population pharmacokinetic models, model-informed precision dosing (MIPD) and electronic clinical decision support (CDS). These tools are complementary: genotype may help estimate a patient's initial metabolic capacity, whereas measured concentrations and clinical response provide dynamic information after treatment has begun (3,4).

Pharmacogenomics is one of the most visible components of individualized treatment. The Clinical Pharmacogenetics Implementation Consortium (CPIC) develops evidence-based guidance for how available genetic results can be used to modify therapy. Gene-drug examples include CYP2C19 and clopidogrel, CYP2C9/VKORC1 and warfarin, CYP3A5 and tacrolimus, DPYD and fluoropyrimidines, TPMT/NUDT15 and thiopurines, and CYP2D6/CYP2C19 with selected antidepressants (3,5-10). Importantly, genetic information does not replace conventional clinical assessment. Regulatory and guideline sources emphasize that genotype is one determinant among many and that treatment decisions must incorporate indication, comorbidity, co-medication, laboratory monitoring and patient preference.

TDM represents a second major pillar of personalization. Drug concentrations can reveal whether the observed exposure is consistent with the intended target and can help distinguish pharmacokinetic variability from nonadherence, drug interactions or disease-related changes (11). MIPD expands this concept by combining population models, individual covariates and observed concentrations to estimate a patient-specific dose more efficiently than trial-and-error adjustment alone (12). Recent developments add machine learning, biosensors and richer electronic health-record data, creating the possibility of continuous or near-continuous dose adaptation (12,13).

The objective of this article is to synthesize current approaches to personalized drug therapy from a clinical pharmacology perspective, identify situations in which personalization is most clinically actionable, and discuss future directions for integrating genomics, TDM, quantitative modeling and digital decision support into routine pharmacotherapy.

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## 2. MATERIALS AND METHODS

A structured narrative review design was used. International peer-reviewed publications and professional guidance relevant to personalized pharmacotherapy were prioritized. The evidence base included reviews, implementation studies, consensus recommendations and CPIC guidelines published mainly from 2014 through 2026, supplemented by landmark clinical pharmacology literature. Search concepts included personalized or precision pharmacotherapy, pharmacogenomics, therapeutic drug monitoring, model-informed precision dosing, pharmacokinetic-pharmacodynamic modeling, clinical decision support, biomarkers and drug-gene interactions.

Sources were selected when they met at least one of the following criteria: (i) provided clinically actionable prescribing recommendations; (ii) evaluated implementation of personalized therapy; (iii) described validated TDM or MIPD principles; or (iv) addressed emerging digital approaches relevant to clinical pharmacology. The review was organized around four domains: baseline patient stratification, initial drug/dose selection, treatment monitoring and adaptive dose modification. Because this article is a literature-based synthesis rather than an interventional clinical study, no new patient-level data were generated and no inferential statistics were performed.

For qualitative synthesis, each approach was assessed according to its clinical input, the mechanism through which it reduces uncertainty, typical use cases, and key implementation limitations. Examples were selected to illustrate established or guideline-supported applications rather than to provide a comprehensive list of every known biomarker or gene-drug association.

## 3. RESULTS

### *3.1. Core components of personalized pharmacotherapy*

The evidence synthesis identified six recurring clinical pharmacology components: pharmacogenomics, TDM, organ-function-based adjustment, disease or safety biomarkers, systematic evaluation of drug interactions, and quantitative dose prediction with MIPD/CDS. Their value depends on whether the information changes a concrete therapeutic decision. A genetic result is most useful when it predicts a clinically meaningful difference in metabolism, efficacy or toxicity and when an alternative dose or drug is available. Similarly, a drug concentration is most useful when a target exposure range or exposure-response relationship is sufficiently characterized.

The PREPARE implementation study demonstrated the feasibility of panel-based pharmacogenetic prescribing across multiple European healthcare settings and provided

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important evidence that pre-emptive pharmacogenetics can be integrated across hospitals, community health centers and pharmacies (7). At the same time, commentators and later implementation literature emphasize that benefit is not uniform for all medicines; the strongest cases remain gene-drug pairs with reproducible biology, clinically important outcomes and clear prescribing recommendations.

**Table 1. Principal clinical pharmacology tools for personalized drug therapy**

| Approach | Primary input | Clinical purpose | Representative use | Main limitation |
|---|---|---|---|---|
| Pharmacogenomics | Inherited variants affecting metabolism, transport, target or immune risk | Select drug or starting dose before exposure | Clopidogrel-CYP2C19; thiopurines-TPMT/NUDT15 | Variant interpretation, ancestry representation, access |
| Therapeutic drug monitoring | Measured drug or active-metabolite concentration | Adjust dose using observed exposure | Tacrolimus and other narrow-therapeutic-index drugs | Sampling time, assay access, target uncertainty |
| Organ-function adjustment | Renal/hepatic function, age, body size | Reduce or increase dose/interval | Renally cleared anti-infectives and anticoagulants | Dynamic physiology, imperfect surrogate markers |
| Biomarker-guided therapy | Molecular or physiologic marker of disease/response | Select therapy or assess pharmacodynamic effect | Oncology biomarkers; toxicity markers | Assay standardization, temporal change |
| Drug-interaction assessment | Co-medications, inhibitors/inducers, diet | Avoid exposure changes or therapeutic failure | CYP-mediated interactions; QT-risk combinations | Polypharmacy and alert fatigue |
| MIPD / clinical decision support | Population model + covariates + | Predict individualized dose and | Immunosuppression, anti-infectives, | Model validation, workflow |

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| Approach | Primary input | Clinical purpose | Representative use | Main limitation |
|---|---|---|---|---|
| | measured concentrations | update it over time | oncology | integration, governance |

The combined use of these tools is important because genetic and non-genetic determinants interact. For example, a genotype-predicted metabolizer phenotype can be functionally modified by a potent enzyme inhibitor, while acute kidney or liver dysfunction can rapidly change exposure even when genotype is constant. Therefore, personalization should be treated as an iterative process rather than a single pre-treatment test (1,12).

### *3.2. Clinically actionable pharmacogenomic examples*

Selected gene-drug pairs illustrate different mechanisms of actionability. CYP2C19 loss-of-function alleles can reduce formation of the active clopidogrel metabolite; CPIC guidance therefore recommends alternative antiplatelet therapy for relevant intermediate or poor metabolizers in high-risk cardiovascular settings when an appropriate alternative is available (5). CYP3A5 expression alters tacrolimus dose-normalized trough concentrations and can inform the initial dose, although concentration monitoring remains necessary after transplantation (9). TPMT and NUDT15 decreased-function variants predict excessive thiopurine toxicity and support genotype-guided starting-dose modification (10). DPYD variants can identify patients at increased risk of severe fluoropyrimidine toxicity and have become an important focus of genotype-based cancer pharmacotherapy (8).

**Table 2. Selected pharmacogenomic examples relevant to personalized prescribing**

| Drug/class | Gene(s) | Mechanism | Clinical implication | Personalized action |
|---|---|---|---|---|
| Clopidogrel | CYP2C19 | Bioactivation of prodrug | Reduced active metabolite in loss-of-function phenotypes | Consider genotype-guided antiplatelet selection (5) |
| Warfarin | CYP2C9, VKORC1, CYP4F2 | Metabolism and pharmacodynamic sensitivity | Variation in dose requirement and bleeding | Use validated pharmacogenetic dosing algorithms when results are |

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| Drug/class | Gene(s) | Mechanism | Clinical implication | Personalized action |
|---|---|---|---|---|
| | | | risk | available (6) |
| Tacrolimus | CYP3A5 | Drug metabolism | Expressers generally require higher dose to reach target exposure | Use genotype to inform starting dose; continue TDM (9) |
| Fluoropyrimidines | DPYD | Drug catabolism | Reduced DPD function increases exposure and severe toxicity risk | Genotype/phenotype-guided dose reduction or alternative therapy (8) |
| Thiopurines | TPMT, NUDT15 | Inactivation of active thiopurine metabolites | Reduced function increases myelosuppression risk | Lower starting dose or avoid full-dose therapy in high-risk phenotypes (10) |
| Serotonin reuptake inhibitors | CYP2D6, CYP2C19, CYP2B6 | Antidepressant metabolism | Altered exposure for selected drugs | Adjust drug or dose for supported gene-drug pairs (14) |

### *3.3. Therapeutic drug monitoring and model-informed precision dosing*

TDM individualizes treatment using measured concentrations rather than predicted metabolism alone. It is especially useful when pharmacokinetic variability is large, exposure is associated with efficacy or toxicity, and clinical endpoints alone respond too slowly to guide dosing. Classic examples include immunosuppressants, selected anti-infectives, antiepileptics and other narrow-therapeutic-index medicines. TDM is also a practical bridge between population evidence and an individual patient's observed pharmacokinetics (11).

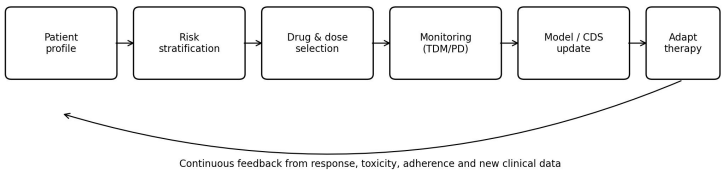
MIPD extends TDM by using mathematical models to estimate individual pharmacokinetic parameters and simulate doses likely to achieve a predefined exposure target. Modern MIPD platforms can incorporate demographics, organ function, genotype, laboratory measurements and prior concentrations, then update predictions as new

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observations become available. Recent reviews highlight growing applications in infectious disease, transplantation, oncology and inflammatory disorders, while emphasizing the need for model qualification, prospective validation and workflow-compatible software (12,15).

Machine learning may complement pharmacometric models by identifying nonlinear relationships in large multidimensional datasets, but the clinical requirement remains unchanged: dose recommendations must be explainable enough for verification, externally validated, and monitored for bias or data drift. AI should therefore function as a decision-support layer rather than an autonomous substitute for clinical pharmacology expertise (13,15).

**Figure 1. Iterative workflow of personalized drug therapy**

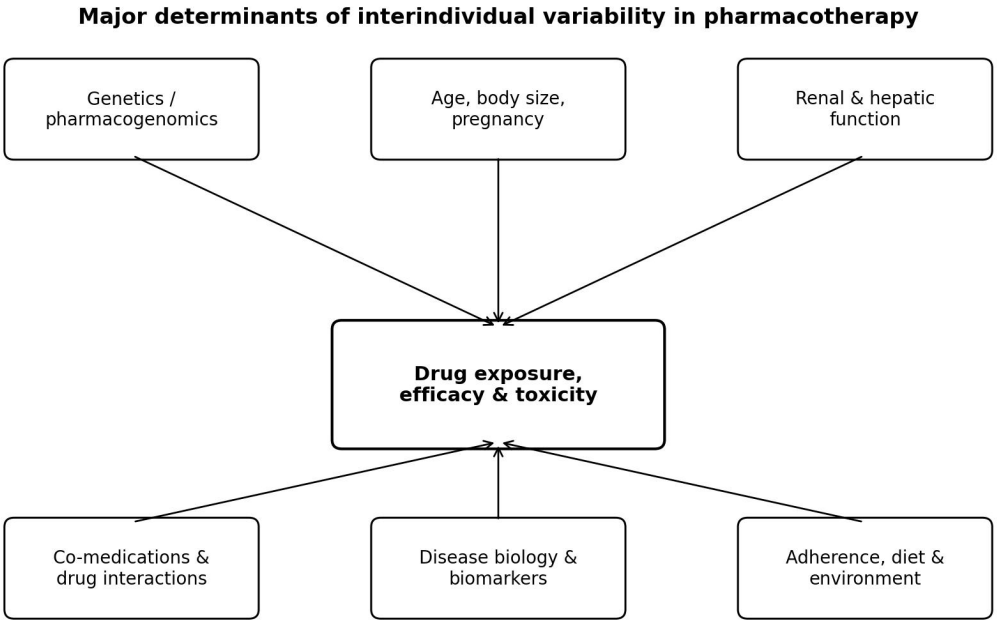



### *3.4. Multimodal determinants of response*

A major finding across the literature is that no single biomarker fully explains interindividual response. A pharmacogenetic result may have high mechanistic relevance but limited predictive value if organ function, adherence or a strong drug interaction dominates exposure. Conversely, concentration monitoring may identify abnormal exposure but not explain whether the cause is genetic, physiologic or behavioral. Personalized therapy is therefore strongest when data streams are combined and interpreted in temporal context. The principal determinants are summarized in Figure 2.

**Figure 2. Major sources of variability affecting individualized pharmacotherapy**

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## 4. DISCUSSION

The contemporary concept of personalized pharmacotherapy is best understood as a layered decision process rather than a single technology. Pharmacogenomics is powerful when inherited variation has a reproducible effect on drug exposure or response and a prescribing action is supported by evidence. TDM is powerful when exposure can be measured and linked to outcomes. MIPD is powerful when a validated model can combine population knowledge with a patient's own covariates and concentrations. Clinical decision support is valuable when it delivers these recommendations at the moment of prescribing without overwhelming clinicians with low-value alerts (3,12,15).

The distinction between baseline and adaptive personalization is clinically important. Pharmacogenetic data are relatively stable over a lifetime and can be reused across encounters, making pre-emptive testing attractive. In contrast, renal function, hepatic function, inflammation, interacting medicines and adherence can change over days or weeks. This means that an initially appropriate genotype-guided dose may become inappropriate as clinical conditions evolve. The most mature personalized systems therefore combine stable prior information with dynamic monitoring and repeated reassessment.

Evidence from cardiovascular pharmacogenomics illustrates both the promise and limits of personalization. Genotype-guided antiplatelet therapy is supported by mechanistic

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and clinical outcome data for CYP2C19 in selected settings (5). Warfarin dosing provides another well-studied example in which genotype can improve initial dose estimation, but ancestry, diet, interacting drugs and repeated INR measurements remain central to safe treatment (6). These examples show why personalized pharmacotherapy should not be equated with genomics alone.

Equity and generalizability remain major challenges. Variant frequencies differ across populations, and historical genomic datasets have not represented all ancestries equally. A test panel optimized for one population may miss relevant variants in another. Similarly, pharmacokinetic models may perform poorly when transferred to patients who differ substantially from the development cohort. Future implementation should therefore include population-specific validation, transparent reporting of model performance and explicit assessment of underrepresented groups (1,4).

Operational barriers are equally important. A clinically useful recommendation must be available at the right time, in a form that fits the prescribing workflow, and with sufficient explanation to support clinician trust. Pharmacogenomic CDS reviews emphasize the importance of integrating results into the electronic health record and minimizing alert fatigue (3). MIPD programs face related barriers, including data interoperability, assay turnaround time, model maintenance and responsibility for software governance (12,15). Education of prescribers, pharmacists and patients is essential because personalized recommendations often require interpretation rather than automatic execution.

Future systems will likely integrate pharmacogenomics, TDM, multi-omics, digital biomarkers and longitudinal electronic health data. Artificial intelligence may help synthesize these inputs, identify patterns and update predictions; however, clinical use should prioritize validated models, human oversight and interpretable recommendations (13). An especially promising direction is the development of adaptive digital pharmacology platforms that begin with a mechanistic or population prior and continuously learn from patient-specific concentrations, response markers and toxicity signals. Such systems could convert personalization from a one-time selection event into a closed-loop therapeutic process.

This review has limitations. It is a structured narrative synthesis rather than a systematic review or meta-analysis, and it does not attempt to grade every gene-drug pair or compare effect sizes across therapeutic areas. The included examples were selected to represent major mechanisms and mature clinical applications. Nonetheless, the synthesis demonstrates a consistent principle: personalized therapy is most valuable when patient-specific information is linked to a clearly defined clinical action and is reassessed as the patient's state changes.

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## 5. CONCLUSION

Personalized drug therapy is an increasingly practical extension of clinical pharmacology. Current approaches include pharmacogenomics, TDM, organ-function-based dosing, biomarkers, interaction assessment, MIPD and electronic decision support. The strongest applications do not rely on a single test; they combine stable predictors such as genotype with dynamic information such as drug concentration, organ function, response and toxicity.

Future progress will depend on prospective validation, equitable population representation, interoperable clinical data, robust governance of predictive models and training that enables clinicians to interpret personalized recommendations. In this framework, the role of clinical pharmacology is to transform diverse patient data into transparent, evidence-based medication choices and adaptive dosing decisions that improve the probability of efficacy while reducing avoidable harm.

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