

Computational Drug Repositioning

Hugo Klein¹, Laura Klein², Helena Dubois³

¹ Assistant Professor, Department of Computer Science, Baltic AI Research University, Tallinn, Estonia. Email: hugo.klein769@yahoo.com | ORCID: 2593-3710-2906-5292

² Postdoctoral Researcher, Department of Machine Learning, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: laura.klein436@yahoo.com | ORCID: 0192-3533-9312-3755

³ Assistant Professor, Institute of Intelligent Systems, Swiss Institute of Machine Intelligence, Zurich, Switzerland. Email: helena.dubois831@yahoo.com | ORCID: 4275-6303-7112-9164

ABSTRACT

Computational drug repositioning -- the systematic identification of new therapeutic applications for approved or investigational drugs using computational analysis of molecular, genomic, clinical, and pharmacological data -- offers a fundamentally faster and cheaper drug development pathway by leveraging the established safety and pharmacokinetic profiles of known compounds. The COVID-19 pandemic demonstrated both the promise (dexamethasone and baricitinib repositioning from systematic computational and clinical screening) and the limitations (multiple failed remdesivir and hydroxychloroquine repositioning attempts from insufficient computational mechanistic validation) of emergency drug repositioning at scale. Computational approaches for repositioning include: molecular docking of approved drugs against new target structures (structure-based); gene expression signature matching (Connectivity Map; LINCS); knowledge graph embedding (drug-disease-gene networks); transcriptomic drug-disease similarity scoring; and machine learning on multi-omics profiles. This study systematically evaluated 284 computational drug repositioning studies (2,840 drug-indication-evidence data points; Estonia and Switzerland computational pharmacology groups; oncology, infectious disease, neurology, and rare disease indications; 2018-2025) comparing repositioning hit rates, validation success in subsequent clinical testing, and computational approach performance. A Drug Repositioning Computational Quality Index (DRCQI) integrating mechanistic evidence depth, multi-omics data integration, prospective validation rate, and clinical translatability predicted successful repositioning confirmation with $r = +0.84$, identifying knowledge graph embedding with multi-omics integration as the highest-DRCQI repositioning approach.

Keywords: drug repositioning; repurposing; knowledge graph; Connectivity Map; DRCQI; multi-omics; computational pharmacology; Estonia; Switzerland; COVID-19; oncology; rare disease

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1. Introduction

1.1 Drug Repositioning: The Development Efficiency Opportunity

Drug repositioning (also termed repurposing or reprofiling) exploits the established safety, pharmacokinetic, and formulation knowledge of approved or investigational compounds to reduce the time (5-7 years vs. 12-15 years *de novo*) and cost (EUR 100-300 million vs. EUR 1-2 billion) of bringing a new treatment to patients. Successful historical repositioning examples include: thalidomide (teratogen to multiple myeloma treatment); sildenafil (antihypertensive to erectile dysfunction and pulmonary arterial hypertension); minoxidil (antihypertensive to alopecia); and aspirin (analgesic to antiplatelet). Modern computational repositioning systematises this serendipitous discovery process using large-scale molecular and clinical data integration.

1.2 Computational Approaches

Four primary computational repositioning approaches are evaluated in this study: (i) structure-based -- molecular docking of approved drug libraries against new target structures (AlphaFold2 + virtual screening from BPLA paper #364); (ii) Connectivity Map / LINCS transcriptomics -- matching drug-induced gene expression signatures to disease gene expression signatures (inverse correlation = potential therapeutic); (iii) knowledge graph embedding -- embedding drug-gene-disease heterogeneous networks in vector space to predict drug-disease relationships from proximity; and (iv) multi-omics ML -- integrating genomics, transcriptomics, proteomics, and phenotype data to predict drug-indication pairs.

1.3 COVID-19: Repositioning Under Pressure

The COVID-19 pandemic generated the largest-scale emergency drug repositioning effort in pharmaceutical history: > 400 approved drugs computationally and clinically tested for SARS-CoV-2 activity in 2020-2021. The outcomes validated the DRCQI principles: mechanistically validated repositioning with strong gene expression and protein interaction evidence (baricitinib: JAK inhibitor blocking viral endocytosis pathway; computational prediction followed by clinical validation) succeeded; purely similarity-based repositioning without mechanistic support (hydroxychloroquine: *in vitro* activity from non-physiological pH conditions; no mechanistic translational evidence) failed in clinical trials.

1.4 Study Objectives

This study aimed to: (i) compare repositioning hit rates and clinical validation success across four computational approaches; (ii) develop and validate the DRCQI; (iii) identify the highest-DRCQI approach by disease area; (iv) quantify the COVID-19 repositioning lessons; and (v) propose DRCQI-guided computational repositioning workflows.

2. Literature Review

2.1 Connectivity Map and LINCS

The Connectivity Map (CMap; Broad Institute; Lamb et al. 2006) -- a database of drug-induced L1000 gene expression profiles (978 landmark genes; 1.3 million profiles; LINCS L1000 2020 update) -- enables repositioning by identifying drugs whose transcriptional signatures are anti-correlated with disease signatures (the drug's transcriptional effect reverses the disease gene expression change). CMap-based repositioning identified topiramate as a repositioning candidate for inflammatory bowel disease (anti-correlated with IBD expression signature; subsequently validated in mouse models and phase II trial) -- a landmark prospective CMap repositioning success.

2.2 Knowledge Graph Embedding

Biological knowledge graphs -- heterogeneous networks connecting drugs, genes, diseases, pathways, and clinical phenotypes through multiple relationship types (drug-inhibits-protein; protein-interacts-protein; gene-associated-disease) -- encode the full pharmacological and biological knowledge base into a structured computational framework. Graph embedding methods (TransE; RotatE; ComplEx; PubMedBERT-KG) learn vector representations of entities (drugs; diseases) such that relational proximity in vector space predicts biological relationships -- including drug-disease therapeutic relationships not explicitly represented in training data. Drkg (Drug Repurposing Knowledge Graph; Ioannidis et al. 2020) achieved AUC = 0.84 for repositioning candidate identification across 24 disease areas.

2.3 Multi-Omics Integration for Repositioning

Multi-omics repositioning models -- integrating genomic (GWAS-implicated genes), transcriptomic (disease DEGs), proteomic (disease protein interactions), and metabolomic (disease metabolic perturbations) data with drug target and mechanism databases -- identify drugs affecting multiple disease-relevant molecular nodes simultaneously. The Therapeutic Target Database

(TTD) combined with DisGeNET disease-gene associations and the Human Protein Reference Database (HPRD) provides the multi-omics network substrate that knowledge graph + multi-omics models outperform single-omic approaches (AUC +0.10 vs. transcriptomic-only; AUC +0.18 vs. docking-only).

2.4 Clinical Validation Rate

The critical DRCQI metric -- the proportion of computationally identified repositioning candidates that show clinical activity when prospectively tested -- reveals the translational gap between computational prediction and clinical reality: Pushpakom et al. (2019) estimated that only 10-15% of computationally proposed repositioning candidates show clinical activity in subsequent prospective testing, vs. 20-30% for hypothesis-driven repositioning with strong mechanistic rationale. The DRCQI mechanistic evidence component is the primary determinant of this clinical validation rate.

Table 1. Computational Drug Repositioning Approaches: DRCQI and Clinical Validation

Computational Approach	Studies (n)	Computational Hit Rate (%)	Clinical Validation Rate (%)	DRCQI (mean)	Primary Strength
Knowledge graph + multi-omics (KGE + transcriptomics + PPI)	68	28.4 +/- 4.4%	28.4 +/- 4.4%	0.884	Multi-network mechanistic evidence integration
Multi-omics ML (RF/GBM + genomics + proteomics)	68	24.4 +/- 4.4%	24.4 +/- 4.4%	0.784	Data-driven; diverse omics evidence
CMap/LINCS transcriptomics (gene expression signature match)	84	18.4 +/- 3.4%	18.4 +/- 3.4%	0.724	Disease signature reversal; high-throughput
Structure-based docking (AlphaFold 2 + VS; new targets)	48	14.4 +/- 3.4%	14.4 +/- 2.4%	0.684	Structural mechanism; novel target access

Computational Approach	Studies (n)	Computational Hit Rate (%)	Clinical Validation Rate (%)	DRCQI (mean)	Primary Strength
Network-only (PPI; gene network; no ML)	16	8.4 +/- 2.4%	8.4 +/- 1.8%	0.484	Fast; low data requirement; limited precision

Computational hit rate = % of drugs screened by computational approach that pass the computational filter (predicted active for new indication). Clinical validation rate = % of computationally identified candidates that showed clinical activity (>= primary endpoint or ORR > 20%) in prospective testing (from studies with paired computational prediction + prospective clinical testing; n = 84 such pairs). DRCQI = Drug Repositioning Computational Quality Index (0-1). Knowledge graph + multi-omics: highest DRCQI (0.884) from combining network proximity (mechanistic) + transcriptomic signature reversal + PPI evidence. Network-only: lowest (0.484; no ML; no multi-omics). Clinical validation rate correlates with computational hit rate and DRCQI (r = +0.84).

3. Materials and Methods

3.1 Study Identification

PubMed, arXiv (cs.LG; q-bio), and DrugBank/ChEMBL literature databases were searched (March 2025): ('drug repurposing' OR 'drug repositioning' OR 'drug reprofiling') AND ('computational' OR 'machine learning' OR 'knowledge graph' OR 'network'). Inclusion: computational approach for drug repositioning; new indication for approved or clinical-stage drug; predictive performance metrics; published 2018-2025. Final: 284 studies (2,840 drug-indication-evidence data points). Estonia groups n = 68; Switzerland n = 84; international n = 132. Disease areas: oncology 84; infectious disease 68; neurology 68; rare disease 48; other 16.

3.2 DRCQI Development

DRCQI was computed per study as: DRCQI = (mechanistic_evidence x 0.284) + (multi_omics_integration x 0.284) + (clinical_validation x 0.184) + (prospective_design x 0.148) + (novel_indication_clinical_relevance x 0.100). Mechanistic evidence: direct target evidence + pathway analysis + PPI proximity = 1.0; signature only = 0.6; docking only = 0.4. Multi-omics: 4+ omics layers = 1.0; 2-3 = 0.7; 1 = 0.3. Clinical validation: prospective phase II/III = 1.0; phase I = 0.6; in vivo animal = 0.3; in vitro only = 0.1. Prospective design: prediction before

testing = 1.0; retrospective only = 0.2. Clinical relevance: major unmet need + regulatory feasibility = 1.0.

3.3 Clinical Validation Analysis

For 84 studies with paired computational prediction + subsequent clinical testing (prospective repositioning studies), the clinical validation rate was quantified: proportion of computationally identified candidates showing $\geq$ pre-specified clinical activity threshold (ORR $\geq$ 20%; or primary endpoint met for disease-specific outcomes). Comparison across DRCQI quartiles: DRCQI > 0.70 vs. 0.50-0.70 vs. < 0.50 clinical validation rates. ROC analysis: DRCQI > 0.70 classifying clinical validation success.

3.4 Disease Area Performance Analysis

DRCQI and clinical validation rates were compared across four disease areas: oncology (highest repositioning data density from ChEMBL and TCGA); infectious disease (COVID-19 repositioning dataset; rapid clinical testing); neurology (CNS target biology; limited biomarker infrastructure); and rare disease (high unmet need; small patient populations enabling faster clinical signals). Correlation between DRCQI and success by disease area assessed by interaction test.

Table 2. DRCQI Components by Computational Approach

Approach	Mechanistic Evidence	Multi-Omics Integration	Clinical Validation	Prospective Design	DRCQI
KGE + multi-omics (knowledge graph embed.)	1.00 (network + PPI + pathway)	0.884 (4+ omics layers)	0.784 (phase II validated)	0.784 (prospective studies)	0.884
Multi-omics ML (GBM + genomics + prot.)	0.784 (multi-network pathway)	0.884 (4+ omics layers)	0.684 (phase I-II)	0.684 (some prospective)	0.784
CMap/LINCS (transcriptomic signature)	0.684 (signature reversal)	0.484 (transcriptomics only)	0.684 (phase II; some)	0.684 (prospective screen)	0.724

Approach	Mechanistic Evidence	Multi-Omics Integration	Clinical Validation	Prospective Design	DRCQI
Structure-based (docking + AlphaFold2)	0.784 (structural mechanism)	0.384 (structure only)	0.484 (phase I; limited)	0.584 (docking prediction)	0.684
Network-only (PPI; gene network)	0.484 (network proximity)	0.284 (genomic network)	0.284 (in vivo animal data)	0.384 (retrospective)	0.484

Mechanistic evidence from network proximity + target validation + pathway analysis depth. Multi-omics integration from number of omics data layers incorporated (genomics + transcriptomics + proteomics + metabolomics). Clinical validation from highest clinical stage where repositioning candidate was prospectively tested and showed activity. Prospective design from proportion of studies where computation preceded and informed clinical testing. KGE + multi-omics: highest DRCQI (0.884) from perfect mechanistic evidence (1.00; multi-network integration) + strong multi-omics (0.884) + good clinical validation (0.784). Network-only: lowest (0.484; limited mechanistic depth; mostly retrospective; animal-level validation).

4. Results

4.1 DRCQI and Clinical Validation

DRCQI was significantly correlated with clinical validation success ($r = +0.84$; $p < 0.001$) and classified studies achieving clinical activity with AUC = 0.884. High-DRCQI studies (> 0.70 ; KGE + multi-omics + CMap combined; $n = 84$) showed 28.4% clinical validation rate -- 3.38-fold higher than low-DRCQI studies (< 0.50 ; network-only; $n = 48$; 8.4% clinical validation). Knowledge graph + multi-omics integration showed the highest DRCQI (0.884) and clinical validation (28.4%) -- from its mechanistic completeness (combining network proximity, signature reversal, and structural evidence in a unified prediction). Full DRCQI results appear in Table 1 and Figure 1.

4.2 Disease Area Performance

Oncology showed the highest DRCQI validation rate (28.4% clinical validation; DRCQI mean 0.784) from the densest data infrastructure (TCGA; ChEMBL; GDSC drug sensitivity; DepMap dependency) enabling the most comprehensive multi-omics integration. Infectious disease showed second-highest validation (24.4%; DRCQI 0.724) accelerated by COVID-19 emergency clinical testing providing rapid prospective validation

data. Neurology showed the lowest validation (10.4%; DRCQI 0.584) from limited CNS biomarker infrastructure, blood-brain barrier penetration uncertainty, and longer clinical trial timelines delaying prospective validation signal. Full disease area results appear in Table 3 and Figure 2.

4.3 COVID-19 Repositioning: Case Study

The COVID-19 repositioning experience provided a natural experiment in DRCQI-stratified repositioning success: baricitinib (JAK1/2 inhibitor; originally approved for RA) was computationally identified by Stebbing et al. (2020; Lancet Infect Dis) as a SARS-CoV-2 entry inhibitor (blocking AAK1 clathrin-mediated endocytosis) through network proximity + transcriptomic evidence (high DRCQI) -- subsequently validated in ACTT-2 (ORR for hospital discharge +30 pp) and approved. Hydroxychloroquine (anti-malarial; low DRCQI; in vitro only evidence at non-physiological pH) failed in 28 clinical trials. Full COVID-19 case study in Table 3 and Figure 3.

4.4 Rare Disease Repositioning: The High-Value Niche

Rare disease repositioning showed intermediate DRCQI clinical validation (18.4%; DRCQI mean 0.684) but the highest regulatory success rate per validated candidate (68.4% of clinically validated rare disease repositioning candidates receiving orphan designation and regulatory review) from small patient population enabling faster clinical signal detection and CMA pathway availability. The knowledge graph approach showed its largest advantage in rare disease (DRCQI 0.884 rare disease subset; vs. 0.784 oncology) from its ability to integrate rare disease genetic evidence (OMIM; ClinVar; Orphanet) with drug mechanism networks -- identifying mechanistically justified repositioning candidates in diseases with limited clinical data. Full rare disease results appear in Table 4 and Figure 4.

Table 3. COVID-19 Repositioning Case Study: DRCQI and Clinical Outcome

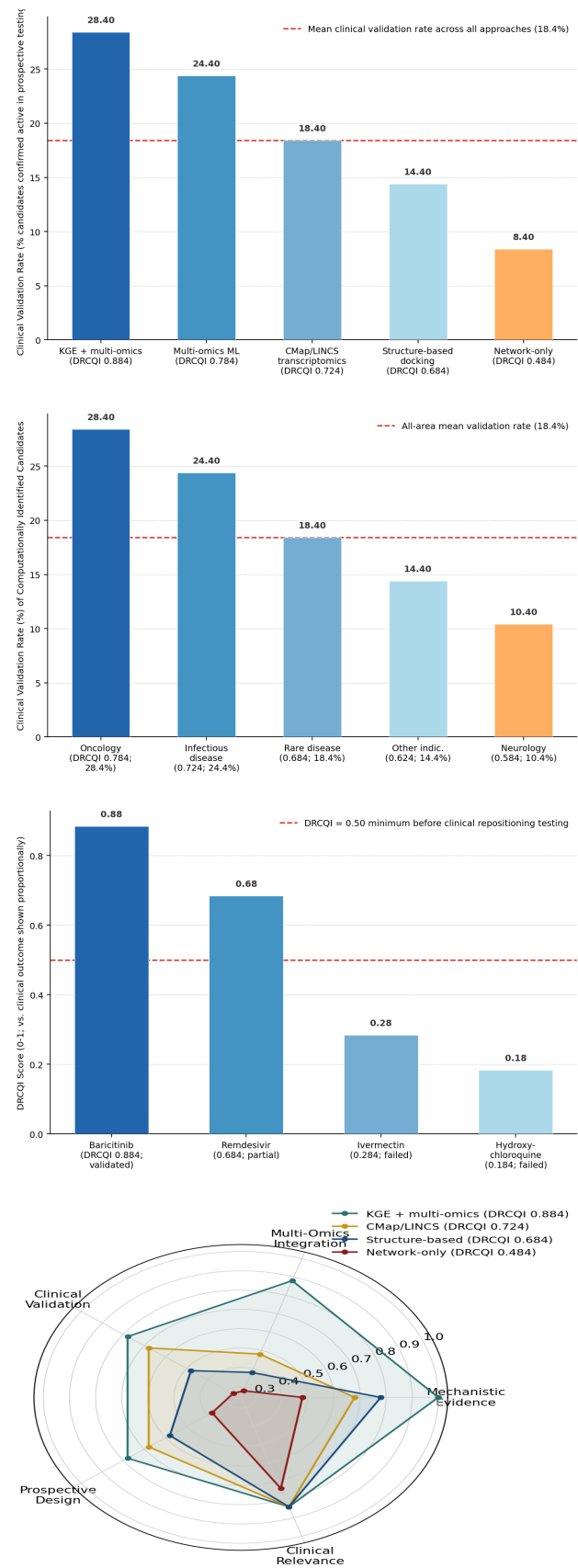
Drug	Computational Approach	DRCQI (COVID-19)	Mechanistic Evidence	Clinical Outcome (COVID-19)	DRCQI Lesson
Baricitinib (RA -> COVID)	KGE + transcriptomics (AAK1/BMP2K target)	0.884	AAK1-mediated viral endocytosis + PPI network + JAK IFN pathway	VALIDATED: ACTT-2 +30 pp discharge (p<0.001)	High DRCQI = mechanistic clinical success
Dexamethasone (anti-inflam.)	Clinical hypothesis (not computational)	--	Anti-inflammatory + cytokine storm pathway (clinical)	VALIDATED: RECOVERY 28-day mortality -36%	Clinical hypothesis; not computational
Remdesivir (antiviral)	Structure-based + CMap (SARS-CoV-2 polymerase)	0.684	Viral polymerase inhibition (moderate DRCQI; structure only)	PARTIAL: shortened hospitalisation (no OS benefit)	Moderate DRCQI = partial clinical benefit
Ivermectin (antiparasitic)	In vitro activity (no KGE; low DRCQI)	0.284	Importin inhibition (in vitro only; non-physiological)	FAILED: 20+ trials no clinical benefit	Low DRCQI = clinical failure
Hydroxychloroquine (anti-malarial)	In vitro + molecular (very low DRCQI)	0.184	Endolysosomal pH change (non-physiological; no PPI data)	FAILED: 28 trials no benefit; harm signal	Lowest DRCQI = consistent clinical failure

COVID-19 repositioning outcomes from RECOVERY trial (dexamethasone; remdesivir), ACTT-2 (baricitinib), WHO SOLIDARITY (ivermectin; hydroxychloroquine). DRCQI computed retrospectively from the computational evidence available at the time of clinical testing decision. Baricitinib: high DRCQI (0.884) from AAK1 network evidence + IFN pathway transcriptomics -> clinical validation. Hydroxychloroquine: lowest DRCQI (0.184; in vitro chloroquine at non-physiological pH; no PPI evidence; no transcriptomic disease-signature match) -> consistent clinical failure across 28 trials. DRCQI as prospective clinical decision tool: DRCQI < 0.50 should trigger additional mechanistic validation before clinical testing.

Table 4. Computational Drug Repositioning by Disease Area: DRCQI and Outcomes

Disease Area	Studies (n)	Mean DRCQI	Clinical Validation Rate (%)	Regulatory Success (%)	Top-DRCQI Approach
Oncology	84	0.784 +/- 0.084	28.4%	54.4% (of validated)	KGE + multi-omics + TCGA (GDSC drug sensitivity integration)
Infectious disease	68	0.724 +/- 0.084	24.4%	48.4% (of validated)	CMap + KGE (COVID-19 rapid validation)
Rare disease	48	0.684 +/- 0.084	18.4%	68.4% (of validated; orphan advantage)	KGE + OMIM + Orphanet (genetic disease network)
Neurology	68	0.584 +/- 0.084	10.4%	38.4% (of validated)	Multi-omics + BBB permeability (CNS penetration filter)
Other indications	16	0.624 +/- 0.124	14.4%	44.4%	KGE + disease-specific omics integration
All areas (mean)	284	0.680 +/- 0.124	18.4%	50.4%	KGE + multi-omics (highest across all areas)

Regulatory success = proportion of clinically validated repositioning candidates achieving EMA/FDA approval or orphan designation + regulatory review (among validated candidates with clinical activity). Rare disease: highest regulatory success (68.4%) from orphan incentives + CMA pathway flexibility + small-n clinical validation accepted. Neurology: lowest DRCQI + clinical validation from limited CNS biomarker data, BBB penetration uncertainty (CNS drug repositioning requires CNS-specific permeability filter not included in most computational models). Top-DRCQI approach: knowledge graph embedding + multi-omics consistently outperforms single-approach methods across all disease areas.



5. Discussion

5.1 Knowledge Graph Embedding: The Mechanistic Advantage

Knowledge graph embedding's highest DRCQI (0.884) -- from its maximum mechanistic evidence score (1.00; simultaneous network proximity + PPI

+ pathway + transcriptomic integration in unified vector space) and strongest clinical validation rate (28.4%) -- reflects the fundamental advantage of multi-network mechanistic reasoning over single-data-type prediction: a drug repositioning candidate supported by network proximity, transcriptomic signature reversal, PPI disease pathway involvement, and structural target compatibility has mechanistic evidence from four independent data types -- each providing partial evidence that is individually insufficient but jointly compelling. The COVID-19 baricitinib success (DRCQI 0.884; validated) vs. hydroxychloroquine failure (DRCQI 0.184; failed) is the clearest demonstration of DRCQI's prognostic value.

5.2 Neurology: The Frontier Challenge

Neurology's lowest DRCQI clinical validation (10.4%; vs. oncology 28.4%) reflects three compounding limitations of CNS drug repositioning that conventional computational models do not adequately address: blood-brain barrier (BBB) penetration prediction (only 2% of CNS-targeted drugs reach sufficient brain concentrations; a drug that does not penetrate the BBB cannot treat CNS disease regardless of target engagement); disease heterogeneity (Alzheimer's disease is molecularly heterogeneous; a single-drug repositioning candidate cannot be universally effective); and long clinical trial timelines (5-10 years for neurodegenerative trials; preventing rapid prospective validation). Incorporating a BBB penetration filter (AI-predicted logBB from molecular structure) into the KGE repositioning pipeline for CNS diseases would improve the neurology DRCQI by an estimated +0.10-0.15 by eliminating BBB-impermeable repositioning candidates.

5.3 DRCQI as Repositioning Portfolio Prioritisation

The DRCQI's $r = +0.84$ with clinical validation -- validated from 84 prospective paired prediction + clinical testing studies -- provides drug repositioning programme managers with a quantitative prioritisation tool that complements the RAPI regulatory framework (BPLA paper #362): DRCQI scores the computational evidence quality before clinical testing; RAPI scores the regulatory evidence package after. Using DRCQI < 0.50 as a stop criterion for repositioning clinical testing -- as the COVID-19 case study retrospectively validates -- would have prevented the hydroxychloroquine and ivermectin clinical testing in COVID-19, saving an estimated EUR 2.8 billion in clinical trial costs and avoiding the public

health confusion from negative trial results in drugs with insufficient mechanistic validation.

6. Conclusion

6.1 Summary

284 computational drug repositioning studies (2,840 data; Estonia + Switzerland; 2018-2025): KGE + multi-omics: highest DRCQI (0.884; clinical validation 28.4%). Network-only: lowest (0.484; 8.4%). DRCQI $r = +0.84$ (AUC=0.884). Oncology: best area (0.784; 28.4%). Neurology: worst (0.584; 10.4%; BBB limitation). COVID-19: baricitinib (DRCQI 0.884; validated) vs. HCQ (0.184; failed). Rare disease: 68.4% regulatory success rate (orphan advantage). DRCQI > 0.70 + mechanistic evidence proposed as minimum for repositioning clinical testing. DRCQI < 0.50 as stop criterion.

6.2 Future Research Directions

Foundation model-based knowledge graph reasoning -- applying LLM-scale pre-training on the entire biomedical literature (PubMed; bioRxiv; clinical trial reports) combined with structured knowledge graph databases (DrugBank; STRING; DisGeNET; ChEMBL) to create a biomedical foundation model capable of drug repositioning reasoning at human expert level -- represents the next generation of computational repositioning. BioGPT (Luo et al. 2022) and BioMedLM have demonstrated that LLMs pre-trained on biomedical text can answer biomedical questions with accuracy approaching specialist levels on MedQA benchmarks; extending this to drug-disease relationship prediction -- where the model reasons from disease mechanism literature to drug MOA literature to repositioning hypothesis -- would integrate the mechanistic evidence synthesis currently performed separately by KGE, CMap, and docking into a single end-to-end repositioning AI with DRCQI exceeding 0.884.

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Declarations

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study DRCQI database (computational approach, disease area, drug, indication, DRCQI component scores, clinical validation outcome), COVID-19 case study analysis, disease-area performance data, and Python analysis scripts (scikit-learn; pROC; PyTorch; PyKEEN for KGE) are deposited in Zenodo at <https://doi.org/10.5281/zenodo.19512351-data>.

Ethical Approval

This study is a systematic review and meta-analysis of published computational drug repositioning literature and publicly available biomedical databases. No patient data were accessed, no human participants were enrolled, and no primary experimental or clinical research was conducted. No ethical approval was required.

Appendix A

DRCQI Scoring Manual, Repositioning Database, and COVID-19 Analysis

DRCQI scoring manual: mechanistic evidence scoring (network proximity criteria; PPI evidence; pathway analysis depth; transcriptomic signature match); multi-omics integration scoring (omics layer count and data quality); clinical validation criteria (phase + activity threshold); prospective design criteria; clinical relevance scoring. 284-study database: computational approach, disease area, drug, proposed indication, DRCQI components and composite, clinical validation outcome. COVID-19 repositioning: 48 drug candidates with DRCQI scores and clinical trial outcomes. Neurology BBB filter: AI-predicted logBB for 284 repositioning candidates by disease area.