# Precision Phytopharmacology: Patient Stratification, Molecular Mechanisms, Exposure Modeling, and Response Prediction for Natural Product-Based Therapeutics

**Erik Van der Meer[1]*, Lieke Jansen[1], Bram de Vries[2]**

*[1]Department of AI for Neurotransmitter Modulation by Plant Alkaloids, Faculty of Pharmacy, Utrecht University, Utrecht, Netherlands.*
*[2]Department of Computational Toxicology for Herbal Hepatotoxicity, Faculty of Pharmacy, University of Groningen, Groningen, Netherlands.*

## ABSTRACT

Natural product-based therapeutics present distinctive precision-pharmacology challenges because botanical identity, phytochemical composition, biological mechanisms, systemic exposure, patient characteristics, concomitant medications, and safety liabilities may vary simultaneously. This article proposes a precision phytopharmacology framework for organizing these sources of variability without implying that natural products can presently be personalized through unvalidated biomarkers or computational predictions. The framework begins with authenticated natural product identity and reproducible phytochemical characterization, followed by structured definition of patient context and development of testable stratification hypotheses. Molecular evidence is organized across candidate biomarkers, targets, pathways, bioactivity findings, network relationships, and mechanistic plausibility. Exposure modeling integrates bioavailability, absorption, distribution, metabolism, excretion, constituent-specific pharmacokinetics, physiologically based pharmacokinetic logic, and provisional exposure–response relationships where adequate evidence exists. Response and safety predictions are treated as research outputs requiring uncertainty estimation, calibration, external validation, and assessment of herb–drug interaction risk. Personalization is therefore restricted to hypothesis generation, research prioritization, validation planning, and identification of evidence gaps. It does not constitute individualized dosing, therapeutic selection, clinical decision support, or proof of clinical utility. The principal contribution is an integrated, safety-aware architecture that connects natural product quality, patient heterogeneity, molecular mechanisms, exposure variability, response hypotheses, expert review, and explicit treatment-claim boundaries within a single translational research framework.

**Key Words:** *Precision phytopharmacology, Natural product therapeutics, Patient stratification, Molecular mechanisms, Exposure modeling, Response prediction*

**eIJPPR 2026; 16(3):66-79**

**HOW TO CITE THIS ARTICLE:** Van der Meer E, Jansen L, de Vries B. Precision Phytopharmacology: Patient Stratification, Molecular Mechanisms, Exposure Modeling, and Response Prediction for Natural Product-Based Therapeutics. Int J Pharm Phytopharmacol Res. 2026;16(3):66-79. https://doi.org/10.51847/OPLexbSKES

## INTRODUCTION

Precision pharmacology seeks to explain and manage variability in pharmacological effects by integrating patient heterogeneity, biological mechanisms, biomarkers, exposure, and treatment context. Its value lies not merely in dividing populations into narrower categories, but in identifying which sources of variation are biologically meaningful, measurable, reproducible, and relevant to a clearly defined pharmacological question. Within this approach, disease state, molecular characteristics, pharmacokinetic variability, pharmacodynamic responses,

**Corresponding author:** Erik Van der Meer
**Address**: Department of AI for Neurotransmitter Modulation by Plant Alkaloids, Faculty of Pharmacy, Utrecht University, Utrecht, Netherlands.
**E-mail:** ✉ e.vandermeer@uu.nl
**Received:** 07 March 2026; **Revised:** 29 May 2026; **Accepted:** 01 June 2026

and uncertainty must be evaluated together rather than treated as independent predictors. Precision pharmacology therefore provides a useful conceptual foundation for natural product research, provided that its outputs remain linked to explicit evidence standards and validation requirements [1].

Genetic variation illustrates both the potential and the limitations of stratified pharmacology. Variants affecting drug-metabolizing enzymes, transporters, receptors, or downstream pathways may contribute to differences in exposure, response, or toxicity, but an association is not automatically a clinically actionable biomarker. Analytical reliability, functional plausibility, replication, population context, effect magnitude, and evidence of clinical utility determine whether a pharmacogenomic signal can move beyond exploratory interpretation. These requirements are especially important for natural products because constituent concentrations, formulations, and multi-compound interactions may differ between investigated preparations [2].

Metabolomics and related molecular profiling approaches may further characterize baseline phenotype, metabolic state, treatment exposure, and biological response. Such measurements can generate pharmacometabolomic hypotheses, identify candidate pathway changes, or reveal previously unrecognized sources of heterogeneity. Nevertheless, metabolite signatures are vulnerable to variation in sampling time, diet, analytical platform, compound annotation, disease state, and statistical analysis. Their role in precision phytopharmacology should therefore be to support structured hypothesis development and validation planning rather than to create an immediate treatment-selection rule [3].

Natural products remain important sources of pharmacologically active chemical diversity, but their translation is complicated by botanical variability, multi-constituent composition, incomplete target characterization, limited bioavailability, uncertain exposure, and inconsistent evidence across experimental and clinical contexts. These characteristics create a need for a framework that connects natural product identity, phytochemical composition, patient heterogeneity, molecular mechanisms, exposure modeling, response prediction, safety assessment, and validation boundaries. The objective of this article is to propose such a precision phytopharmacology framework while maintaining a strict separation between research prioritization and individualized therapeutic recommendation [4].

*Precision phytopharmacology*

Precision phytopharmacology may be defined as the evidence-structured study of how variability in natural product composition, patient context, molecular biology, exposure, response, and safety could influence pharmacological hypotheses. It is narrower than generic personalized medicine because it focuses specifically on pharmacologically relevant variability associated with botanical or naturally derived therapeutic materials. It also differs from traditional phytotherapy, which may emphasize historical use or standardized indications, because precision phytopharmacology requires product-specific chemical evidence, mechanistic support, measurable exposure, and explicit validation. Pharmacogenetic findings involving natural products suggest that inherited variation may contribute to pharmacokinetic or pharmacodynamic differences, but this evidence remains product-, pathway-, and context-dependent and cannot independently establish individualized therapy [5].

The framework must also account for the fact that many natural products are complex mixtures rather than single, chemically invariant entities. Constituents may interact additively, synergistically, antagonistically, or through effects on solubility, transport, metabolism, target engagement, and toxicity. Consequently, an observed extract-level effect cannot automatically be attributed to one marker compound, and a constituent studied in isolation may not reproduce the pharmacology of the complete preparation. Precision claims therefore require clear documentation of compound composition, relative abundance, extraction conditions, stability, batch consistency, and the experimental level at which a proposed interaction has been demonstrated [6].

High-dimensional analytical methods can improve chemical annotation, dereplication, metabolite identification, bioactivity prioritization, and linkage between chemical features and experimental effects. These approaches are particularly valuable when a preparation contains many incompletely characterized constituents or when bioactivity must be traced across fractions and related chemical families. However, analytical association, molecular similarity, or co-variation with bioactivity does not demonstrate target engagement, exposure relevance, or therapeutic response. Omics-enabled natural product analysis should therefore supply traceable inputs to mechanistic and exposure models rather than function as a substitute for pharmacological validation [7].

Natural product identity and research quality form the entry boundary for the entire precision phytopharmacology process. Botanical authentication, voucher documentation, extraction and formulation details, chemical characterization, appropriate experimental controls, reproducibility, and transparent reporting are prerequisites for interpreting differences between patients or studies. A model cannot meaningfully stratify response when the investigated material is inadequately defined or when

nominally identical preparations differ chemically. Precision phytopharmacology should thus be distinguished from unvalidated response prediction by its insistence on traceable materials, fit-for-purpose evidence, explicit uncertainty, independent validation, and prohibition of treatment or dosing recommendations from exploratory findings [8].

*Patient stratification and molecular mechanisms*

Patient stratification in precision phytopharmacology should begin with a defined pharmacological question rather than an unrestricted search for subgroups. Clinical phenotype and disease subtype may provide an initial context, while genotype, organ function, metabolic state, concomitant exposures, and molecular profiles may be considered when supported by relevant evidence. Pharmacogenomic variables are most informative when they can be linked to a plausible enzyme, transporter, target, or toxicity pathway, whereas metabolomic profiles may reflect baseline physiology, exposure, or emerging response [2]. Microbiome composition and function represent an additional potential source of heterogeneity because microbial communities may transform phytochemicals, alter metabolite production, or modify biological pathways [9]. Molecular networking can help organize chemical families, metabolites, and biotransformation products, but the resulting relationships remain analytical evidence rather than confirmation of a clinical mechanism [10].

Mechanistic interpretation requires a structured progression from compound identity to bioactivity, target evidence, pathway effects, system-level consequences, and exposure plausibility. Network pharmacology can organize multi-compound and multi-target relationships, particularly when natural product constituents may influence several biological processes. Nevertheless, predicted edges, pathway enrichment, centrality measures, and literature-derived associations do not establish causal action. A mechanism becomes more credible when supported by reproducible bioactivity, orthogonal target assays, temporal pathway evidence, perturbational experiments, and concentrations compatible with measured or defensible exposure [11]. Within the proposed framework, transcriptomic, proteomic, inflammatory, and immune profiles are therefore treated as candidate context variables or mechanistic readouts unless their measurement validity and relationship to the stated pharmacological outcome have been independently established.

Microbiome-related evidence illustrates why patient stratification and mechanism mapping must remain connected. Individual microbial communities can differ in their capacity to metabolize xenobiotics, creating a plausible basis for variation in parent-compound or metabolite exposure [12]. Gene-level mapping can further identify bacterial enzymes or pathways capable of mediating particular transformations, thereby strengthening biological plausibility without proving that the same process determines therapeutic response in vivo [13]. Biomarker-guided pharmacology likewise requires a distinction between an exploratory signal and a validated marker: a candidate measure must be analytically reliable, mechanistically interpretable, temporally appropriate, reproducible, and meaningfully related to the intended outcome before it can support clinical interpretation [14]. Microbiome-mediated biotransformation may contribute to interindividual exposure heterogeneity, but taxonomic or functional microbiome differences do not independently establish therapeutic suitability [9, 12, 13].

The proposed stratification process consequently assigns each variable an explicit evidentiary status. Clinical phenotypes and disease subtypes define the initial research context; genotype and pharmacogenomic evidence identify potential inherited modifiers; transcriptomic, proteomic, metabolomic, microbiome, inflammatory, and immune measurements describe candidate biological states; and target, pathway, network, and bioactivity findings contribute to a graded mechanism model. The potential output is not a responder label, but a testable subgroup, biomarker, or mechanism hypothesis accompanied by uncertainty and a stated validation requirement. **Table 1** summarises patient stratification and molecular mechanism components required for precision phytopharmacology.



**Table 1.** Patient Stratification and Molecular Mechanism Components for Precision Phytopharmacology: Clinical Phenotype, Disease Subtype, Pharmacogenomics, Omics Profiles, Biomarker Hypotheses, Target Evidence, Pathway Evidence, Network Pharmacology, Bioactivity Evidence, Mechanistic Plausibility, and Validation Boundaries

| Stratification or mechanism component | Core precision question | Required evidence | Interpretive function | Potential output | Risk of overinterpretation | Validation requirement | Framework role |
|---|---|---|---|---|---|---|---|
| **Clinical phenotype** | Which observable clinical characteristics | Standardized phenotype definitions, reliable | Establishes the clinical research context | Phenotype-based subgroup hypothesis | Treating broad clinical categories as | Independent replication and assessment | Patient-context foundation |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | may define pharmacologically relevant heterogeneity? | measurement, temporal context | | | homogeneous response classes | of within-group variability | |
| **Disease subtype** | Could mechanistically distinct forms of a condition differ in exposure, response, or safety? | Reproducible subtype criteria and pathophysiological evidence | Links disease heterogeneity to pharmacological questions | Disease-subtype hypothesis | Assuming subtype membership determines treatment suitability | Prospective confirmation and subgroup-interaction testing | Stratification layer |
| **Genotype where supported** | Could inherited variation alter enzymes, transporters, targets, or toxicity pathways? | Reproducible associations, allele-function evidence, population context | Generates genotype-specific PK or PD hypotheses | Genotype–exposure or genotype–response hypothesis | Treating association as causal or actionable | Functional validation, replication, and utility assessment | Pharmacogenomic modifier |
| **Pharmacogenomic evidence where supported** | Is the genetic evidence sufficiently mature for the proposed context? | Effect estimates, replication, biological coherence, treatment-interaction evidence | Separates exploratory variants from credible markers | Evidence-tier assignment | Transferring evidence between non-equivalent products | Product- and context-specific validation | Validated-biomarker boundary |
| **Transcriptomic profile** | Do expression patterns indicate relevant pathway states or responses? | Standardized sampling, normalization, batch control, replicated signatures | Characterizes dynamic molecular activity | Transcriptomic stratification hypothesis | Equating correlated expression with target engagement | Independent replication and perturbational confirmation | Dynamic molecular-state layer |
| **Proteomic profile** | Do protein abundance or modification patterns reflect target or pathway activity? | Validated assays, temporally appropriate sampling, tissue relevance | Adds functional molecular evidence | Proteomic mechanism or response hypothesis | Assuming circulating proteins represent tissue pharmacology | Orthogonal assay confirmation and outcome association | Mechanism and biomarker layer |
| **Metabolomic profile** | Do endogenous or xenobiotic metabolites distinguish phenotype, exposure, or response? | Quality-controlled analysis, metabolite identification, timing and diet control | Connects metabolic state with pharmacology | Pharmacometabolomic hypothesis | Treating unidentified or unstable features as biomarkers | Compound identification, replication, prospective validation | Exposure–response bridge |
| **Microbiome profile where supported** | Could microbial composition or function alter biotransformation or effect? | Functional microbiome data, metabolite measurements, confounder control | Identifies microbial modifiers of metabolism | Microbiome–exposure hypothesis | Inferring function from taxonomy alone | Functional confirmation and host-context validation | Patient-specific metabolism modifier |
| **Inflammatory or immune markers where supported** | Could immune state alter pathway response or safety? | Validated assays, disease-specific evidence, | Defines immune-context hypotheses | Immune-state subgroup hypothesis | Treating nonspecific inflammation as a selection marker | Replication, specificity assessment, outcome- | Contextual PD modifier |



ISSN (Online) 2249-6084 (Print) 2250-1029

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | longitudinal measurement | | | | interaction testing | |
| **Biomarker hypothesis** | Does a candidate measure plausibly index mechanism, exposure, response, or risk? | Biological rationale, reliable assay, preliminary association | Records a provisional candidate for testing | Ranked biomarker hypothesis | Calling an exploratory association a validated marker | Analytical validation, replication, calibration, clinical relevance | Hypothesis-generation output |
| **Target evidence** | Does a constituent engage a relevant target at plausible exposure? | Binding or functional assays, selectivity, concentration relevance | Links a constituent to a proximal mechanism | Target-engagement hypothesis | Equating in vitro activity with in vivo engagement | Orthogonal assays and exposure-matched confirmation | Mechanistic evidence layer |
| **Pathway evidence** | Are downstream pathways altered coherently and reproducibly? | Multi-assay measurements, temporal ordering, perturbation evidence | Connects target activity to system effects | Pathway-response hypothesis | Assuming pathway association proves therapeutic causality | Perturbational validation and alternative-pathway testing | Mechanistic integration layer |
| **Network pharmacology evidence** | Do multiple compounds and targets form a coherent evidence network? | Curated compound–target data, confidence scores, directionality, exposure plausibility | Organizes multi-constituent mechanisms | Evidence-weighted mechanism network | Treating predicted links or centrality as proof | Experimental testing of prioritized nodes and edges | Multi-component mechanism map |
| **Bioactivity evidence** | Are observed biological effects reproducible and exposure-relevant? | Appropriate controls, concentration–response data, orthogonal assays | Filters weak or nonspecific findings | Ranked bioactivity evidence | Ignoring assay artifacts, cytotoxicity, or implausible concentrations | Reproduction and exposure-relevance assessment | Evidence-quality gate |
| **Mechanistic plausibility** | Is the proposed chain from constituent to target, pathway, and phenotype coherent? | Integrated chemical, temporal, biological, and exposure evidence | Evaluates whether a mechanism is testable | Mechanistic hypothesis with confidence grading | Presenting plausibility as demonstrated causality | Prospective perturbational and translational validation | Mechanism-synthesis stage |
| **Validated biomarker boundary** | Has a candidate met requirements for its intended context of use? | Analytical validity, clinical validity, reproducibility, calibration, utility evidence | Prevents exploratory markers from entering decision logic | Exploratory, replicated, validated, or unsuitable status | Assuming validation transfers across contexts | Context-specific prospective validation | Hard personalization boundary |

*Exposure modeling and response prediction*

Exposure modeling in precision phytopharmacology begins with the investigated material rather than with the patient alone. Botanical identity, formulation, extraction, phytochemical profile, constituent concentrations, batch variability, and chemical stability determine what has actually been administered and therefore what can reasonably be modeled. Physiologically based pharmacokinetic approaches may integrate compound properties, absorption, distribution, metabolism, excretion, and physiological covariates to generate mechanistic exposure hypotheses for natural medicines, but their credibility depends on the completeness and quality of constituent-specific inputs [15]. Modeling of hyperforin-mediated interactions involving St John's wort demonstrates how a constituent-specific PBPK structure

can be used to evaluate interaction scenarios, while also showing why conclusions depend on preparation-specific composition and defensible parameter assumptions [16].

Patient context must then be incorporated into exposure interpretation. Disease-associated physiological changes, organ dysfunction, transporter regulation, genotype, microbiome activity, diet, and concomitant medications may alter the disposition of natural product constituents or co-administered drugs. Preclinical evidence showing combined effects of silymarin exposure and liver disease on hepatic transporters illustrates the possibility that a comorbidity and natural product may jointly modify pharmacokinetic risk, although such findings cannot be assumed to translate directly to humans [17]. Recommended approaches for natural product–drug interaction modeling consequently emphasize verified constituent identity, relevant concentrations, enzyme and transporter mechanisms, model selection, sensitivity analysis, and comparison with clinical evidence where available [18]. PBPK and related interaction models can support exposure-scenario evaluation only when constituent identity, composition, mechanistic parameters, and independent verification are adequate [15, 16, 18].

Exposure models may support response research only when the proposed pharmacodynamic relationship is clearly defined. A PK/PD structure requires temporally aligned exposure and response measurements, plausible biological linkage, appropriate handling of active metabolites or delayed effects, and evaluation of alternative explanations. Pharmacodynamic biomarkers may contribute to this process when they are analytically reliable and meaningfully related to the proposed mechanism or outcome [14]. Response prediction should therefore produce a bounded research probability or ranking rather than a therapeutic conclusion, with uncertainty, calibration, missing-data handling, and intended population specified in advance. When interaction predictions require clinical confirmation, studies should use characterized natural products, justified probe substrates or endpoints, suitable participant criteria, and sampling capable of testing the proposed mechanism [19].

Safety-risk prediction must be integrated rather than appended after efficacy-oriented modeling. ADMET findings, toxicity evidence, organ-function context, co-medications, interaction mechanisms, exposure margins, and uncertainty should determine whether a response hypothesis remains suitable for further investigation. Negative in vitro screening cannot guarantee absence of interaction, while a predicted interaction does not establish its clinical magnitude. Research prioritization can instead combine prevalence of use, clinical signals, mechanistic plausibility, exposure evidence, potential severity, and feasibility to identify which natural products require more rigorous evaluation [20]. The decision boundary remains explicit: exposure and response models may support scenario analysis, study design, hypothesis prioritization, and validation planning, but they cannot provide individualized dosing, establish efficacy, certify safety, or recommend treatment. **Table 2** maps exposure modeling and response prediction requirements for natural product-based therapeutic research.



**Table 2.** Exposure Modeling and Response Prediction Requirements for Natural Product-Based Therapeutics: Phytochemical Profile, Compound Composition, Bioavailability, ADME, PBPK Logic, PK/PD Logic, Exposure–Response Hypotheses, Safety-Risk Prediction, Herb–Drug Interaction Risk, Patient Context, and Validation Needs

| Modeling component | Core pharmacology question | Required input | Modeling or prediction function | Potential output | Uncertainty source | Validation requirement | Decision boundary |
|---|---|---|---|---|---|---|---|
| **Phytochemical profile** | Which measurable constituents are present in the investigated material? | Authenticated source, analytical spectra, reference standards, batch metadata | Defines the modeled chemical entity | Batch-specific constituent profile | Unidentified features, extraction differences, degradation | Orthogonal identification and repeat-batch analysis | No exposure model without adequate product characterization |
| **Compound composition** | What are the concentrations and relative proportions of relevant constituents? | Quantitative assays, marker compounds, formulation information | Supplies dose and mixture inputs | Composition vector with uncertainty ranges | Assay error, batch variability, unmeasured constituents | Independent quantification and stability assessment | No transfer across chemically non-equivalent preparations |
| **Chemical standardization** | Is the investigated material sufficiently | Specifications, acceptance ranges, | Controls consistency of model inputs | Standardization status | Incomplete specifications | Prospective batch verification | Poorly standardized |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | reproducible for comparison? | manufacturing and storage records | | | and matrix effects | | materials remain exploratory |
| **Bioavailability** | What fraction of relevant constituents may reach systemic or local sites? | Solubility, permeability, first-pass metabolism, formulation data | Estimates available exposure | Bioavailability hypothesis or distribution | Sparse human data and constituent interactions | Comparison with measured concentration data | Bioavailability estimates do not establish efficacy |
| **Absorption** | How rapidly and variably are constituents absorbed? | Dissolution, permeability, gastrointestinal physiology, food context | Models entry into systemic circulation | Absorption-rate estimates | Formulation, food, microbiome, and transporter effects | Clinical or defensible translational PK evidence | Administered quantity is not equivalent to absorbed exposure |
| **Distribution** | Where may constituents and metabolites distribute? | Protein binding, tissue partitioning, transporter data, physicochemical properties | Estimates plasma and tissue exposure | Distribution profile | Active transport, species differences, uncertain tissue data | Plausibility checks and observed PK comparison | Tissue exposure remains provisional without supporting measurements |
| **Metabolism** | Which host or microbial pathways transform the constituents? | Enzyme kinetics, metabolite identification, genotype and microbiome information | Models clearance and metabolite formation | Parent–metabolite exposure profile | Enzyme variability, induction, inhibition, unknown pathways | In vitro–in vivo evaluation and metabolite verification | Predicted metabolism does not prove biological benefit |
| **Excretion** | How are constituents and metabolites eliminated? | Renal, biliary, transporter, recovery, and physicochemical data | Models elimination and accumulation | Clearance or accumulation hypothesis | Organ dysfunction, transporter variability, incomplete recovery | Observed elimination or mass-balance evidence where feasible | Complete ADME cannot be claimed when excretion evidence is missing |
| **PBPK logic where supported** | Can physiology and compound data be integrated into mechanistic simulations? | Defined compounds, ADME parameters, physiological variables, uncertainty distributions | Simulates concentrations across populations and scenarios | Exposure distributions and interaction scenarios | Parameter identifiability and model-structure assumptions | Verification against independent observed PK data | PBPK supports hypothesis testing, not dosing recommendations |
| **PK/PD logic where supported** | Is exposure quantitatively associated with a biological response? | Valid PK data, repeated PD measures, temporal information, mechanistic rationale | Estimates provisional exposure–effect relationships | PK/PD hypothesis | Hysteresis, active metabolites, confounding, sparse sampling | Model diagnostics and independent or prospective validation | No therapeutic-response claim without validated linkage |
| **Exposure–response hypothesis** | Could exposure variation plausibly explain variation in a measured response? | Exposure measurements, defined response endpoint, covariates, temporal alignment | Tests graded exposure–response relationships | Exposure–response hypothesis | Confounding, reverse causation, measurement error | Independent confirmation and sensitivity analysis | Association does not establish causality or clinical benefit |
| **Response prediction** | Can prespecified inputs estimate a clearly defined | Representative data, defined outcome, | Produces individual or subgroup | Calibrated research prediction | Overfitting, dataset shift, outcome | Internal validation, calibration, | No treatment recommendation |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | research outcome? | candidate predictors, missing-data plan | probabilities for research | | misclassification | discrimination, external validation | from unvalidated probabilities |
| **Safety-risk prediction** | Can available evidence identify elevated toxicity or interaction hypotheses? | Toxicity data, exposure, organ function, comorbidities, co-medications | Generates risk hypotheses or priority categories | Safety-risk research tier | Rare events, underreporting, uncertain exposures | External validation and safety-focused expert review | Prediction supplements but does not replace clinical assessment |
| **ADMET evidence** | Are computational and experimental disposition findings concordant? | Assay data, chemical descriptors, model provenance, applicability domain | Screens pharmacokinetic and liability hypotheses | ADMET evidence profile | Model-domain limits and assay inconsistency | Experimental confirmation in relevant systems | In silico ADMET alone cannot establish safety |
| **Toxicity evidence** | Are adverse biological effects reproducible at plausible exposure? | Concentration–response assays, organ-relevant models, exposure context | Characterizes hazard and potential risk | Toxicity evidence tier | Species translation, high-concentration artifacts, mixture effects | Repeated and exposure-relevant confirmation | Unresolved toxicity blocks personalization claims |
| **Herb–drug interaction risk** | Could constituents alter enzymes, transporters, or pharmacodynamic pathways? | Composition, inhibition or induction evidence, exposure, co-medication properties | Predicts interaction scenarios | Interaction-risk hypothesis | Unknown constituents, variable exposure, disease effects | Mechanistic modeling and clinical evaluation where warranted | Negative screening does not guarantee compatibility |
| **Patient-context variables** | Which patient factors may change exposure, effect, or safety? | Age, organ function, phenotype, genotype, microbiome, diet, disease and medication context | Conditions simulations or predictions on supported covariates | Context-adjusted research estimate | Missingness, measurement error, correlated variables | Prespecified definitions and independent evaluation | Only evidence-supported variables may influence outputs |
| **Uncertainty estimation** | How reliable are the inputs, parameters, and resulting predictions? | Input distributions, measurement error, model assumptions, sensitivity analyses | Quantifies confidence and identifies influential unknowns | Uncertainty interval or evidence-confidence grade | Sparse data, structural uncertainty, hidden correlations | Transparent reporting and prospective error assessment | Point predictions must not be interpreted without uncertainty |
| **External validation need** | Does performance persist in independent products, populations, and settings? | Locked model, independent dataset, predefined metrics | Tests transportability | External performance assessment | Population shift, batch shift, assay shift, setting differences | Adequately sized independent validation | No clinical-utility inference without relevant external validation |

*Natural product-based therapeutic personalization*

Natural product-based therapeutic personalization should be understood as a staged research hypothesis rather than an individualized clinical recommendation. Its purpose is to identify whether defined patient-context variables, molecular features, exposure determinants, or safety factors justify targeted investigation in a particular research population. Structured knowledge representations can assist this process by linking botanical materials, constituents, enzymes, transporters, interacting drugs, and reported pharmacokinetic relationships while preserving evidence provenance. A natural product–drug interaction

knowledge graph, for example, may reveal mechanistic connections or evidence gaps that deserve further study, but it does not determine whether a product is safe, effective, or suitable for an individual [21].

Safety considerations impose an early constraint on every personalization hypothesis. St John's wort illustrates how a chemically active botanical preparation may alter the exposure of concomitant medications through enzyme and transporter induction, with the magnitude and clinical relevance of risk depending on product composition, co-medication characteristics, and patient context [22]. More broadly, botanical–drug interaction evaluation requires authenticated and chemically characterized products, plausible mechanistic evidence, exposure information, and appropriately designed clinical studies where the potential risk warrants investigation [23]. Herb–drug interaction screening should therefore be used to prioritize unresolved safety questions rather than to provide reassurance about co-administration or instructions to modify existing therapy.

Biomarker-guided and mechanism-guided personalization require similarly strict evidentiary boundaries. Pharmacogenomic findings may help define hypotheses concerning metabolism, transport, target activity, response, or toxicity, but implementation depends on reproducible associations, functional interpretation, population relevance, and evidence that the information improves a defined decision process [24]. Machine-learning methods may combine molecular, chemical, pharmacokinetic, clinical, or safety variables to support candidate ranking and response-prediction research, yet their performance depends on representative data, valid outcomes, suitable model design, transparent handling of uncertainty, and independent evaluation [25]. A predicted subgroup or response probability should thus be treated as a candidate for validation rather than evidence that a natural product should be selected, avoided, or administered differently.

The personalization layer of precision phytopharmacology integrates patient subgroup hypotheses, candidate biomarkers, mechanistic evidence, exposure estimates, toxicity findings, herb–drug interaction risk, comorbidity context, and concomitant medications. Multidisciplinary review is required to identify unsupported assumptions, contradictory findings, product-specific limitations, and possible harms. Translation beyond research prioritization would require representative external validation, evaluation within the intended workflow, prospective safety assessment, and evidence that use of the framework improves clinically relevant decisions or outcomes [26]. Until such evidence exists, the framework must not generate dosing suggestions, treatment recommendations, medication-change advice, declarations of therapeutic suitability, or claims of clinical utility.

*Proposed framework*

The proposed precision phytopharmacology framework begins with a natural product identity foundation. Botanical source, taxonomic authentication, voucher documentation, extraction procedure, formulation, storage, phytochemical profile, compound composition, chemical standardization, batch consistency, and evidence provenance define the object being investigated. These inputs are treated as mandatory because changes in preparation may alter constituent exposure, biological activity, interaction risk, and model transportability. Each analytical measurement and literature-derived relationship should therefore be associated with a specific preparation, method, and confidence level rather than generalized to all products sharing a botanical name.

The second stage defines patient context and generates stratification hypotheses. Clinical phenotype, disease subtype, organ function, genotype where supported, pharmacogenomic evidence where supported, transcriptomic, proteomic, metabolomic, or microbiome profiles where supported, inflammatory or immune state, comorbidities, concomitant medications, diet, and other defensible modifiers may be considered. Variables should enter the framework only when they are measurable, relevant to the pharmacological question, and supported by an explicit rationale. Because predictive probabilities can appear persuasive even when they are systematically inaccurate, calibration must be assessed before response or safety estimates can be interpreted [27]. The resulting output is a provisional stratification hypothesis, not a responder classification.

The third and fourth stages connect molecular mechanism mapping with exposure modeling. Constituents are linked cautiously to bioactivity evidence, targets, pathways, network relationships, and mechanistic plausibility, with each connection graded according to experimental support and exposure relevance. Exposure modeling then integrates bioavailability, absorption, distribution, host and microbial metabolism, excretion, physiological characteristics, formulation effects, and interaction mechanisms. Transfer of a mechanism or model between products, populations, laboratories, or clinical settings cannot be presumed because differences in chemical composition, measurement systems, patient characteristics, and care contexts may materially alter performance [28]. Failed transportability should trigger model revision, restriction of the intended context, or rejection of the hypothesis rather than post hoc reinterpretation.

The fifth stage addresses response prediction and safety-risk assessment. A response model must define its intended outcome, target population, predictors, time horizon, uncertainty, and validation strategy before analysis. Safety assessment should integrate ADMET evidence, toxicity findings, organ-function context, herb–drug interaction mechanisms, concomitant medications, and unresolved evidence gaps. Development and evaluation should involve natural product chemists, pharmacologists, pharmacometricians, toxicologists, clinicians, statisticians, computational scientists, and ethics or governance expertise as appropriate, because model performance alone cannot identify all pathways to harm [29]. Calibration, context-specific transportability, and safety-centered interdisciplinary oversight are concurrent requirements for interpreting predictive outputs responsibly [27-29].

The final stages comprise personalization-hypothesis generation, expert review, validation planning, and controlled feedback updating. Prediction-model evidence should be examined for bias and applicability arising from participant selection, predictor definition, outcome measurement, and analytical methods before it informs a research priority [30]. External validation should use an independent and adequately sized dataset capable of estimating calibration and discrimination with useful precision rather than relying on generic sample-size conventions [31]. New analytical data, experimental findings, pharmacokinetic observations, safety signals, expert corrections, and clinical evidence where available may update the framework through version-controlled feedback, but material or model changes require renewed validation. Transparency, reproducibility, ethical acceptability, and demonstrated effectiveness remain necessary before computational outputs could be considered for patient-benefit applications [32]. **Table 3** presents the proposed precision phytopharmacology framework for natural product-based therapeutics. **Figure 1** illustrates the proposed precision phytopharmacology framework linking natural product identity, patient stratification, molecular mechanisms, exposure modeling, response prediction, safety-risk assessment, expert review, validation planning, and personalization boundaries.

**Table 3.** Proposed Precision Phytopharmacology Framework for Natural Product-Based Therapeutics: Natural Product Identity, Phytochemical Characterization, Patient Context, Stratification Hypotheses, Molecular Mechanisms, Exposure Modeling, Response Prediction, Safety-Risk Assessment, Personalization Hypotheses, Expert Review, Validation Planning, Feedback, and Treatment-Claim Boundaries

| Framework stage | Core purpose | Required input | Precision pharmacology function | Potential output | Validation need | Failure risk | Feedback mechanism | Decision boundary |
|---|---|---|---|---|---|---|---|---|
| **Natural product identity foundation** | Define the investigated botanical or naturally derived material precisely | Botanical taxonomy, voucher documentation, source, extraction, formulation, storage, provenance | Establishes traceable product identity | Product identity record and provenance status | Independent authentication where feasible | Species substitution, contamination, misidentification, non-equivalent preparations | Revise identity record when source or processing changes | No downstream precision claim from inadequately identified material |
| **Phytochemical and quality characterization** | Define constituent composition and batch consistency | Analytical fingerprint, constituent concentrations, stability data, quality specifications | Establishes the chemical input for mechanism and exposure models | Batch-specific composition profile | Orthogonal analytical confirmation and repeat-batch assessment | Hidden batch effects, unidentified constituents, incorrect attribution | Feed analytical discrepancies back to sourcing and standardization | No extrapolation across preparations without demonstrated equivalence |
| **Patient-context definition** | Specify variables that may modify exposure, response, or safety | Phenotype, disease context, organ function, medications, genotype and omics where supported | Structures patient heterogeneity | Patient-context schema | Reliability and relevance assessment for each variable | Missing context, measurement error, unsupported covariates | Add, remove, or redefine variables as evidence changes | Context definition does not establish therapeutic suitability |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient stratification hypothesis** | Generate testable subgroup hypotheses | Standardized subgroup definitions, biological rationale, representative data | Organizes heterogeneity for research design | Candidate subgroup hierarchy | Independent replication and prospective interaction testing | Spurious subgroups, multiplicity, unstable classification | Revise or remove strata that fail replication | Subgroup membership is not a treatment-selection rule |
| **Molecular mechanism mapping** | Link constituents with targets, pathways, biological systems, and phenotypes | Bioactivity, target, pathway, network, temporal, and exposure evidence | Constructs an evidence-weighted mechanistic chain | Mechanism map with confidence grading | Orthogonal, perturbational, and exposure-relevant confirmation | Association networks interpreted as causality | Update evidence weights when confirming or contradictory findings emerge | Mechanistic plausibility does not prove therapeutic response |
| **Exposure modeling** | Estimate parent-compound and metabolite exposure under defined conditions | Composition, ADME properties, formulation, physiology, disease and interaction inputs | Generates mechanistic exposure scenarios | PBPK, PK, or descriptive exposure estimate with uncertainty | Verification against independent observed pharmacokinetic data | Parameter uncertainty, structural misspecification, non-identifiability | Recalibrate, restrict, or reject models when predictions fail | No individualized dosing output |
| **Response prediction** | Estimate a prespecified research outcome | Locked predictors, valid outcome definition, representative data, time horizon | Produces bounded probabilistic research predictions | Calibrated response hypothesis with uncertainty | Internal validation and relevant external validation | Overfitting, poor calibration, outcome misclassification, dataset shift | Monitor prediction errors and update only under a prespecified protocol | No treatment-selection output |
| **Safety-risk assessment** | Integrate toxicity, exposure, interaction, and patient-context evidence | ADMET evidence, toxicity data, exposure, organ function, comorbidities, co-medications | Prioritizes unresolved safety concerns | Safety-risk research category and evidence-gap register | Independent and prospective safety evaluation where appropriate | False reassurance, missed rare risks, incomplete interaction evidence | Escalate new signals and revise evidence categories | The framework cannot certify safety |
| **Personalization hypothesis generation** | Combine evidence into bounded subgroup or therapeutic-suitability research questions | Identity, stratification, mechanism, exposure, response, and safety layers | Ranks hypotheses for future testing | Personalization research hypothesis | Prospective confirmation | Composite outputs conceal weak or contradictory evidence | Decompose failed hypotheses and revise deficient stages | Explicitly not individualized therapy |
| **Expert review** | Evaluate evidence fit, uncertainty, contradictions, feasibility, and possible harm | Complete evidence dossier, model documentation, provenance, uncertainty analysis | Applies multidisciplinary scientific judgment | Approve, revise, defer, or reject a research hypothesis | Reviewer independence, expertise, and documented rationale | Automation bias, disciplinary blind spots, inconsistent review | Record disagreements and incorporate justified corrections | Expert judgment does not substitute for clinical evidence |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Validation planning** | Convert hypotheses into predefined experimental or clinical research plans | Ranked hypotheses, endpoints, expected failure modes, sample-size rationale | Specifies how each claim will be tested | Validation protocol | Independent execution and transparent reporting | Selective validation, inadequate comparators, outcome switching | Validation findings update evidence tiers and uncertainties | A validation plan is not evidence of successful validation |
| **Feedback updating** | Incorporate new chemical, mechanistic, exposure, safety, and outcome evidence | New data with provenance, quality assessment, and version information | Revises evidence weights and identifies model drift | Versioned framework state | Revalidation after material, variable, or model changes | Uncontrolled updating, irreproducibility, hidden performance decline | Formal monitoring, version control, audit trails, and rollback | Updated outputs remain research-only until revalidated |
| **No treatment-recommendation boundary** | Prevent research outputs from becoming medical advice | Explicit output restrictions, governance rules, interface controls, reviewer oversight | Separates hypothesis generation from clinical decision-making | Boundary statement attached to every framework output | Periodic governance and misuse audit | Unsupported treatment, dosing, discontinuation, or monitoring advice | Record attempted boundary violations and strengthen safeguards | The framework cannot prescribe, dose, select, discontinue, or endorse therapy |

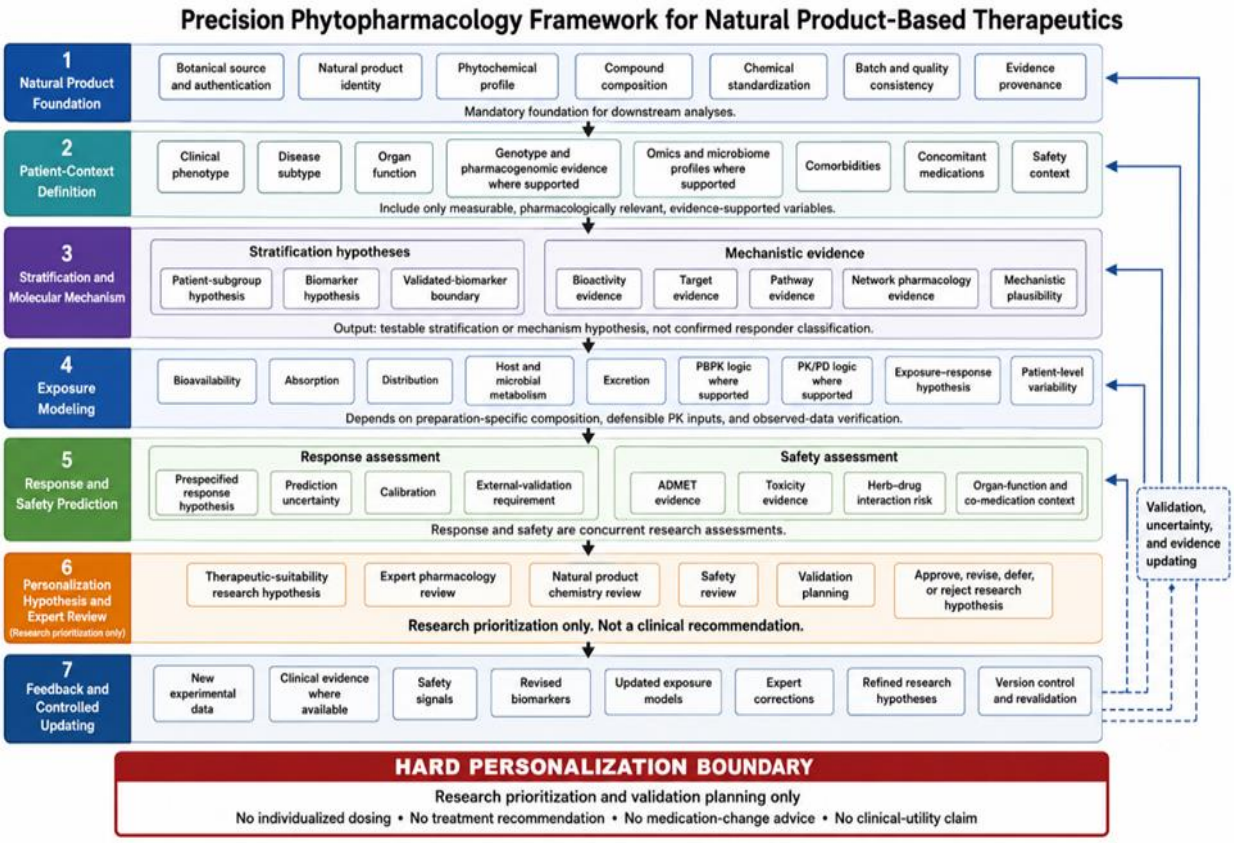


**Figure 1.** Precision Phytopharmacology Framework for Natural Product-Based Therapeutics

*Alt-text description*

A conceptual framework showing natural product identity and patient context flowing into stratification hypotheses, molecular mechanism mapping, exposure modeling, response prediction, safety-risk assessment, expert review,

validation planning, feedback loops, and treatment-claim boundaries.

## CONCLUSION

This article proposes a precision phytopharmacology framework that integrates natural product identity, phytochemical and quality characterization, patient-context definition, patient stratification, molecular mechanisms, exposure modeling, response prediction, safety-risk assessment, expert review, validation planning, and controlled feedback updating. Its central contribution is not a method for selecting or dosing natural product-based therapeutics, but a structured architecture for developing, prioritizing, and testing pharmacological hypotheses under explicit evidentiary and safety constraints. Precision claims require validated biomarkers, reproducible product characterization, defensible exposure evidence, mechanistic support, safety and interaction assessment, independent validation, and clinical evidence where relevant. The framework therefore maintains a firm boundary between research decision-making and treatment recommendation and should be interpreted as a conceptual foundation for future investigation rather than an implemented or clinically validated personalization system.

**Acknowledgments:** None

**Conflict of interest:** None

**Financial support:** None

**Ethics statement:** None

## REFERENCES

[1] Hampel H, Vergallo A, Aguilar LF, Benda N, Broich K, Cuello AC, et al. Precision pharmacology for Alzheimer's disease. Pharmacol Res. 2018;130:331-65. doi:10.1016/j.phrs.2018.02.014

[2] Lauschke VM, Milani L, Ingelman-Sundberg M. Pharmacogenomic biomarkers for improved drug therapy—recent progress and future developments. AAPS J. 2018;20(1):4. doi:10.1208/s12248-017-0161-x

[3] Pang H, Jia W, Hu Z. Emerging applications of metabolomics in clinical pharmacology. Clin Pharmacol Ther. 2019;106(3):544-56. doi:10.1002/cpt.1538

[4] Atanasov AG, Zotchev SB, Dirsch VM; International Natural Product Sciences Taskforce; Supuran CT. Natural products in drug discovery: Advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200-16. doi:10.1038/s41573-020-00114-z

[5] Rao T, Tan Z, Peng J, Guo Y, Chen Y, Zhou H, et al. The pharmacogenetics of natural products: A pharmacokinetic and pharmacodynamic perspective. Pharmacol Res. 2019;146:104283. doi:10.1016/j.phrs.2019.104283

[6] Caesar LK, Cech NB. Synergy and antagonism in natural product extracts: When 1 + 1 does not equal 2. Nat Prod Rep. 2019;36(6):869-88. doi:10.1039/C9NP00011A

[7] Wolfender JL, Litaudon M, Touboul D, Queiroz EF. Innovative omics-based approaches for prioritisation and targeted isolation of natural products—new strategies for drug discovery. Nat Prod Rep. 2019;36(6):855-68. doi:10.1039/C9NP00004F

[8] Heinrich M, Appendino G, Efferth T, Fürst R, Izzo AA, Kayser O, et al. Best practice in research—overcoming common challenges in phytopharmacological research. J Ethnopharmacol. 2020;246:112230. doi:10.1016/j.jep.2019.112230

[9] Dey P. Gut microbiota in phytopharmacology: A comprehensive overview of concepts, reciprocal interactions, biotransformations and mode of actions. Pharmacol Res. 2019;147:104367. doi:10.1016/j.phrs.2019.104367

[10] Quinn RA, Nothias LF, Vining O, Meehan M, Esquenazi E, Dorrestein PC. Molecular networking as a drug discovery, drug metabolism, and precision medicine strategy. Trends Pharmacol Sci. 2017;38(2):143-54. doi:10.1016/j.tips.2016.10.011

[11] Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, Schmidt HHHW. Network pharmacology: Curing causal mechanisms instead of treating symptoms. Trends Pharmacol Sci. 2022;43(2):136-50. doi:10.1016/j.tips.2021.11.004

[12] Javdan B, Lopez JG, Chankhamjon P, Lee YJ, Hull R, Wu Q, et al. Personalized mapping of drug metabolism by the human gut microbiome. Cell. 2020;181(7):1661-79.e22. doi:10.1016/j.cell.2020.05.001

[13] Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature. 2019;570(7762):462-7. doi:10.1038/s41586-019-1291-3

[14] Theile D, Cho WC. Pharmacodynamic monitoring using biomarkers to individualize pharmacotherapy. Biomark Med. 2019;13(5):393-408. doi:10.2217/bmm-2018-0355

[15] Jia Q, He Q, Yao L, Li M, Lin J, Tang Z, et al. Utilization of physiologically based pharmacokinetic modeling in pharmacokinetic study of natural

medicine: An overview. Molecules. 2022;27(24):8670. doi:10.3390/molecules27248670

[16] Adiwidjaja J, Boddy AV, McLachlan AJ. Physiologically based pharmacokinetic modelling of hyperforin to predict drug interactions with St John's wort. Clin Pharmacokinet. 2019;58(7):911-26. doi:10.1007/s40262-019-00736-6

[17] Montonye ML, Tian DD, Arman T, Lynch KD, Hagenbuch B, Paine MF, et al. A pharmacokinetic natural product-disease-drug interaction: A double hit of silymarin and nonalcoholic steatohepatitis on hepatic transporters in a rat model. J Pharmacol Exp Ther. 2019;371(2):385-93. doi:10.1124/jpet.119.260489

[18] Cox EJ, Tian DD, Clarke JD, Rettie AE, Unadkat JD, Thummel KE, et al. Modeling pharmacokinetic natural product-drug interactions for decision-making: A NaPDI Center recommended approach. Pharmacol Rev. 2021;73(2):847-59. doi:10.1124/pharmrev.120.000106

[19] Cox EJ, Rettie AE, Unadkat JD, Thummel KE, McCune JS, Paine MF. Adapting regulatory drug-drug interaction guidance to design clinical pharmacokinetic natural product-drug interaction studies: A NaPDI Center recommended approach. Clin Transl Sci. 2022;15(2):322-9. doi:10.1111/cts.13172

[20] Johnson EJ, González-Peréz V, Tian DD, Lin YS, Unadkat JD, Rettie AE, et al. Selection of priority natural products for evaluation as potential precipitants of natural product-drug interactions: A NaPDI Center recommended approach. Drug Metab Dispos. 2018;46(7):1046-52. doi:10.1124/dmd.118.081273

[21] Taneja SB, Callahan TJ, Paine MF, Kane-Gill SL, Kilicoglu H, Joachimiak MP, et al. Developing a knowledge graph for pharmacokinetic natural product-drug interactions. J Biomed Inform. 2023;140:104341. doi:10.1016/j.jbi.2023.104341

[22] Soleymani S, Bahramsoltani R, Rahimi R, Abdollahi M. Clinical risks of St John's wort (Hypericum perforatum) co-administration. Expert Opin Drug Metab Toxicol. 2017;13(10):1047-62. doi:10.1080/17425255.2017.1378342

[23] Grimstein M, Huang SM. A regulatory science viewpoint on botanical-drug interactions. J Food Drug Anal. 2018;26(2 Suppl). doi:10.1016/j.jfda.2018.01.013

[24] Roden DM, McLeod HL, Relling MV, Williams MS, Mensah GA, Peterson JF, et al. Pharmacogenomics. Lancet. 2019;394(10197):521-32. doi:10.1016/S0140-6736(19)31276-0

[25] Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463-77. doi:10.1038/s41573-019-0024-5

[26] Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. BMC Med. 2019;17(1):195. doi:10.1186/s12916-019-1426-2

[27] Van Calster B, McLernon DJ, van Smeden M, Wynants L, Steyerberg EW; Topic Group "Evaluating Diagnostic Tests and Prediction Models" of the STRATOS Initiative. Calibration: The Achilles heel of predictive analytics. BMC Med. 2019;17(1):230. doi:10.1186/s12916-019-1466-7

[28] Futoma J, Simons M, Panch T, Doshi-Velez F, Celi LA. The myth of generalisability in clinical research and machine learning in health care. Lancet Digit Health. 2020;2(9). doi:10.1016/S2589-7500(20)30186-2

[29] Wiens J, Saria S, Sendak M, Ghassemi M, Liu VX, Doshi-Velez F, et al. Do no harm: A roadmap for responsible machine learning for health care. Nat Med. 2019;25(9):1337-40. doi:10.1038/s41591-019-0548-6

[30] Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS; PROBAST Group. PROBAST: A tool to assess the risk of bias and applicability of prediction model studies. Ann Intern Med. 2019;170(1):51-8. doi:10.7326/M18-1376

[31] Snell KIE, Archer L, Ensor J, Bonnett LJ, Debray TPA, Phillips B, et al. External validation of clinical prediction models: Simulation-based sample size calculations were more reliable than rules-of-thumb. J Clin Epidemiol. 2021;135:79-89. doi:10.1016/j.jclinepi.2021.02.011

[32] Vollmer S, Mateen BA, Bohner G, Király FJ, Ghani R, Jonsson P, et al. Machine learning and artificial intelligence research for patient benefit: 20 critical questions on transparency, replicability, ethics, and effectiveness. BMJ. 2020;368. doi:10.1136/bmj.l6927