

TruRISK

A Scientific Framework for Patient-Specific Medication Risk Stratification

Integrating pharmacokinetic exposure, phenoconversion, drug-drug-gene interactions, pharmacodynamic risk, and patient context

SCIENTIFIC WHITE PAPER

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Purpose and scope

This paper describes the scientific rationale underlying the proposed TruRISK framework. It distinguishes established pharmacologic evidence from TruRISK-specific inference. It is not a clinical validation study, does not establish a numerical probability of an adverse event, and does not replace clinician judgment, FDA-approved labeling, or evidence-based prescribing guidelines.

Executive Summary

Medication risk is traditionally evaluated through separate lenses: drug-drug interactions (DDIs), pharmacogenomics (PGx), disease contraindications, dose, organ function, and known adverse-effect profiles. These sources are clinically valuable, but a binary interaction alert does not by itself determine whether a specific patient is currently experiencing pharmacokinetic conditions that could increase or decrease systemic drug exposure.

TruRISK is proposed as a dynamic medication-risk stratification framework in which established medication risks are interpreted in the context of the patient's current pharmacokinetic state. The central scientific premise is that, for an adverse effect or interaction whose mechanism is exposure-dependent, evidence suggesting increased exposure to one or more implicated drugs can increase the biological plausibility and potential clinical relevance of that risk.

Central TruRISK hypothesis

Known medication risk + patient-specific exposure modifiers + pharmacodynamic/disease context can provide a more individualized assessment of risk relevance than the known interaction alone.

The premise is supported by established pharmacology. FDA guidance recognizes exposure-response relationships and the effects of intrinsic and extrinsic factors, including concomitant medications, on drug exposure. FDA drug-interaction guidance likewise recognizes that DDIs can change systemic exposure and thereby alter efficacy or produce adverse effects. Peer-reviewed literature demonstrates that genotype, enzyme inhibition/induction, and phenoconversion can jointly alter functional metabolic phenotype and drug concentrations [1-7].

The novel step is not the proposition that altered clearance can alter exposure; that is established pharmacology. The proposed innovation is the systematic use of current exposure-related information to re-weight the clinical relevance of known risks across an entire medication regimen. This inference requires prospective and retrospective validation before TruRISK outputs should be interpreted as calibrated probabilities of clinical events.

Key Scientific Conclusions

- Drug exposure is influenced by absorption, distribution, metabolism, and elimination, and concomitant medications can materially change exposure.
- Genotype-predicted metabolic phenotype may not equal the patient's functional phenotype when inhibitors, inducers, or other factors produce phenoconversion.
- Drug-drug-gene interactions can produce additive or opposing effects on metabolism and systemic drug concentration.
- Not every known DDI results in an adverse event; patient-specific susceptibility and exposure are important determinants of clinical relevance.
- For exposure-dependent toxicities, a mechanistically supported increase in exposure is a rational factor for increasing risk priority.
- A TruRISK score should initially be characterized as risk stratification or mechanistic risk weighting, not as an absolute event probability, unless calibrated against clinical outcomes.

1. The Clinical Problem: Static Alerts in a Dynamic Patient

Polypharmacy creates a moving pharmacologic system. A new prescription can inhibit or induce a metabolic enzyme or transporter, change the clearance of another drug, alter active-metabolite formation, and potentially change the relevance of risks that were present before the new medication was added. Conversely, discontinuing an inhibitor may restore metabolic activity and change exposure again.

Traditional interaction databases are designed primarily to identify known or potential interactions. That function is essential, but it answers a different question from the one TruRISK is intended to address. A DDI alert asks whether a risk relationship exists. TruRISK asks a second question: given the patient's current medication regimen and available biologic information, are there exposure-related conditions that make this particular known risk more or less clinically salient right now?

Layer	Traditional question	TruRISK-oriented question
Known interaction	Can A and B interact?	What adverse effect/mechanism is established?
Patient PK state	Often not individualized	Is exposure to A or B plausibly increased or decreased?
Patient context	Separate alerts	Do disease, organ function, dose, or PD effects amplify the risk?
Output	Interaction severity category	Patient-specific risk priority / mechanistic plausibility

2. Scientific Foundation

2.1 Exposure-response relationships

The relationship between drug exposure and clinical response is a core principle of clinical pharmacology. FDA guidance describes the use of dose-concentration and concentration-response relationships and explicitly identifies intrinsic and extrinsic factors that can affect exposure, including organ dysfunction, differences in ADME, and concomitant medications [1]. This provides the regulatory-pharmacology foundation for treating altered exposure as clinically meaningful rather than as a purely theoretical signal.

2.2 Drug-drug interactions can alter systemic exposure

FDA's drug-interaction materials describe CYP enzymes and transporters as major mechanisms through which coadministered drugs can alter absorption, metabolism, transport, and elimination. The resulting change in systemic exposure can alter therapeutic effect or contribute to unexpected side effects [2,3]. Thus, a DDI is not merely a pairwise database relationship; in many cases its clinical importance is mediated through a measurable or inferable change in exposure.

2.3 Pharmacogenomics and functional phenotype

Genetic variation can alter enzyme activity and thereby affect clearance, active-metabolite formation, and exposure. However, genotype is not necessarily equivalent to functional enzyme activity at a given moment. CPIC guidelines explicitly recognize modification of predicted CYP2D6 phenotype by drug-drug interactions. For example, strong CYP2D6 inhibition may functionally convert a genetically predicted metabolizer to a poor-metabolizer state [4,5].

2.4 Phenoconversion

Phenoconversion is the mismatch between genetically predicted phenotype and observed or functionally inferred phenotype caused by non-genetic factors such as enzyme inhibition or induction. In polypharmacy, phenoconversion is particularly relevant because the medication regimen itself can change the metabolic phenotype that is used to interpret another medication. A 2025 review emphasized the need for phenoconversion models that estimate joint drug-interaction and genetic effects in polypharmacy [6].

2.5 Drug-drug-gene interactions

Malki and Pearson described pharmacokinetic drug-drug-gene interactions as situations in which genetic variation and a perpetrator drug jointly affect metabolism or transport and can markedly alter systemic concentrations. Their framework includes inhibitory, induction, and phenoconversion interactions [7]. A separate review concluded that pharmacogenetic factors can influence the clinical relevance of pharmacokinetic DDIs and that DDGIs may affect toxicity or ineffectiveness [8].

3. Proposed TruRISK Scientific Model

TruRISK can be conceptualized as a layered inference model rather than a new source of primary pharmacologic facts. The primary facts should come from validated sources: FDA labeling and guidance, peer-reviewed pharmacokinetic literature, PGx guidelines, established DDI evidence, disease contraindications, dose information, and patient-specific clinical data. TruRISK's proposed role is to integrate these facts and prioritize their relevance to the current patient.

Conceptual model

Established risk evidence → Current functional PK state → Estimated exposure direction/magnitude → Mechanism concordance → Patient susceptibility → Risk prioritization

3.1 Layer 1 - Establish the known risk

The process begins with a documented medication-related risk: a known DDI, an exposure-related adverse effect, a pharmacodynamic interaction, a disease-related contraindication or precaution, or another evidence-supported medication hazard. TruRISK should preserve the provenance and strength of this evidence rather than treating all alerts as equivalent.

3.2 Layer 2 - Determine the current pharmacokinetic context

The next layer evaluates factors that can alter exposure, including genetically predicted enzyme function when available; drug-induced inhibition or induction; phenoconversion; competing pathways;

transporter effects where supported; dose; renal or hepatic function when available; and other clinically validated modifiers. The objective is not to claim a measured plasma concentration when none exists, but to determine whether the direction of exposure change is pharmacologically supported.

3.3 Layer 3 - Test mechanism concordance

Increased exposure should not automatically increase every type of risk. The inference is strongest when the adverse effect is known to be dose- or concentration-dependent, or when the DDI mechanism itself is an exposure increase. A pharmacodynamic interaction with little relationship to systemic concentration may require different weighting. Mechanism concordance is therefore a critical safeguard against overgeneralization.

3.4 Layer 4 - Integrate patient susceptibility

Disease state, organ function, age, prior adverse reactions, electrolyte abnormalities, dose, duplicate pharmacology, and other patient-specific variables may modify susceptibility. TruRISK can conceptually integrate these factors, but each variable should be separately evidence-graded and validated before it materially changes an algorithmic score.

3.5 Layer 5 - Prioritize rather than over-predict

Until clinical calibration is complete, the most defensible output is a relative priority or mechanistic risk category. Examples include 'established risk with no identified exposure amplification,' 'established risk with plausible exposure amplification,' and 'established risk with multiple concordant patient-specific amplifiers.' Such categories communicate useful differentiation without implying a validated absolute probability.

4. Illustrative Risk-Stratification Scenarios

The following scenarios are conceptual and are not intended as treatment recommendations or validated TruRISK thresholds.

Scenario	Known risk	PK context	Interpretive consequence
A	Drug A + Drug B have an established exposure-related interaction	Both drugs expected to have usual exposure	Baseline established interaction remains relevant
B	Same interaction	Drug A exposure plausibly increased by reduced metabolic activity	Greater mechanistic concern if the adverse effect is exposure-dependent
C	Same interaction	Both drugs have concordant exposure-increasing factors	Potentially higher priority, subject to mechanism and evidence strength
D	Same interaction	A factor lowers exposure or offsets	Risk may not be amplified; direction

		inhibition	and net effect require evidence-based interpretation
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5. Relationship of TruTYPE to TruRISK

Within the proposed architecture, TruTYPE serves as the pharmacokinetic intelligence layer that estimates the patient's current functional metabolic context from available genetic and non-genetic information. TruRISK then uses that context as one input when evaluating the relevance of known medication risks. This separation is scientifically useful: TruTYPE addresses 'what is the likely functional processing state now?' whereas TruRISK addresses 'how might that state change the relevance of established medication risks?'

Important distinction

TruTYPE-derived exposure inference should not be represented as therapeutic drug monitoring. Unless a concentration is measured, the output is an evidence-based estimate of exposure direction or relative change, not a laboratory measurement of AUC, Cmax, trough concentration, or tissue concentration.

6. Proposed Evidence-Grading Framework

A transparent evidence hierarchy can reduce the risk of treating mechanistic hypotheses as equivalent to clinical outcome evidence.

Tier	Evidence type	Suggested role
Tier 1	FDA labeling/guidance; CPIC/DPWG or equivalent guideline; replicated clinical PK/outcome evidence	Primary rule or high-confidence modifier
Tier 2	Well-designed clinical PK study; strong peer-reviewed DDI/DDGI evidence	Quantitative or directional modifier with documented assumptions
Tier 3	Mechanistic/in vitro evidence; smaller observational studies; case series	Supportive modifier, lower confidence
Tier 4	Biologically plausible inference without direct validation	Flag as hypothesis; do not use as a strong quantitative multiplier

7. Validation Requirements

The central scientific challenge is moving from plausible mechanistic weighting to demonstrated clinical prediction. A staged validation program would allow TruRISK to establish analytical validity, clinical validity, calibration, and utility.

Stage 1 - Knowledge-base validation

Verify drug pathways, inhibitor/inducer classifications, adverse-effect mechanisms, contraindications, and evidence provenance against authoritative sources.

Stage 2 - Algorithm verification

Use synthetic and curated clinical cases to confirm that the same inputs produce reproducible outputs and that directional PK effects are correctly propagated through the regimen.

Stage 3 - Retrospective clinical validation

Compare TruRISK categories with documented adverse drug events, drug discontinuations, dose reductions, emergency visits, laboratory abnormalities, or measured drug concentrations in existing datasets.

Stage 4 - Prospective observational validation

Generate TruRISK outputs without directing therapy and test whether higher risk strata prospectively identify patients with more exposure-related adverse outcomes.

Stage 5 - Clinical utility study

Evaluate whether clinician access to TruRISK improves medication review efficiency, reduces preventable adverse events, or changes medication-management decisions without increasing inappropriate alerts.

7.1 Statistical considerations

- Pre-specify primary outcomes and distinguish exposure-related ADRs from all-cause symptoms.
- Assess discrimination (for example, AUROC where appropriate) and, importantly, calibration across risk strata.
- Compare TruRISK with a baseline model containing conventional DDI severity, age, medication count, and major clinical covariates.
- Perform ablation analyses to quantify the incremental contribution of TruTYPE/phenoconversion information.
- Validate across independent health systems and clinically different populations to reduce overfitting.
- Where absolute probabilities are eventually reported, calibrate them against observed event rates and periodically revalidate as the knowledge base changes.

8. Scientific Limitations and Guardrails

- Inferred exposure is not the same as measured exposure. Therapeutic drug monitoring remains the direct method for drugs where validated concentration monitoring exists.

- CYP activity is substrate-specific and can be influenced by factors beyond genotype and co-medications; a single activity construct may not perfectly predict every substrate.
- Not all adverse effects are concentration-dependent. Exposure amplification should only modify risk when the mechanism supports it.
- Multiple pathways can compensate for one another, and the net effect of simultaneous inhibitors, inducers, genetics, renal clearance, and transporters may be uncertain.
- Published DDI evidence varies in quality, dose, population, and clinical relevance. Source provenance and confidence should be visible.
- A mechanistic risk score can rank concern without proving causation in an individual patient.
- Clinical use should preserve clinician interpretation and should not substitute an algorithmic inference for patient assessment, FDA labeling, or established guidelines.

9. Potential Clinical Applications

If validated, the framework could be useful in medication reconciliation, polypharmacy review, new-drug evaluation, PGx interpretation, transitions of care, and longitudinal medication management. Its distinctive value proposition would be the ability to reassess risk whenever the regimen changes rather than treating medication risk as a static result.

This dynamic feature is especially relevant to phenoconversion. A patient's germline genotype does not change, but the functional consequences of that genotype may change when an inhibitor or inducer is added or removed. A longitudinal system can therefore reassess the same known risk under a new pharmacokinetic context.

10. Testable Research Hypotheses

1. Among patients with the same established DDI, those with concordant exposure-increasing factors will have a higher rate of exposure-related adverse outcomes than those without those factors.
2. Adding phenoconversion-adjusted functional phenotype to conventional DDI severity will improve prediction of selected exposure-related adverse drug events.
3. The incremental predictive value of TruRISK will be greatest in polypharmacy patients and for drugs with narrow therapeutic indices or well-characterized concentration-toxicity relationships.
4. Dynamic reassessment after medication changes will identify clinically relevant changes in risk that are not captured by a static PGx report.
5. A mechanism-specific TruRISK model will outperform a model that indiscriminately increases risk whenever predicted exposure rises.

11. Conclusion

The scientific rationale for TruRISK is grounded in established principles of clinical pharmacology: systemic exposure matters; DDIs can change exposure; genetic variation can alter metabolism; concomitant medications can produce phenoconversion; and the clinical relevance of an interaction varies among patients. The literature therefore supports the premise that current pharmacokinetic context can add meaningful information to the interpretation of known medication risks.

The principal TruRISK innovation is the proposed integration of these established facts into a dynamic, patient-specific risk-prioritization process. The appropriate scientific claim at this stage is that TruRISK

provides a mechanistically informed framework for stratifying the relevance of known medication risks. Claims that it predicts the absolute probability of an adverse event should await formal clinical calibration and validation.

Scientific positioning statement

TruRISK does not create a new drug interaction. It seeks to determine whether patient-specific pharmacokinetic and clinical conditions provide additional evidence that an already established medication risk may be more clinically relevant for this patient at this time.

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Source Notes

The cited literature supports the component scientific principles described in this paper. No cited publication is represented as a validation of the proprietary TruRISK algorithm itself. Before external scientific or regulatory use, references should undergo formal literature verification, and product-specific claims should be reviewed against the final implemented algorithm and validation data.

Suggested Citation

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