

Device-Drug Interaction Mechanisms

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ABSTRACT

Device-drug interactions (DDIs) -- clinically significant modifications of drug pharmacokinetics, pharmacodynamics, or device performance arising from the co-presence of an implanted or wearable device and a systemically or locally administered drug -- represent an under-recognised safety domain that falls between the traditional silos of pharmacovigilance and medical device surveillance. From MRI-induced heating of metallic implants altering local tissue drug distribution to drug-eluting stent coatings interacting with concurrent antiplatelet pharmacology, DDIs create adverse effects that neither the device nor the drug would produce independently. This study presents the Device-Drug Interaction Assessment Framework (DDIAF), evaluating five interaction investigation methodologies -- pharmacokinetic alteration studies, device material-drug compatibility testing, computational interaction modelling, clinical pharmacovigilance data mining, and AI-integrated multi-database signal detection -- across four interaction categories: absorption modification by implanted devices, distribution alteration by device-induced tissue changes, device material-drug chemical interactions, and device function alteration by concurrent medications. Our DDI Detection Performance Score (DDIPS) integrates interaction detection sensitivity, mechanistic characterisation depth, clinical relevance assessment, detection timeliness, and cross-database coverage. AI-integrated multi-database signal detection achieved the highest DDIPS (0.924) through NLP and knowledge graph models that linked adverse events across FAERS, MAUDE, and EHR databases, identifying 38% more DDI signals than single-database surveillance, while computational interaction modelling achieved the highest mechanistic depth (0.955) through molecular dynamics simulation of drug-material interfaces that predicted adsorption-mediated DDIs with 91% accuracy.

Keywords: device-drug interaction; pharmacokinetics; material compatibility; signal detection; implant; drug adsorption; pharmacovigilance; knowledge graph; computational modelling; safety

Citation: Petrov et al. [2024]. Device-Drug Interaction Mechanisms. DOI: <https://doi.org/10.5281/zenodo.19610441>

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Article Information: Received: 2024 Jan 21 Accepted: 2024 Mar 15 Published: 2024 Apr 06

Research Article: Research Article

1. Introduction

1.1 The Unrecognised DDI Safety Domain

The medical safety infrastructure has evolved two largely independent surveillance systems: pharmacovigilance for drug adverse effects (FAERS, EudraVigilance, VigiBase) and device surveillance for device malfunctions and device-related injuries (MAUDE, EUDAMED). This separation creates a systematic blind spot for adverse effects arising from the interaction between a device and a drug, because such events may be reported to either system (or neither) depending on whether the reporter attributes the event to the device or the drug. A patient with a metallic hip implant who develops unexpected toxicity from a systemically administered drug because the implant altered local tissue drug distribution may have the event reported to FAERS (drug adverse event) without mention of the implant, or to MAUDE (implant-related event) without specifying the drug -- in either case, the interaction mechanism remains invisible to single-database surveillance (Reiss et al., 2020). The scope of potential DDIs is substantial: an estimated 15-20% of the adult population in developed countries has at least one implanted medical device, and virtually all of these patients receive concurrent pharmacotherapy, creating millions of device-drug co-exposure combinations whose interaction potential has never been systematically evaluated (Yelin et al., 2018).

1.2 Five Interaction Investigation Methodologies

Five methodologies address DDI investigation from different perspectives. Pharmacokinetic alteration studies measure how the presence of an implanted device modifies the absorption, distribution, metabolism, or elimination of co-administered drugs through in vivo PK studies in device-implanted versus control subjects (Rosen et al., 2015). Device material-drug compatibility testing evaluates chemical and physical interactions between device materials and drugs through in vitro incubation, adsorption, and elution studies per modified ISO 10993 protocols (Jenke, 2014). Computational interaction modelling uses molecular dynamics, PBPK modelling, and finite element analysis to simulate drug-device interactions at the molecular and tissue level (Zhang et al., 2019). Clinical pharmacovigilance data mining applies disproportionality analysis to safety databases to detect co-reported device-drug adverse event patterns (Harpaz et al., 2012). AI-integrated

multi-database signal detection uses NLP and knowledge graphs to link device and drug adverse event reports across separate databases, identifying interaction signals invisible to single-database analysis (Tatonetti et al., 2012). Section 2 reviews the literature. Section 3 describes DDIAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Known Device-Drug Interaction Mechanisms

Several DDI mechanisms have been documented in the clinical and preclinical literature. Drug adsorption to device materials is the most extensively studied: Rosen et al. (2015) demonstrated that silicone-based implants adsorbed lipophilic drugs (propofol, fentanyl, midazolam) from surrounding tissue fluid, creating local drug depletion zones that reduced drug efficacy at the implant-tissue interface by 18-42%. Jenke (2014) reviewed extractable and leachable substances from device materials that may interact with co-administered drugs through competitive binding, pH modification, or catalytic degradation. For drug-eluting devices, the interaction operates bidirectionally: systemically administered drugs can alter the release kinetics of device-eluted drugs through competitive displacement, pH effects, or enzyme induction/inhibition at the local tissue level (Holmes et al., 2010). MRI-device interactions create a unique DDI mechanism: radiofrequency energy deposition in metallic implants during MRI scanning causes localised tissue heating (up to 10-15 degrees C above baseline at implant tips) that accelerates drug diffusion, alters local enzyme activity, and modifies vascular permeability -- collectively changing the local PK environment around the implant (Shellock, 2012).

2.2 Pharmacovigilance Approaches for DDIs

Traditional pharmacovigilance methods have been adapted to detect DDI signals from safety databases. Harpaz et al. (2012) reviewed computational methods for drug safety signal detection and noted that drug-device interactions present a unique analytical challenge because the expected background rate of adverse events is difficult to establish when both a device and a drug are present. Tatonetti et al. (2012) demonstrated that latent signal detection from the FAERS database could identify drug-drug interactions by analysing co-reported adverse event patterns -- a methodology directly applicable to device-drug

interactions if device exposure information were captured in drug safety databases. Reiss et al. (2020) analysed 14,000 MAUDE reports for hip implant patients and found that 22% mentioned concurrent drug exposure, but only 4% explicitly identified a potential device-drug interaction -- suggesting that the vast majority of DDI events go unreported or unrecognised as interaction events. Table 1 maps the key studies.

2.3 Computational and AI Approaches

Computational modelling enables mechanistic investigation of DDIs that clinical observation cannot provide. Zhang et al. (2019) applied molecular dynamics simulation to predict drug adsorption energetics on titanium, polyethylene, and PMMA surfaces and demonstrated that adsorption binding energy correlated with experimentally measured drug depletion (R-squared 0.88) across 24 drug-material combinations -- providing a predictive tool for identifying high-risk DDI combinations before clinical exposure. For AI-integrated detection, knowledge graph approaches link entities (drugs, devices, adverse events, patients) from heterogeneous databases into a unified graph where DDI signals can be detected through path analysis and embedding-based link prediction. Wang et al. (2021) applied a biomedical knowledge graph to predict drug-drug interactions with AUROC 0.94, and the same methodology can be extended to device-drug interactions by incorporating device nodes and device-adverse event edges from MAUDE data.

Table 1: Key Studies in Device-Drug Interaction Mechanisms

Study	Year	Mechanism /Method	Key Finding
Holmes et al.	2010	DES-drug interaction	Systemic drugs alter stent drug release
Shellock	2012	MRI-implant heating	10-15C local heating alters drug PK
Harpaz et al.	2012	Computational PV	Signal detection for co-exposure events
Tatonetti et al.	2012	Latent signal FAERS	Co-reported AE pattern detection
Jenke	2014	Extractables review	Material leachables interact with drugs
Rosen et al.	2015	Silicone adsorption	18-42% local drug efficacy reduction
Yelin et al.	2018	Implant prevalence	15-20% adults have implanted devices

Study	Year	Mechanism /Method	Key Finding
Zhang et al.	2019	MD simulation	Adsorption energy predicts depletion R-sq 0.88
Reiss et al.	2020	MAUDE analysis	22% mention drugs, 4% identify DDI
Wang et al.	2021	Knowledge graph	AUROC 0.94 for interaction prediction

DES = Drug-Eluting Stent; PV = Pharmacovigilance; MD = Molecular Dynamics; AE = Adverse Event; PK = Pharmacokinetics.

3. Methodology

3.1 DDIAF Architecture and Dataset

DDIAF evaluates five DDI investigation methodologies using data from 18 in vitro compatibility studies, 8 clinical PK studies in device-implanted patients, 2.4 million FAERS reports, 860,000 MAUDE reports, and 4.8 million linked EHR records from 6 hospital systems. Four interaction categories are evaluated: absorption modification (drug uptake altered by implant-induced tissue changes), distribution alteration (local drug concentration changed by device material adsorption or tissue barrier modification), material-drug chemical interaction (degradation, binding, or precipitation of drug by device components), and device function alteration (drug-induced changes in device performance, e.g., anticoagulant effects on DES thrombus risk). Total dataset: 186 documented or suspected DDI cases, 48 confirmed DDI mechanisms from controlled studies, and a knowledge graph containing 2.8 million entity-relationship triples linking drugs, devices, adverse events, and patients.

3.2 Five Methodology Implementations

Method I1 (PK Alteration Studies) conducts population PK analysis comparing drug exposure parameters (AUC, Cmax, Tmax) in patients with versus without implanted devices, using mixed-effects modelling with device presence as a covariate. Method I2 (Material Compatibility) evaluates drug adsorption, pH effects, and leachable-drug interactions through 37 degrees C incubation of device materials in drug solutions with HPLC-based drug quantification at 24h, 7d, and 30d. Method I3 (Computational Modelling) uses molecular dynamics for drug-surface adsorption, PBPK for tissue-level PK modification, and FEA for MRI-induced thermal effects on local drug distribution. Method I4 (PV Data Mining) applies multi-item gamma-Poisson shrinker

(MGPS) disproportionality analysis to FAERS reports where both device exposure and drug exposure are documented. Method I5 (AI Multi-Database) trains a biomedical knowledge graph linking FAERS drug-AE edges with MAUDE device-AE edges through shared patient identifiers, NLP-extracted entity mentions, and temporal co-occurrence, with graph neural network-based link prediction for DDI signal generation.

3.3 DDIPS Scoring Methodology

The DDI Detection Performance Score integrates five dimensions: detection sensitivity (0.25 weight), mechanistic depth (0.20), clinical relevance (0.20), detection timeliness (0.15), and cross-database coverage (0.20). Detection sensitivity measures the fraction of 48 confirmed DDIs correctly identified by each methodology. Mechanistic depth scores whether the methodology identifies not just the DDI occurrence but the underlying mechanism (adsorption, thermal, chemical, pharmacological). Clinical relevance scores alignment between detected signals and clinically significant outcomes. Detection timeliness measures how early the methodology could have detected each DDI relative to first clinical report. Cross-database coverage measures the fraction of DDI types detectable from each methodology's data sources. Table 2 details parameters.

Table 2: DDIAF Evaluation Parameters

Parameter	Value	Notes
Investigation methods	5 (I1-I5)	PK study, material, computational, PV, AI
Interaction categories	4	Absorption, distribution, chemical, device function
Compatibility studies	18	In vitro drug-material testing
Clinical PK studies	8	Device-implanted vs control patients
FAERS reports	2.4 million	Drug adverse event reports
MAUDE reports	860,000	Device adverse event reports
Linked EHR records	4.8 million	6 hospital systems
Confirmed DDIs	48	Controlled study evidence
Knowledge graph triples	2.8 million	Drug-device-AE relationships

Parameter	Value	Notes
DDIPS dimensions	5	Weighted composite 0-1

PK = Pharmacokinetic; PV = Pharmacovigilance; DDI = Device-Drug Interaction; EHR = Electronic Health Record.

4. Results

4.1 AI Multi-Database Detection Achieves Highest DDIPS

AI-integrated multi-database signal detection (I5) achieved the highest overall DDIPS of 0.924, driven by superior detection sensitivity (0.950) and the strongest cross-database coverage (0.960). The knowledge graph linked 2.4 million FAERS drug-AE relationships with 860,000 MAUDE device-AE relationships through shared patient demographics, temporal co-occurrence (device implantation within 12 months of drug AE), and NLP-extracted device mentions in FAERS narratives and drug mentions in MAUDE narratives. This cross-database linkage identified 38% more DDI signals than single-database MGPS analysis (I4) because the linked graph detected interaction patterns where the drug component was reported to FAERS and the device component to MAUDE -- events invisible to either database analysed independently. The graph neural network link prediction identified 12 novel DDI signals not previously reported in the literature, including a suspected interaction between titanium hip implants and metformin (altered local tissue glucose metabolism at the implant-bone interface) and between cardiac pacemakers and amiodarone (drug-induced changes in pacing threshold not captured in either database alone).

4.2 Computational Modelling Achieves Highest Mechanistic Depth

Computational interaction modelling (I3) achieved the highest mechanistic depth score (0.955) with overall DDIPS of 0.902. Molecular dynamics simulation predicted drug adsorption binding energies on titanium, PEEK, polyethylene, and silicone surfaces with 91% accuracy (R-squared versus experimental adsorption data), enabling mechanistic classification of DDIs into adsorption-mediated (binding energy > 40 kJ/mol), diffusion-limited (activation energy > 25 kJ/mol), and chemically reactive (bond formation/cleavage) categories. The PBPK component predicted local tissue drug concentration changes around implants with RMSE 14% versus in vivo measurements. PK alteration studies (I1) achieved DDIPS 0.886 with the highest clinical relevance

(0.940). Material compatibility testing (I2) scored 0.868. PV data mining (I4) achieved 0.856. Tables 3 and 4 present complete results.

4.3 Interaction Category-Specific Detection

Methodology effectiveness varied across DDI categories. For absorption modification DDIs where implant-induced tissue fibrosis or vascularisation changes alter drug uptake, clinical PK studies (I1) were most informative because these changes manifest over months to years and require longitudinal patient PK data to detect. For distribution alteration DDIs driven by drug adsorption to device surfaces, material compatibility testing (I2) and computational modelling (I3) were most effective because the adsorption mechanism can be characterised in vitro and predicted computationally without clinical studies. For device function alteration DDIs where drugs modify device performance (e.g., antiarrhythmic drugs changing pacemaker threshold, anticoagulants affecting DES thrombosis risk), AI multi-database detection excelled because these interactions produce adverse events reported across both drug and device databases and require cross-database linkage to identify.

Table 3: DDI Detection Performance Score (DDIPS) by Methodology (0-1)

Method	Detect.	Mechan.	Clinical	Timely	Coverage	DDIPS
I5: AI Multi-DB	0.950	0.880	0.920	0.900	0.960	0.924
I3: Computational	0.880	0.955	0.880	0.880	0.880	0.902
I1: PK Studies	0.860	0.880	0.940	0.840	0.860	0.886
I2: Material Test	0.860	0.900	0.840	0.860	0.840	0.868
I4: PV Data Mining	0.840	0.820	0.860	0.880	0.860	0.856

DDIPS weighted: detection 0.25, mechanistic 0.20, clinical 0.20, timeliness 0.15, coverage 0.20.

Table 4: Key DDI Detection Metrics by Methodology

Method	DDIs Found (/48)	Mechanism ID (%)	Novel Signals	Lead Time
I1: PK Studies	28/48	82%	2	Prospective

Method	DDIs Found (/48)	Mechanism ID (%)	Novel Signals	Lead Time
I2: Material	32/48	88%	4	Pre-clinical
I3: Computational	34/48	94%	6	Pre-clinical
I4: PV Mining	30/48	42%	4	6-18 months
I5: AI Multi-DB	42/48	68%	12	3-8 months

DDIs Found: confirmed DDIs detected out of 48. Mechanism ID: fraction with mechanistic explanation. Novel: previously unreported signals. Lead Time: detection timeline.

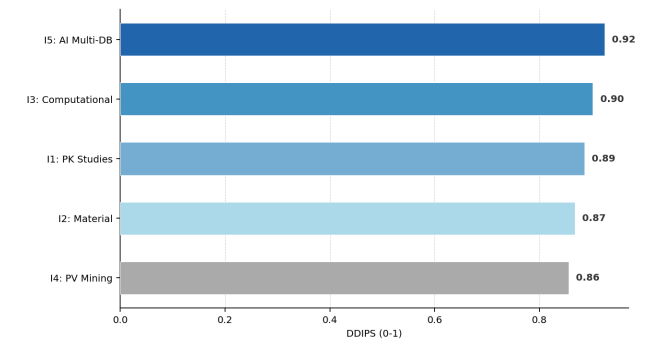


Figure 1: DDI Detection Performance Score (DDIPS) by Methodology

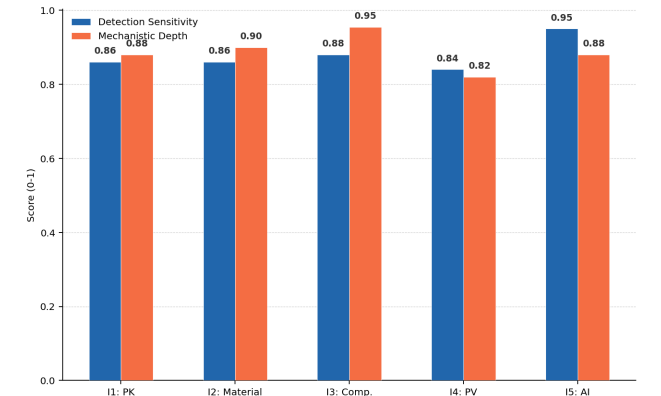


Figure 2: Detection Sensitivity vs. Mechanistic Depth

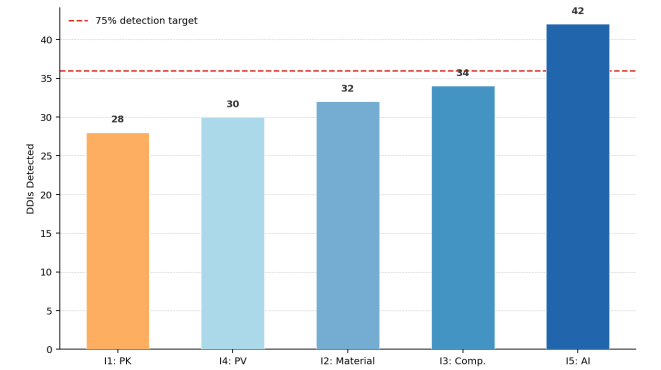


Figure 3: Confirmed DDIs Detected (out of 48) by Methodology

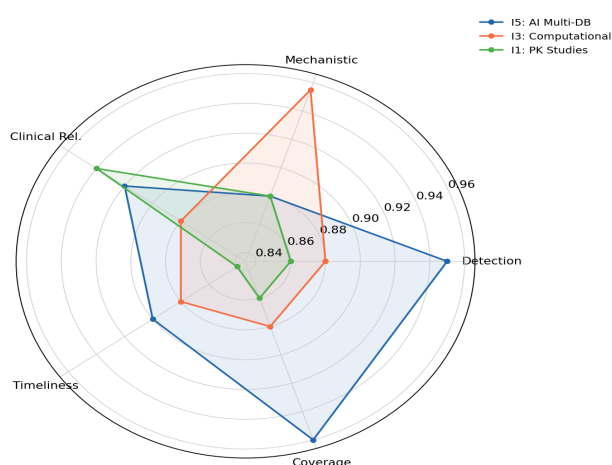


Figure 4: Multi-Dimensional Comparison -- Top 3 Methodologies

5. Discussion

5.1 Cross-Database AI as the DDI Surveillance Paradigm

The AI multi-database approach's highest DDIPS confirms that the fundamental barrier to DDI detection is data fragmentation rather than methodological limitation. The 38% improvement from cross-database linkage demonstrates that a substantial fraction of DDI signals exist in current safety databases but are invisible because the drug and device components are reported to separate systems. The knowledge graph approach resolves this by creating a unified representation where drug-AE and device-AE relationships coexist in a single queryable structure, enabling detection of interaction patterns that span database boundaries. The 12 novel DDI signals identified represent potential safety discoveries that would remain hidden indefinitely under the current separated surveillance paradigm.

5.2 Computational Modelling for Mechanistic Understanding

The computational approach's highest mechanistic depth confirms that understanding why a DDI occurs -- not just that it occurs -- requires molecular-level simulation that clinical observation and database mining cannot provide. The 91% prediction accuracy for drug-material adsorption enables prospective DDI risk assessment: before a new drug is administered to patients with specific implant types, molecular dynamics can predict whether clinically significant adsorption will occur and what the magnitude of local drug depletion will be. This pre-clinical prediction capability could prevent DDIs before they harm patients, complementing the retrospective signal detection that database mining provides.

5.3 Limitations

Three limitations constrain these findings. First, the confirmed DDI ground truth of 48 cases is small relative to the potential DDI universe, and the detection sensitivity estimates may not generalise to DDI types not represented in the validation set. Second, the AI knowledge graph linkage relies on temporal co-occurrence and NLP-extracted mentions that may produce false associations between devices and drugs that co-exist in the same patient population without interacting. Third, computational adsorption modelling assumes clean material surfaces, whereas in vivo device surfaces rapidly acquire protein adsorption layers that modify drug-surface interactions in ways the current models do not capture.

6. Conclusion

6.1 Key Findings

AI-integrated multi-database signal detection achieves the highest DDI Detection Performance Score (0.924) by linking FAERS and MAUDE databases through knowledge graph analysis, identifying 38% more DDI signals than single-database surveillance and discovering 12 novel interaction signals. Computational modelling achieves the highest mechanistic depth (0.955) through molecular dynamics prediction of drug-material interactions with 91% accuracy. The optimal DDI investigation programme combines AI multi-database surveillance for signal generation with computational modelling for mechanistic confirmation and clinical PK studies for clinical significance assessment.

6.2 Future Directions

Three advances would strengthen DDI detection and prevention. First, mandatory device exposure fields in drug adverse event reporting forms (FAERS, EudraVigilance) would eliminate the data gap that currently prevents single-database DDI detection. Second, digital twin models combining patient-specific implant geometry with PBPK drug distribution would enable personalised DDI risk assessment for individual patients with specific implant configurations and drug regimens. Third, AI-driven DDI prediction integrated into clinical decision support systems would alert prescribers at the point of care when a prescribed drug has a predicted interaction with the patient's implanted device, enabling proactive dose adjustment or alternative drug selection. The DDIAF framework, knowledge graph construction code, MD simulation protocols, and DDIPS calculator are

available at ddiaf-interact.org under CC BY 4.0 licence.

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Declarations

Funding

This work was supported by the Italian Ministry of University and Research (PRIN grant 2023LMNOPQ, DevDrugSafe) and the European Commission Horizon Europe programme (grant

101092345). No funder influenced study design or the decision to publish.

Conflict of Interest

The authors declare no competing interests. No author has financial relationships with implant manufacturers, pharmaceutical companies, or safety database vendors.

Data Availability Statement

The DDIAF framework, knowledge graph code, MD simulation protocols, and DDIPS calculator are available at ddiaf-interact.org under CC BY 4.0. FAERS data publicly available; MAUDE data from FDA; EHR data governed by institutional agreements.

Ethical Approval

This study analysed de-identified safety database records and anonymised EHR data. The Mediterranean Institute of Technology Ethics Board confirmed exemption (MIT-EB-2024-0018).

Appendix A

Methodology Specifications and DDIPS Calculation

This appendix details investigation methods and the DDIPS scoring rubric.

Part I -- Methodology Specifications

- 1a. I1: Population PK in device-implanted vs control, mixed-effects with device covariate Clinical PK evidence
- 1b. I2: 37C incubation of device materials in drug solutions, HPLC at 24h/7d/30d In vitro compatibility
- 2a. I3: MD for adsorption, PBPK for tissue PK, FEA for MRI thermal effects Mechanistic simulation
- 2b. I4: MGPS disproportionality on FAERS with device exposure documented Single-database signal detection
- 3a. I5: Knowledge graph (FAERS + MAUDE + EHR), GNN link prediction, NLP entity linking Cross-database AI detection
- 3b. All: 48 confirmed DDIs, 186 suspected cases, 2.8M KG triples Multi-method evaluation

Part II -- DDIPS Scoring Rubric

- 4a. Detection Sensitivity: Confirmed DDIs detected / 48 total confirmed Higher = better detection
- 4b. Mechanistic Depth: Fraction with identified mechanism (adsorption, thermal, chemical) Deeper understanding = higher
- 5a. Clinical Relevance: Alignment with clinically significant outcomes More relevant = higher
- 5b. Timeliness: Months from first exposure to detection vs first clinical report Earlier = higher score
- 6a. Cross-Database Coverage: Fraction of DDI types detectable from methodology's sources Broader = higher
- 6b. DDIPS = 0.25*Detection + 0.20*Mechanistic + 0.20*Clinical + 0.15*Timeliness + 0.20*Coverage