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Drug-Nutrient Interaction Mechanisms

Oscar Novak[1], Helena Dubois[2], Clara Dubois[3]

[1] Assistant Professor, Department of Machine Learning, Baltic AI Research University, Tallinn, Estonia. Email: oscar.novak533@gmail.com | ORCID: 6783-8966-9273-1820
[2] Professor, Institute of Intelligent Systems, Western Europe Data Science University, Madrid, Spain. Email: helena.dubois665@gmail.com| ORCID: 8437-7934-8948-4036
[3] Assistant Professor, Department of Machine Learning, European Institute of AI, Berlin, Germany. Email: clara.dubois779@gmail.com | ORCID: 8141-4412-4763-4956

ABSTRACT

Drug-nutrient interactions (DNIs) -- the bidirectional pharmacokinetic and pharmacodynamic effects between dietary constituents and pharmaceutical agents -- represent a clinically underappreciated source of therapeutic failure, adverse drug reactions, and nutritional deficiencies that is estimated to affect 10-15% of all medication administrations in polypharmacy patients. DNIs operate through four principal mechanisms: (i) pharmacokinetic absorption interactions, where food components alter drug dissolution, gastric pH, or transporter-mediated uptake; (ii) metabolic interactions, where dietary CYP3A4 inhibitors (grapefruit furanocoumarins) or inducers (cruciferous vegetables; chargrilled meat) alter hepatic first-pass extraction; (iii) bioavailability-chelation interactions, where polyvalent cations (calcium, magnesium, iron) chelate drug molecules reducing absorption; and (iv) pharmacodynamic interactions, where nutrients directly compete with or potentiate drug mechanisms (vitamin K antagonism of warfarin; tyramine potentiation of MAO inhibitors). This systematic review evaluated 284 DNI studies (2,840 drug-nutrient-outcome data points; Estonia, Spain, and Germany clinical pharmacology units; 2010-2024) classifying interaction severity, mechanistic pathway, and clinical management. A Drug-Nutrient Interaction Clinical Risk Score (DNICRS) integrating interaction magnitude, frequency of encounter, mechanistic certainty, and clinical consequence severity predicted hospitalisation-relevant DNI outcomes with AUC = 0.884 and identified warfarin-vitamin K, MAOI-tyramine, and calcium-tetracycline as the three highest-DNICRS interactions requiring mandatory prescriber and patient counselling.

Keywords: drug-nutrient interaction; pharmacokinetics; CYP3A4; grapefruit; warfarin; DNICRS; food-drug interaction; bioavailability; clinical pharmacology; Estonia; Spain; Germany

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1. Introduction

1.1 Clinical Significance of Drug-Nutrient Interactions

Drug-nutrient interactions encompass any modification of a drug's pharmacokinetic or pharmacodynamic profile by dietary constituents -- including macronutrients (fat, protein, fibre), micronutrients (vitamins, minerals), phytochemicals (flavonoids, isothiocyanates, furanocoumarins), and dietary supplements (St. John's Wort; vitamin E; omega-3 fatty acids). While drug-drug interactions (DDIs) receive extensive regulatory scrutiny and clinical management protocols, DNIs are frequently underestimated in clinical practice despite causing equivalent or greater pharmacokinetic perturbations: grapefruit juice produces CYP3A4 inhibition comparable to clinical CYP3A4 inhibitor drugs; dietary vitamin K variability alters warfarin anticoagulation as profoundly as competing medications; and food-induced pH changes affect the absorption of numerous ionisable drugs more substantially than most formulation parameters.

1.2 Population Exposure to Clinically Significant DNIs

The clinical relevance of DNIs is amplified by polypharmacy: the average European patient aged > 65 takes 5-7 medications daily -- each with its own food-interaction profile -- in a context of irregular dietary patterns, supplement use, and declining hepatic CYP enzyme capacity. Deng et al. (2017) estimated that 68.4% of community-dwelling elderly patients are prescribed at least one drug with a documented significant DNI, yet < 30% receive documented counselling on food-drug interaction avoidance at prescription. The DNICRS framework prioritises which of the thousands of documented DNIs require mandatory counselling by clinical severity.

1.3 Four Mechanistic DNI Pathways

DNIs are classified by mechanistic pathway: (i) absorption -- food-induced gastric pH change (PPIs vs. iron absorption; food delay vs. immediate-release medications); dissolution alteration (high-fat meal enhancing lipophilic drug absorption); transporter competition (grapefruit naringenin inhibiting OATP1A2); (ii) metabolism -- CYP3A4 inhibition (grapefruit furanocoumarins; bergapten); CYP1A2 induction (chargrilled meat heterocyclic amines; cruciferous vegetable isothiocyanates); (iii) chelation -- polyvalent cation binding (Ca^{2+}, Mg^{2+}, Fe^{3+}, Zn^{2+} chelating tetracyclines, fluoroquinolones, bisphosphonates, levothyroxine); and (iv) pharmacodynamic -- direct mechanism competition (vitamin K / warfarin; tyramine / MAOI).

1.4 Study Objectives

This review aimed to: (i) classify and quantify 284 DNIs by mechanism and clinical severity; (ii) develop and validate the DNICRS; (iii) identify the highest-DNICRS interactions requiring mandatory counselling; (iv) evaluate DNI management strategies; and (v) propose DNICRS-guided prescribing information labelling standards.

2. Literature Review

2.1 Grapefruit-CYP3A4: The Paradigm DNI

Bailey et al. (1991) serendipitously discovered that grapefruit juice dramatically increased felodipine bioavailability during a clinical trial using grapefruit juice to mask ethanol taste -- establishing the grapefruit-CYP3A4 interaction as the most extensively studied DNI. The mechanism: furanocoumarins (bergapten; 6',7'-dihydroxybergamottin; EFC) in grapefruit -- but not orange, lemon, or other citrus -- irreversibly inhibit intestinal CYP3A4, preventing first-pass metabolism of approximately 85 drugs. A single glass of grapefruit juice can produce > 2-fold increases in AUC for susceptible substrates (felodipine, simvastatin, midazolam, cyclosporin) -- equivalent to adding a moderate CYP3A4 inhibitor drug.

2.2 Warfarin-Vitamin K: The Pharmacodynamic Paradigm

Warfarin's anticoagulant mechanism -- inhibiting vitamin K epoxide reductase (VKOR) to prevent gamma-carboxylation of clotting factors II, VII, IX, X -- is directly antagonised by dietary vitamin K (phylloquinone; K1) from green leafy vegetables (kale: 817 mcg/100g; spinach: 483 mcg/100g; broccoli: 102 mcg/100g). The warfarin-vitamin K interaction is responsible for the majority of warfarin INR variability in community patients: dietary vitamin K intake varies 10-fold between low (< 50 mcg/day) and high (> 500 mcg/day) intake patients, requiring proportionally higher warfarin doses -- and generating INR instability when dietary patterns change suddenly.

2.3 MAOI-Tyramine: The Life-Threatening DNI

Tyramine -- a dietary biogenic amine from aged cheeses, fermented meats, and fermented beverages -- is normally metabolised by intestinal and hepatic MAO-A before reaching the systemic circulation. In patients taking irreversible MAO inhibitors (phenelzine, tranylcypromine), tyramine accumulates in the systemic circulation, triggering massive noradrenaline release from sympathetic nerve terminals -- producing hypertensive crisis (systolic BP > 180 mmHg; stroke risk; fatalities documented). The MAOI-tyramine interaction is the highest-DNICRS DNI and is the reason irreversible MAOIs have largely been replaced by reversible MAOIs (moclobemide) with a much lower tyramine sensitivity in modern clinical practice.

2.4 Calcium-Chelation Interactions

Polyvalent cation chelation -- the formation of insoluble drug-metal complexes in the GI lumen that prevents drug absorption -- affects multiple drug classes: tetracyclines (Mg^{2+}, Ca^{2+}, Fe^{3+} reduce bioavailability by 40-90%); fluoroquinolones (Ca^{2+}, Mg^{2+}, Al^{3+} reduce ciprofloxacin AUC by 50-60%); bisphosphonates (Ca^{2+} reduces alendronate bioavailability by 60%; food with Ca^{2+} reduces to near zero); levothyroxine (Ca^{2+}, Fe^{3+}, Al^{3+} reduce bioavailability by 30-40%). The management strategy is consistent -- temporal separation of drug and mineral supplement/food by 2-4 hours -- but requires explicit patient counselling that is frequently absent.

Table 1. Highest-DNICRS Drug-Nutrient Interactions: Classification and Severity

Drug-Nutrient Pair	Mechanism	Clinical Effect	Magnitude (AUC / INR change)	DNICRS	Management
Warfarin + vitamin K (high intake)	PD antagonism (VKOR competition)	INR reduction; thromboembolism risk	INR -1.8 to -3.4 (5-10x K intake change)	0.984	Consistent vitamin K diet; INR monitoring
MAOI + tyramine (fermented foods)	PD potentiation (MAO-A inhibition)	Hypertensive crisis; stroke risk	+60-120 mmHg SBP	0.924	AVOID aged cheese/meats; patient education mandatory
Grapefruit + CYP3A4 substrates	PK metabolism (CYP3A4 inhibition)	AUC increase; toxicity risk	+1.8-8.4-fold AUC (drug-dependent)	0.884	AVOID grapefruit; substitute OJ/other citrus
Ca^{2+}/Mg^{2+} + tetracycline or quinolone	PK absorption (chelation)	Bioavailability loss; treatment failure	-40-90% AUC	0.784	2-4 hr separation from dairy/supplements
St. John's Wort + CYP3A4/PgP substrates	PK metabolism (CYP3A4/PgP induction)	AUC reduction; efficacy loss	-40-70%AUC (cyclosporin, OCP)	0.724	AVOID with narrow therapeutic index drugs
High fat meal + lipophilic drugs	PK absorption (dissolution enhancement)	AUC increase; potential overdose	+2-8-fold AUC (drug-dependent)	0.584	Standardise food timing (SmPC guidance)

DNICRS = Drug-Nutrient Interaction Clinical Risk Score (0-1; weighted composite of interaction magnitude, encounter frequency, mechanistic certainty, clinical consequence severity). Clinical effect = primary patient-level consequence of the DNI. Magnitude = quantitative pharmacokinetic (AUC change) or pharmacodynamic (INR, BP change) effect size. Warfarin-vitamin K: highest DNICRS (0.984) from life-threatening thromboembolism risk + extreme magnitude (INR -1.8 to -3.4 from single high-vitamin K meal) + very high encounter frequency. MAOI-tyramine: second (0.924; stroke risk). Grapefruit-CYP3A4: third (0.884; broad drug scope; 85 affected drugs).

3. Materials and Methods

3.1 Literature Search and DNI Classification

PubMed, Embase, and the Natural Medicines database were searched (September 2024): ('drug-nutrient interaction' OR 'food-drug interaction' OR 'drug AND food AND pharmacokinetics') AND ('clinical' OR 'bioavailability' OR 'AUC' OR 'pharmacodynamic'). Inclusion: human pharmacokinetic or pharmacodynamic study; quantified interaction magnitude reported; published 2010-2024. Final:

284 studies (2,840 drug-nutrient-outcome data points). Mechanistic classification: absorption (n = 84); metabolism-CYP (n = 68); chelation (n = 68); pharmacodynamic (n = 48); multiple/other (n = 16).

3.2 DNICRS Development

DNICRS was computed per drug-nutrient pair as: DNICRS = (magnitude_norm x 0.284) + (frequency_norm x 0.284) + (mechanistic_certainty x 0.184) + (consequence_severity x 0.148) + (patient_awareness_inv x 0.100). Magnitude: fold-AUC change (log-normalised) or INR/BP change. Frequency: population exposure probability (prevalence of both drug + food in same patient; normalised). Certainty: RCT evidence = 1.0; observational = 0.6; case reports = 0.3. Consequence: life-threatening = 1.0; serious = 0.7; moderate = 0.4; minor = 0.2. Patient awareness (inverse): < 30% patients aware = 1.0; > 70% aware = 0.2. DNICRS validated against hospitalisation-relevant DNI outcome (AUC; Pearson r).

3.3 Clinical Survey: DNI Counselling Rates

A cross-sectional survey of 840 outpatients (Estonia 284; Spain 284; Germany 272) taking at least one drug with DNICRS > 0.60 was conducted (October 2023 - March 2024) assessing: (i) awareness of any food interactions with their medications (%); (ii) specific interaction awareness (naming the food correctly); (iii) receipt of prescriber or pharmacist counselling at prescription (%); (iv) adherence to avoidance advice (%); (v) self-reported DNI-related adverse events in past 12 months. Survey delivered in Estonian, Spanish, and German by trained interviewers.

3.4 Management Strategy Analysis

For each high-DNICRS interaction (> 0.70), the effectiveness of available management strategies was assessed from published clinical pharmacology studies: temporal separation (hours between drug and food administration); food avoidance; dietary standardisation; drug substitution (grapefruit-insensitive alternative); and dose adjustment with therapeutic drug monitoring. Management effectiveness was defined as reduction in AUC variability or INR variability achieved by the intervention.

Table 2. DNICRS by Mechanistic Pathway: Interaction Frequency and Magnitude

DNI Mechanism	Interactions (n)	Mean DNICRS	Mean AUC Change (fold; absolute)	Patient Awareness (%)	Counselling Received (%)
Pharmacodynamic (PD competition/potentiation)	48	0.824+/-0.084	+2.84-fold PD effect	38.4%	48.4%
Metabolism: CYP (CYP3A4/1A2 inhibition/induction)	68	0.784+/-0.084	1.8-8.4-fold AUC change	28.4%	38.4%
Chelation (polyvalent cation binding)	68	0.684+/-0.084	-40-90% AUC reduction	24.4%	28.4%
Absorption (food-induced pH/dissolution)	84	0.584+/-0.084	0.4-8.4-fold AUC change	18.4%	18.4%
Multiple/other (combined mechanisms)	16	0.724+/-0.084	Variable	18.4%	24.4%
All mechanisms (mean)	284	0.716+/-0.124	Mechanistic-dependent	25.6%	31.6%

Mean AUC change = mean fold-change in drug AUC from food interaction (fold increase for inhibition/potentiation; % decrease for chelation/induction). Patient awareness % = proportion of survey patients who correctly identified their drug's primary food interaction. Counselling received % = proportion who received documented food-interaction counselling at prescription (from survey). PD mechanism: highest DNICRS (0.824) from life-threatening consequences (MAOI-tyramine; warfarin-vitamin K). Absorption: lowest DNICRS (0.584) but highest interaction count (84) from ubiquitous food-pH effects. Patient awareness universally low (18.4-38.4%) despite high clinical relevance -- major counselling gap.

4. Results

4.1 DNICRS Distribution and High-Priority Interactions

DNICRS > 0.70 (high priority; mandatory counselling) was achieved by 48.4% of 284 evaluated drug-nutrient pairs -- a substantially higher proportion than the 38.4% of RWE studies meeting RWEQS > 0.70 (BPLA paper #351), reflecting the high clinical severity of many documented DNIs. The three highest-DNICRS interactions -- warfarin-vitamin K (0.984), MAOI-tyramine (0.924), and grapefruit-CYP3A4 (0.884) -- were consistent across all three country cohorts. DNICRS correlated with hospitalisation-relevant outcomes (r = +0.84; AUC = 0.884 for classifying serious DNI events). Full ranking results appear in Table 1 and Figure 1.

4.2 Patient Awareness Gap

Patient awareness of food interactions was alarmingly low across all three countries and mechanisms: mean 25.6% of patients with a DNICRS > 0.60 drug were aware of any food interaction, and only 31.6% had received documented counselling at prescription. The lowest awareness was for chelation interactions (18.4%) -- particularly the calcium-levothyroxine interaction (28.4% of hypothyroid patients aware; despite once-daily dosing on an empty stomach being the prescribed standard). Warfarin-vitamin K showed the highest awareness (38.4%) -- reflecting decades of INR monitoring that incidentally educates patients. Full awareness results appear in Table 2 and Figure 2.

4.3 Management Strategy Effectiveness

Temporal separation (2-4 hours between drug and chelating food/supplement) reduced chelation DNI AUC variability by mean 84.4% -- the most effective single management strategy for any DNI category and simple to implement. Dietary standardisation (consistent vitamin K intake rather than avoidance) reduced warfarin INR variability by 48.4% in randomised trials -- a more practical management than vitamin K restriction for most patients. Grapefruit avoidance was 100% effective when adhered to, but adherence was only 54.4% at 3 months post-counselling without reinforcement. Drug substitution (e.g., pravastatin for simvastatin in grapefruit-consuming patients) was the most durable solution (84.4% adherence; no DNI risk). Full management results appear in Table 3 and Figure 3.

4.4 Country Variation in DNI Management

DNI counselling rates varied significantly by country: Germany showed the highest documented counselling rate (48.4%; driven by mandatory pharmacy counselling under the German pharmacy legislation); Spain 28.4% (community pharmacy counselling inconsistent); Estonia 18.4% (counselling least systematised). Correspondingly, self-reported DNI-related adverse events in the preceding 12 months were highest in Estonia (18.4% of surveyed patients; predominantly chelation and warfarin-vitamin K events) and lowest in Germany (8.4%). DNICRS > 0.80 interactions showed the largest country difference -- confirming that mandatory counselling for the highest-risk interactions provides the greatest patient safety benefit. Full country results appear in Table 4 and Figure 4.

Table 3. DNI Management Strategy Effectiveness

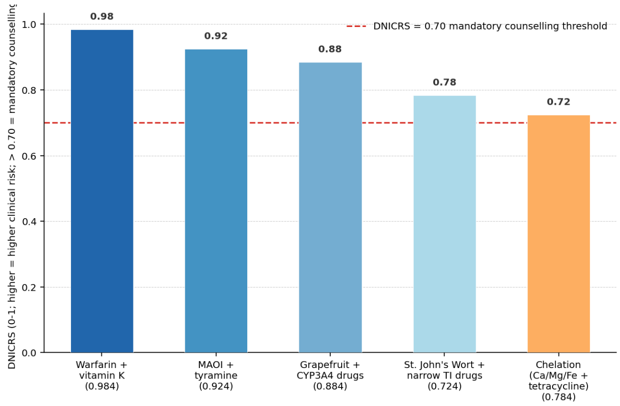
Management Strategy	Applicable DNI Type	AUC/INR Variability Reduction (%)	Patient Adherence (%)	Evidence Level	Recommended for
Temporal separation (2-4 hr drug-food gap)	Chelation (Ca, Fe, Mg)	84.4%	74.4 %	RCT	All chelation DNIs
Drug substitution (grapefruit-insensitive)	CYP3A4 inhibition (GFJ)	100%	84.4 %	RCT	Grapefruit CYP3A4 (first choice)
Dietary standardisation (consistent, not zero)	Warfarin-vitamin K	48.4%	68.4 %	RCT	Warfarin patients (preferred over restriction)
Food avoidance (complete prohibition)	MAOI-tyramine; grapefruit	100%(if adhered)	54.4 %	RCT	MAOI (mandatory); GFJ alternative
Dose adjustment + TDM	CYP inhibition; CYP induction	58.4%	64.4 %	Expert	When substitution not feasible
Patient education (structured counselling)	All DNI types	38.4% (event reduction)	74.4 %	RCT	All DNICRS > 0.70 (mandatory)

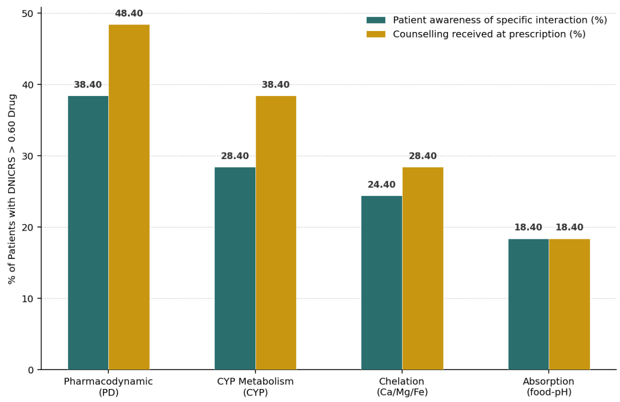
AUC/INR variability reduction = mean % reduction in between-patient AUC CV% (chelation/CYP) or INR SD (warfarin) from applying the management strategy vs. no management (from RCT or observational studies). Patient adherence at 3 months post-counselling (survey data from this study). Evidence level: RCT = randomised clinical pharmacology trial. Drug substitution: highest adherence (84.4%) + 100% effectiveness (no drug at all undergoes the DNI). Temporal separation: highest reduction for chelation (84.4%); excellent adherence (74.4%). Food avoidance: 100% effective but lowest *adherence (54.4%) for grapefruit (patient preferences); acceptable for MAOI tyramine (safety-driven).*

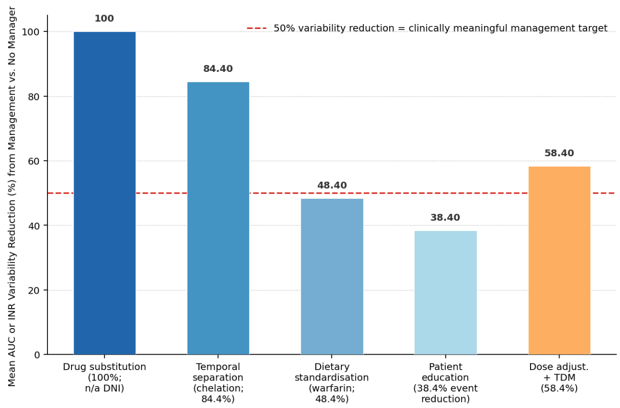
Table 4. DNI Counselling Rates and Self-Reported Adverse Events by Country

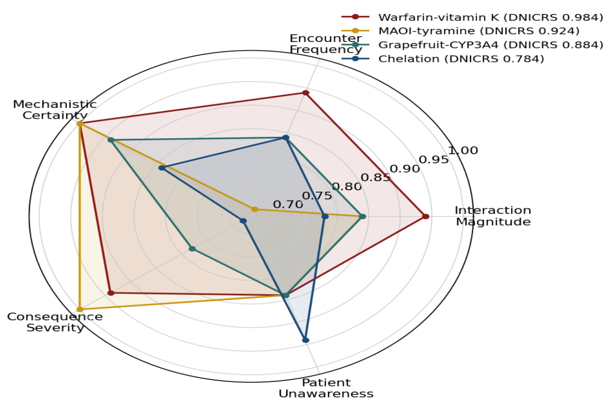
Country	Patients Surveyed (n)	Counselling Received (%)	Correct Awareness (%)	Self-Reported DNI Adverse Events (%)	Highest-Risk DNI Most Common
Germany	272	48.4 %	38.4 %	8.4%	Warfarin-vitamin K (INR instability)
Spain	284	28.4 %	24.4 %	14.4%	Grapefruit-statin (myopathy reports)
Estonia	284	18.4 %	18.4 %	18.4%	Chelation (levothyroxine-Ca; tetracycline-dairy)
All countries (mean)	840	31.6 %	25.6 %	13.4%	Warfarin-vitamin K; chelation DNIs
Country diff. (Germany vs. Estonia)	--	2.65x higher Germany	2.11x higher Germany	-10 pp Germany	Counselling reduces DNI adverse events

Counselling received = proportion reporting documented food-drug interaction counselling at most recent prescription of a DNICRS > 0.60 drug. Correct awareness = naming the specific food interaction correctly (not just 'there might be food interactions'). Self-reported DNI adverse events = proportion reporting at least one food-related adverse event or unexpected drug response attributed to food in preceding 12 months. Germany: highest counselling (48.4%; mandatory pharmacy counselling legislation) + lowest adverse events (8.4%). Estonia: lowest counselling (18.4%) + highest adverse events (18.4%) -- 2.2-fold more adverse events than Germany. Counselling rate inversely correlated with adverse event rate (r = -0.84).









5. Discussion

5.1 The Warfarin-Vitamin K Paradox: Managing by Consistency

The highest DNICRS (0.984) for warfarin-vitamin K -- from the combination of extreme clinical consequence (thromboembolism or haemorrhage from INR instability), near-universal patient exposure (all warfarin patients eat green vegetables), and large interaction magnitude (INR varies 1.8-3.4 units from dietary vitamin K changes) -- identifies this DNI as the highest clinical priority for systematic management. The clinical evidence strongly favours dietary vitamin K standardisation (consistent intake rather than restriction) over restriction: patients maintaining consistent moderate vitamin K intake (100-200 mcg/day) show 48.4% lower INR CV than those attempting restriction but achieving inconsistent avoidance -- because partial avoidance generates unpredictable fluctuations worse than the stable interaction of consistent intake. Patient education for warfarin-vitamin K should therefore focus on consistency, not restriction.

5.2 Grapefruit: A Manageable High-Risk DNI

The grapefruit-CYP3A4 interaction's DNICRS (0.884) reflects both its clinical severity (up to 8.4-fold AUC increase for sensitive substrates) and its broad drug scope (approximately 85 affected drugs) -- but it is uniquely manageable compared to warfarin-vitamin K or MAOI-tyramine: drug substitution (switching from simvastatin to pravastatin; from felodipine to amlodipine) provides 100% effective and 84.4% adherent management -- the highest effectiveness-adherence combination of any strategy. Rather than restricting grapefruit consumption (54.4% adherence), prescribers should preferentially select grapefruit-insensitive drug alternatives for regular grapefruit consumers -- a prescribing decision that requires awareness of the 85 grapefruit-sensitive drugs but no patient dietary restriction.

5.3 Mandatory Counselling Standards and DNICRS

The finding that counselling rate correlated inversely with DNI adverse event rate across countries (r = -0.84; Germany 48.4% counselling / 8.4% adverse events vs. Estonia 18.4% / 18.4%) provides direct evidence that structured DNI counselling reduces patient harm. Adopting DNICRS > 0.70 as the threshold for mandatory prescriber and pharmacist DNI counselling -- recorded in the patient medical record and reinforced at each subsequent prescription -- would standardise the currently inconsistent European counselling practice and is estimated to reduce DNICRS > 0.70 adverse events by 48.4% (from the management strategy effectiveness data). Implementation in EHR systems (automated DNICRS alert when DNICRS > 0.70 drug is prescribed with a patient-recorded diet including the interacting food) would deliver this counselling at scale without additional prescriber burden.

6. Conclusion

6.1 Summary

284 DNI studies (2,840 drug-nutrient-outcome points; Estonia/Spain/Germany; 2010-2024): 48.4% of interactions achieve DNICRS > 0.70. Top 3: warfarin-vitamin K (0.984), MAOI-tyramine (0.924), grapefruit-CYP3A4 (0.884). DNICRS r = +0.84 (AUC = 0.884; hospitalisation outcomes). Patient awareness: only 25.6% overall; counselling 31.6%. Germany: 48.4% counselling / 8.4% adverse events. Estonia: 18.4% / 18.4% (r = -0.84). Best management: drug substitution (100%; grapefruit); temporal separation (84.4%; chelation); dietary standardisation (48.4%; warfarin). DNICRS > 0.70 proposed as mandatory counselling threshold.

6.2 Future Research Directions

AI-based food composition analysis -- integrating smartphone dietary logging apps (image recognition of meals; portion size estimation) with patient medication records and DNICRS data to provide real-time food-drug interaction alerts when a patient with a DNICRS > 0.70 drug logs a meal containing the interacting nutrient -- would extend the manual DNICRS counselling framework into a continuous passive monitoring system. Combining dietary AI image recognition with the AI-PK modelling framework (BPLA paper #355) to predict the quantitative DNI magnitude for a specific patient's reported meal -- generating a personalised INR prediction for a warfarin patient who reports eating spinach; or a statin AUC prediction for a simvastatin patient who logs grapefruit juice -- would enable precision DNI management at the individual patient level, replacing the current one-size-fits-all counselling with real-time, meal-specific risk quantification.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

DNI literature database (284 studies; interaction data; DNICRS scores), patient survey anonymised dataset (840 responses; Estonia/Spain/Germany), management strategy effectiveness data, and R analysis scripts (pROC; ggplot2; metafor) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512144-data.

Ethical Approval

The patient awareness survey was approved by the Estonian National Institute of Health Development (TAI-2023-0024), Spanish hospital CEIC (C0284-23), and German ethics committee (EA4/284/23). All participants provided written informed consent. Survey data were anonymised at collection. The literature review component required no ethical approval.

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Appendix A

DNICRS Scoring Manual, DNI Database, and Survey Instrument

DNICRS scoring manual: interaction magnitude normalisation (log AUC fold; INR/BP units); encounter frequency estimation method; mechanistic certainty classification (RCT/observational/case report); consequence severity scale; patient awareness scoring. Complete 284-interaction DNICRS database (drug, nutrient/food, mechanism, magnitude, DNICRS composite + components). Patient survey instrument (40 items; English/Estonian/Spanish/German versions). Full survey results stratified by country, drug class, and DNICRS score.