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Review Article

AI-Enabled Drug Repurposing: Accelerating the Discovery of New Therapeutic Uses

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ABSTRACT

Objective: To critically examine how artificial intelligence (AI) is being used to identify new therapeutic uses for existing or investigational medicines, with emphasis on validation, reproducibility, clinical translation and regulatory considerations.

Methods: A structured narrative literature search was conducted on 18 October 2026 using PubMed/MEDLINE, publisher platforms for peer-reviewed biomedical literature, and U.S. Food and Drug Administration (FDA) regulatory sources. Searches covered drug repurposing/repositioning combined with artificial intelligence, machine learning, deep learning, natural language processing, knowledge graphs, graph neural networks, generative AI, validation and clinical translation. Priority was given to primary studies, comparative benchmarking studies, authoritative reviews and current regulatory documents. Title/abstract screening was followed by full-text assessment for relevance; reference-list citation chasing was used to identify additional key studies. This was a narrative review and was not designed as a PRISMA systematic review or meta-analysis.

Findings: AI can integrate heterogeneous molecular, omics, literature and clinical data and can prioritize drug–disease associations. However, reported performance is highly dependent on dataset construction and evaluation design. TxGNN, a graph foundation model, improved zero-shot indication and contraindication prediction relative to benchmark methods, whereas recent benchmarking studies show that random or transductive splits can inflate performance because of similarity, redundancy and information leakage. AI-assisted hypotheses have reached experimental and clinical validation in selected examples, notably baricitinib for COVID-19 and generative-AI prioritization of Alzheimer disease candidates using real-world electronic health records; these examples demonstrate different levels of evidence and should not be interpreted as proof that computational predictions alone establish efficacy.

Conclusion: AI-enabled drug repurposing is best viewed as a hypothesis-generation and candidate-prioritization approach. Its translational value will depend on leakage-resistant external validation, mechanistic and pharmacokinetic feasibility, prospective clinical evaluation, transparent reporting, regulatory engagement and multidisciplinary review involving pharmacists, pharmacologists and clinicians.

Keywords: Drug repurposing; Drug repositioning; Artificial intelligence; Machine learning; Deep learning; Natural language processing; Knowledge graphs; Graph neural networks; Foundation models; Generative AI; Drug discovery; Pharmacology; Pharmacokinetics; Drug safety.

1. Introduction

Drug repurposing, also termed drug repositioning, refers to identifying a new therapeutic use for a medicine that has already been approved or clinically investigated for another indication.[1,2] The approach can reduce uncertainty because prior development may have generated information on pharmacology, pharmacokinetics, manufacturing, dosing and human safety. These advantages do not eliminate the need to establish efficacy and safety for the proposed new use, but they can alter the starting point of development compared with a de novo drug candidate.[2]

AI has expanded the scale at which repurposing hypotheses can be generated. Machine learning (ML), deep learning (DL), natural language processing (NLP), knowledge graphs (KGs), graph neural networks (GNNs) and foundation models can integrate relationships among drugs, targets, genes, pathways, phenotypes, diseases and clinical records.[3-6] The resulting predictions may help researchers prioritize candidates for laboratory or clinical testing rather than examining every possible drug–disease pair manually.

A critical distinction is therefore required between computational prediction and therapeutic evidence. A high prediction score does not demonstrate target engagement at clinically achievable concentrations, efficacy in humans, or an acceptable benefit–risk balance. Recent benchmarking work shows that apparently strong computational performance can be reduced when evaluation is designed to test genuinely unseen drugs, targets or diseases.[7,8] The central translational sequence is: existing drug → data integration → AI prediction → mechanistic/pharmacological assessment → experimental validation → clinical evaluation → regulatory decision.

2. Methodology / Literature Search Strategy

Review design. This manuscript was revised as a structured narrative review rather than a systematic review or scoping review. The purpose was to synthesize representative evidence across AI methodologies, validation studies, disease

applications, safety, regulatory science and pharmacist involvement. No meta-analysis was performed because the included studies used heterogeneous datasets, tasks, endpoints and validation designs.

Search date. The principal literature search and reference verification were performed on 18 October 2026. The search therefore included publications and regulatory materials available online by that date.

Information sources. PubMed/MEDLINE was used for biomedical indexing and primary-study verification. Publisher and journal platforms, including Nature Portfolio, Wiley, Oxford Academic and Elsevier/ScienceDirect, were used to verify bibliographic details and obtain full-text information where available. FDA and Federal Register sources were used for current U.S. regulatory information.

Core search strategies. The following representative Boolean searches were used:

- ("drug repurposing" OR "drug repositioning") AND ("artificial intelligence" OR "machine learning" OR "deep learning")
- ("drug repurposing" OR "drug repositioning") AND ("graph neural network" OR GNN OR "knowledge graph")
- ("drug repurposing") AND ("generative AI" OR ChatGPT OR "foundation model")
- ("drug repurposing") AND ("clinical translation" OR validation OR "real-world evidence" OR "clinical trial")
- ("drug repurposing") AND (oncology OR cancer OR neurological OR Alzheimer* OR infectious OR antimicrobial OR "rare disease")
- ("drug repurposing") AND (safety OR pharmacokinetic* OR regulatory OR patent OR exclusivity)

Eligibility. Priority was given to peer-reviewed primary studies that reported an AI-enabled repurposing method or a validation study; comparative benchmarking studies examining generalization or leakage; authoritative reviews that synthesized the field; and current FDA/Federal Register documents. Foundational drug-repurposing and AI methodology papers were retained regardless of publication year when necessary to define concepts.

Exclusion. Articles unrelated to therapeutic repurposing, purely technical AI studies without a relevant drug-repurposing application, duplicate publications, promotional material, and reports without sufficient methodological or bibliographic information were excluded from the synthesis.

Screening and synthesis. Records were screened first by title/abstract relevance and then by full-text relevance to the review questions. Reference lists of key reviews and primary studies were also examined to identify seminal or corroborative evidence. Because this was a narrative review conducted by the author rather than a registered systematic review, a PRISMA flow diagram and formal risk-of-bias meta-analysis were not claimed. Quantitative performance values are reported only when they could be verified from the original publication.

Reporting transparency. For AI studies, the synthesis emphasized dataset composition, split strategy, evaluation metric, internal versus external validation, experimental/clinical validation, reproducibility resources and translational status. This approach was adopted because recent benchmarking studies show that evaluation design can substantially influence reported performance.[7,8]

3. Background

3.1 Drug repurposing

Drug repurposing involves finding a new therapeutic indication, population, formulation, route, dosing strategy or combination for an existing medicine.[1,2] The major attraction is that prior development can provide information that would otherwise have to be generated during early development. Nevertheless, a new indication can involve a different disease mechanism, tissue exposure, dose, duration, patient population or concomitant medication profile, so previous safety experience cannot simply be transferred without qualification.[2] [28]

3.2 Why AI is relevant [29,30]

Traditional repurposing may depend on literature review, mechanistic reasoning, clinical observation, phenotypic screening and serendipitous findings. AI enables systematic analysis of larger heterogeneous datasets. ML methods can learn associations from drug–disease or drug–target matrices; DL can learn nonlinear representations; NLP can mine biomedical text; KGs represent entities and relationships; and GNNs can learn from graph topology and biological context.[3-6] [29,30,31]

The major conceptual advantage is not that AI makes a drug clinically effective, but that it can reduce the search space and identify testable hypotheses. This distinction is central to responsible interpretation of AI-enabled repurposing. [28,32]

4. Current Evidence

4.1 Machine learning and deep learning

Traditional ML methods used in repurposing include random forests, support vector machines, logistic regression, gradient-boosting methods and matrix factorization. DL methods include multilayer neural networks and graph-based architectures. Their applications include drug–target interaction prediction, drug–disease association prediction, molecular representation learning, response prediction and integration of omics data.[3-5] [29,30]

The evidence base has expanded rapidly, but model-to-model comparison remains difficult because studies use different datasets, negative-sample definitions, train/test splits and evaluation metrics. A 2026 systematic literature review of ML and DL-based drug repositioning highlighted the rapid growth of these methods but also the heterogeneity of computational approaches and validation practices.[9] [29]

4.2 Knowledge graphs and graph neural networks [32]

KG-based methods represent biomedical entities as nodes and their relationships as edges, for example drug–target–gene–pathway–disease relationships. They can integrate heterogeneous information and support link prediction. However, KG performance can be affected by literature bias, node-degree effects and incomplete or unevenly curated relationships.[6,10] [32]

GNNs extend this approach by learning representations from graph neighborhoods. Their potential is particularly relevant to complex diseases in which therapeutic effects may arise through multiple interacting biological pathways. Yet the same graph structure that makes these models powerful can also create shortcuts: a model may appear to generalize while exploiting similarities or information already represented in the training graph.[7,8] [32]

4.3 Foundation models and zero-shot repurposing

TxGNN is an important example of a graph foundation model designed for multi-disease, zero-shot drug repurposing. It used a medical knowledge graph covering 17,080 diseases and ranked drugs for potential indications and contraindications. Under stringent zero-shot evaluation, TxGNN improved indication prediction by 49.2% and contraindication prediction by 35.1% relative to the benchmark comparison reported by the authors; under another AUPRC-based zero-shot analysis, it achieved a 19.0% gain for indications and 23.9% for contraindications over the next-best method.[11] Importantly, many predictions aligned with off-label prescribing in a large healthcare system, and an explanation module exposed multi-hop knowledge paths. These findings support model utility for prioritization and interpretability, but they do not constitute prospective clinical efficacy evidence.

4.4 Critical appraisal of model performance

Recent evidence suggests that performance should be interpreted according to the deployment question. Random pair splits can be useful for benchmarking within a known data distribution, but they may be optimistic when highly similar drugs, targets or diseases occur in both training and test sets. de la Fuente et al. showed that transductive DTI approaches can produce inflated performance and poor generalization when evaluated using conventional protocols.[7] Réda et al. similarly benchmarked 11 collaborative-filtering models across eight drug-repurposing datasets and showed that uncontrolled bias in unknown associations can cause severe leakage and misestimate performance.[8]

The implication is that future studies should report at least one stringent evaluation such as drug-cold, target-cold, disease-cold, scaffold-based or temporal splitting, together with independent external validation where possible. Recent work on KG embedding further found substantial performance loss when moving from random/cold-start test sets to an independent Orphanet-based test set, reinforcing the importance of realistic evaluation.[12]

Reproducibility also requires disclosure of data versions, preprocessing, negative-sample construction, split rules, model code, random seeds and hyperparameters. Open code and data availability in studies such as TxGNN and de la Fuente et al. provide useful examples of transparent computational reporting.[7,11]

5. Clinical Applications

5.1 Oncology

Oncology is well suited to repurposing because cancer biology generates extensive molecular, transcriptomic and clinical data. AI can prioritize drugs against cancer-associated targets, identify pathway similarities, predict combinations and stratify opportunities according to molecular biomarkers.[5,13] However, the oncology evidence base contains many computational candidates that remain preclinical. A 2026 review specifically emphasized the need to distinguish candidate ranking from experimental and clinical validation and highlighted toxicity-aware modeling, interpretability and multi-omics integration as important translational priorities.[13] [30,31]

For oncology, a credible AI claim should therefore progress beyond an association score to evidence of target engagement, clinically achievable exposure, tumor-model activity, combination safety and—when justified—prospective clinical testing.

5.2 Neurological disorders

Central nervous system diseases are attractive targets because conventional development is difficult and disease biology is highly heterogeneous. AI can combine genetics, brain transcriptomics, protein interactions, drug perturbation data and clinical records. The 2024 generative-AI Alzheimer disease study provides a useful example of real-world validation: ChatGPT-generated candidates were screened against electronic health records from Vanderbilt University Medical Center and the NIH All of Us Research Program. In meta-analysis, metformin, simvastatin and losartan were associated with lower incident Alzheimer disease risk; however, the study was observational, some estimates were inconsistent between datasets, and the authors emphasized that additional preclinical and clinical studies are required.[14] [31]

5.3 Infectious diseases

The COVID-19 pandemic demonstrated both the promise and the limitations of AI-assisted repurposing. BenevolentAI identified baricitinib as a candidate for COVID-19 based on a combination of its known JAK inhibition and predicted effects on host-cell viral entry pathways.[15] Subsequent experimental work provided mechanistic support, including evidence of antiviral and anti-inflammatory activity, and a randomized ACTT-2 trial involving 1,033 hospitalized adults found that baricitinib plus remdesivir shortened median recovery time from 8 to 7 days (rate ratio for recovery 1.16; 95% CI 1.01–1.32; P=0.03).[16,17] This is an example in which an AI-derived hypothesis progressed through mechanistic evidence to randomized clinical evaluation. The trial, however, evaluated a specific treatment combination and clinical

context; it does not validate AI prediction as a standalone regulatory endpoint.

Conversely, the COVID-19 experience with other computationally prioritized drugs demonstrated that early in-silico signals may fail in larger clinical studies. Thus, infectious-disease repurposing illustrates the necessity of experimental and prospective clinical validation.

5.4 Rare diseases

Rare diseases are characterized by small patient populations, heterogeneous phenotypes and limited treatment data. These features make zero-shot and knowledge-graph approaches attractive because they can transfer information from related diseases and biological pathways.[11,18] TxGNN is particularly relevant because its evaluation included diseases without established treatments. Nevertheless, rare-disease predictions are especially vulnerable to sparse and biased data, making independent clinical or laboratory validation essential.

5.5 Antimicrobial resistance [32]

Drug repurposing has been investigated as one strategy for expanding the antimicrobial pipeline, including identification of drugs with direct antimicrobial effects, host-directed effects or synergy with existing antibiotics.[19] AI may accelerate candidate ranking by integrating pathogen targets, host–pathogen networks, resistance mechanisms and chemical information. However, antimicrobial repurposing must also consider achievable concentrations, tissue penetration, pathogen susceptibility, resistance selection and stewardship implications.

6. Safety & Limitations

6.1 Dataset quality and information leakage

AI models are only as reliable as the datasets and labels on which they are trained. Missing data, inconsistent annotations, duplicate records, publication bias, class imbalance and uncertain negative examples can distort model performance.[6,8,12] Information leakage is a particularly important problem: near-duplicate drugs, targets or disease relationships may cross train/test boundaries, causing models to memorize rather than generalize. Recent methodological studies show that leakage-controlled or cold-start evaluations can substantially reduce apparent performance.[7,12]

6.2 Algorithmic and population bias [33]

Biomedical data are not neutral samples of the entire population. EHRs, clinical trials and published literature may underrepresent children, older adults, minority populations, patients with multiple comorbidities and healthcare settings outside major academic systems. Models trained on these data may therefore produce predictions that do not transport to other populations.

6.3 Explainability and causal inference [34]

A prediction can identify an association without explaining whether the relationship is causal. KGs may also reflect literature popularity rather than true biological importance. Explainable AI can provide mechanistic paths or feature contributions, but an explanation generated by a model is not itself experimental proof. TxGNN's explainer is a useful example of increasing interpretability, while KG literature has warned that connectivity and literature bias can influence predictions.[6,11]

6.4 Pharmacokinetic and pharmacodynamic feasibility [28]

A predicted target interaction is clinically useful only if the drug can reach the relevant site at an effective concentration without unacceptable toxicity. Key considerations include absorption, distribution, metabolism, elimination, protein binding, active metabolites, tissue penetration, blood–brain barrier penetration, dose limits, organ impairment and drug–drug interactions. These factors are particularly important when AI predicts a use requiring a dose or exposure different from the approved indication. [28,34]

6.5 Safety and benefit–risk assessment

Previous human exposure provides valuable safety information but does not guarantee safety in a different population, dose, duration or disease state. AI pipelines should therefore incorporate toxicity, contraindications, drug interactions and pharmacovigilance data rather than ranking candidates only by predicted efficacy. [28]

6.6 Regulatory and intellectual-property challenges [33,34]

Regulatory approval remains evidence-based. The FDA states that new uses of approved drugs must be supported by safety and effectiveness data; the Agency's 2026 drug-repurposing initiative specifically sought input on potential candidates for unmet medical needs and emphasized factors such as strength of evidence, disease burden and public-health impact.[20,21] A computational prediction is therefore an upstream hypothesis, not a substitute for the evidence needed for a new indication.

The regulatory route depends on the product and proposed change. Where additional clinical investigation is required, an IND may be appropriate before studies in humans. A sponsor seeking marketing authorization must provide adequate evidence for the proposed use and appropriate labeling; FDA describes the NDA as the formal application through which sponsors seek approval and evaluates safety, effectiveness, labeling and manufacturing quality.[22] For some products and development situations, a 505(b)(2) application may provide an abbreviated pathway when permitted, but the appropriate route is case-specific and should be confirmed with FDA rather than assumed solely because a drug is already approved.[23]

Intellectual-property and commercial incentives also influence repurposing. Patents may cover a drug substance, formulation or method of use, while FDA exclusivity is a separate legal mechanism. FDA notes that 'other' or new-clinical-investigation exclusivity may provide three years in qualifying circumstances, while patent terms and other exclusivities may operate independently.[24] For off-patent medicines, limited

commercial incentives can make it difficult to fund confirmatory trials even when a scientific signal exists.[25]

7. Emerging Advances

7.1 Generative AI

Generative AI can rapidly synthesize biomedical literature and generate candidate hypotheses. Its limitation is that language models may reproduce literature frequency, outdated information or unsupported associations. The Alzheimer disease study demonstrates a useful model of responsible use: generative AI was used for candidate prioritization, while independent real-world datasets were used for subsequent evaluation.[14] [34]

7.2 Multimodal and multi-omics AI [30,31]

Future models are likely to integrate genomics, transcriptomics, proteomics, metabolomics, radiomics, molecular structure and EHR phenotypes. Such integration may improve biological context and enable patient-specific repurposing, but it also increases complexity, missingness and opportunities for leakage. The 2026 Annual Review of Medicine emphasizes the potential of combining AI/ML with genetics, multi-omics and real-world evidence while identifying translational questions that remain unresolved.[26]

7.3 Explainable and mechanism-aware AI

Mechanism-aware models should provide not only a ranking but also a biologically plausible rationale, including relevant targets, pathways, biomarkers and predicted exposure. This could make computational hypotheses easier to challenge experimentally and more useful to clinicians.

7.4 Digital twins and synthetic data [30]

Synthetic clinical data and patient-level computational models may support trial design, subgroup identification and hypothesis generation. However, synthetic data must be validated against real-world distributions and clinically meaningful outcomes; otherwise, generated datasets may reproduce or amplify bias.

7.5 Human–AI collaboration

The emerging direction is not autonomous drug selection but collaborative decision-making. Pharmacists, pharmacologists and clinicians can evaluate whether an AI-ranked candidate is pharmacologically plausible, clinically feasible, safe and ethically appropriate.

8. Pharmacist's Role

Pharmacists provide an essential bridge between computational prediction and medication use. Their contribution should include: [35]

- Evidence appraisal: distinguish computational association from mechanistic, preclinical and clinical evidence.
- Medication safety: assess adverse effects, contraindications, drug–drug interactions and dose-related toxicity.
- PK/PD assessment: evaluate dose, exposure, organ-function adjustments, therapeutic drug monitoring and tissue penetration.
- Patient-specific assessment: consider age, comorbidities, renal/hepatic function, concomitant medicines and prior adverse reactions.
- Clinical implementation: support protocol development, monitoring and patient counselling when a repurposed use enters practice.
- Pharmacovigilance: detect and document new adverse reactions, interactions, medication errors and unexpected long-term effects.
- Antimicrobial stewardship: assess susceptibility, dosing, resistance selection and combination therapy when repurposing antimicrobials.
- AI literacy: communicate that an AI-predicted use is not equivalent to an approved clinical indication. [35]

9. Research Gaps and Novel Contributions

The principal evidence gaps are not simply technological. They concern whether computational improvements translate into better therapeutic decisions. [29,33,34]

- External validation: many studies remain dependent on internal benchmarks; independent disease, drug and healthcare-system datasets are needed. [29,32]
- Leakage-resistant evaluation: random splits should be supplemented by drug-cold, target-cold, disease-cold, temporal or similarity-controlled evaluation.
- Prospective validation: few computational predictions progress to prospective clinical trials designed specifically to test the AI-generated hypothesis. [29]
- Reproducibility: data versions, preprocessing, negative sampling, code, random seeds and model checkpoints should be reported.
- Causal inference: models should distinguish biological association from causal therapeutic effect.
- Safety-aware ranking: contraindications, toxicity and pharmacokinetic feasibility should be incorporated at candidate-selection stages.
- Negative evidence: failed predictions and negative experimental results should be reported to reduce publication and survivorship bias.
- Regulatory science: standardized expectations for AI-derived repurposing hypotheses, evidence packages and validation are still evolving. [33,34]
- Human–AI evaluation: studies should measure whether AI actually improves expert decision-making rather than only whether a model achieves a higher benchmark score. [35]

Novel contribution of this review. Unlike technology-focused summaries that primarily catalogue AI methods, this review organizes the evidence around the translational chain from prediction to patient use. It explicitly separates computational performance, experimental validation, real-world evidence and randomized clinical evidence; highlights leakage and external-validation problems; integrates current 2026 FDA repurposing initiatives; and positions pharmacists as evidence and medication-safety reviewers within an AI-assisted repurposing workflow.

10. Future Perspectives

Future progress should prioritize clinical utility over benchmark performance alone. Models should be developed around clearly defined decisions—for example, which candidate should proceed to experimental testing, which patient subgroup should be studied, or which approved drug has a sufficiently favorable benefit–risk profile for a prospective trial. [30,31]

- Multimodal AI integrating molecular, omics, imaging, clinical and real-world data.
- Leakage-controlled, temporal and external validation as routine reporting requirements.
- Mechanism-aware and explainable models that provide testable biological rationales.
- Personalized repurposing using genotype, phenotype, comorbidities, biomarkers and medication history. [31]
- AI-assisted clinical-trial design, recruitment, endpoint selection and responder stratification.
- Greater application to rare and neglected diseases through zero-shot and transfer-learning approaches.
- Safety-aware candidate ranking incorporating pharmacokinetics, toxicity, contraindications and interactions.
- Earlier regulatory engagement and clearer pathways for evidence generated from repurposing programs. [33,34]
- Pharmacist-integrated clinical decision support to ensure computational recommendations are translated into safe medication use.

11. Clinical Translation Pathway

An AI-generated repurposing hypothesis should be treated as one component of an evidence-development pathway:

AI prediction → independent computational validation → mechanistic/target validation → exposure and PK/PD feasibility → in vitro/in vivo validation → IND/appropriate regulatory interaction when required → clinical trials → evidence of benefit–risk → regulatory submission/label update → post-marketing pharmacovigilance.

This pathway is consistent with FDA principles that approval decisions depend on evidence of safety, effectiveness, appropriate labeling and manufacturing quality, rather than on the origin of the hypothesis.[22]

12. Conclusion

AI-enabled drug repurposing has matured from simple association mining toward graph-based, multimodal and foundation-model approaches capable of generating hypotheses across large disease spaces. The strongest evidence does not support treating AI output as clinical proof; instead, AI is most defensible as a prioritization tool that narrows a large search space for subsequent biological and clinical investigation.[3-8,11,26] [28,29,30]

The critical scientific issue is therefore translation. Benchmark performance can be inflated by data leakage, similarity between training and test entities, incomplete negative labels and disease-specific shortcuts. Robust evaluation requires leakage-resistant splits, independent datasets, transparent reporting and, ultimately, prospective experimental or clinical validation.[7,8,12] Case studies such as AI-assisted baricitinib repurposing illustrate that a computational hypothesis can progress through mechanistic and randomized clinical evidence, while the Alzheimer disease generative-AI study illustrates a lower evidence level in which observational EHR associations require further testing.[14-17] [29,32]

For clinical practice, pharmacists have an important role in evaluating dose, PK/PD feasibility, interactions, contraindications, patient-specific safety, evidence quality and pharmacovigilance. The future of repurposing is therefore likely to be multidisciplinary: AI can accelerate hypothesis generation, while pharmacology, experimental science, clinical trials, regulatory science and pharmacy practice determine whether a prediction becomes a safe and effective therapeutic use. [35]

13. Declarations

Funding: No external funding was received for preparation of this narrative review.

Conflict of interest: The author declares no conflict of interest.

Ethics approval: Not applicable. This article synthesizes published literature and publicly available regulatory information and does not involve new human or animal research.

Author contributions: The author conducted the literature search and reference verification, synthesized the evidence, and prepared and revised the manuscript.

Data availability: No original patient-level or experimental dataset was generated. Search and synthesis procedures are described in the Methodology section.

Use of AI-assisted tools: AI-assisted tools may have been used for language organization and figure preparation; all scientific claims and references included in the manuscript should be checked against the cited primary or authoritative sources before journal submission.

14. Tables and Figures

Table 1. Comparative evidence from key AI-based drug-repurposing studies

Study	AI model	Dataset	Major finding	Validation	Key limitation
Richardson et al., 2020[15]	BenevolentAI/knowledge graph	Drug/target/mechanism data; COVID-19 biology	Baricitinib prioritized for COVID-19	Mechanistic/experimental work; subsequently randomized ACTT-2	Initial prediction was hypothesis-generating; clinical effect depended on treatment context.
Huang et al., 2024[11]	TxGNN; GNN + metric learning + KG	Medical KG; 17,080 diseases; 9,388 indications and 30,675 contraindications	49.2% higher indication and 35.1% higher contraindication prediction accuracy under stringent zero-shot evaluation	Holdout/zero-shot benchmarking; human explanation evaluation; alignment with off-label use	Primarily computational and retrospective; clinical efficacy not established prospectively.
Peterson et al., 2024[14]	Generative AI/ChatGPT	Literature-derived hypotheses; VUMC and All of Us EHRs	Metformin, simvastatin and losartan associated with lower AD risk in meta-analysis	Two real-world EHR datasets and meta-analysis	Observational associations; possible confounding; inconsistent losartan direction across datasets; no proof of treatment efficacy.
Réda et al., 2025[8]	Collaborative filtering / matrix-factorization benchmarks	8 drug-repurposing datasets; 11 models	Demonstrated that unknown-association bias can cause leakage and misestimate performance	Reproducible multi-model benchmarking	Benchmark study rather than discovery of a clinically validated candidate.
de la Fuente et al., 2025[7]	Graph-based DTI models	Drug–target interaction datasets	Transductive approaches showed inflated performance and limited generalization; biologically driven negative sampling identified interactions missed by conventional sampling	Robust benchmarking plus in vitro validation	Focused on DTI inference; generalization depends on split design and task definition.
Wei et al., 2025[6]	KG-based ML/DL/GNN approaches	Biomedical knowledge graphs	Synthesized strengths and limitations of KG-based repurposing	Comparative review of methods/tools	Review evidence; does not itself establish clinical efficacy.
Brière et al., 2026[12]	Knowledge-graph embedding benchmarks	Multiple biomedical KGs plus independent Orphanet test set	Performance dropped substantially on independent real-world inference data	Random, cold-start and independent test-set comparisons	Highlights evaluation bias; not a therapeutic validation study.

Table 2. Comparison of conventional and AI-enabled drug repurposing

Parameter	Conventional approach	AI-enabled approach
Candidate identification	Literature, clinical observation, mechanistic reasoning	ML/DL/KG/GNN-driven prioritization
Data scale	Usually smaller and manually reviewed	Large heterogeneous datasets
Major data sources	Literature, experiments, clinical records	Omics, EHRs, molecular databases, KGs, literature
Strength	Direct human and biological interpretation	Rapid large-scale hypothesis generation
Major weakness	Time and search-space limitations	Bias, leakage, interpretability and generalization
Validation requirement	Experimental/clinical	Experimental/clinical; computational validation is insufficient
Clinical decision	Clinician/researcher-led	AI-assisted but human-supervised

Table 3. AI approaches and their principal roles

Approach	Principal role	Typical repurposing use	Important limitation
Machine learning	Pattern recognition	Drug–disease association	Depends strongly on labels and split design
Deep learning	Nonlinear representation learning	Drug response/DTI prediction	Data-hungry; interpretability
NLP	Text mining	Literature and EHR mining	Language/model hallucination and corpus bias
Knowledge graphs	Relationship integration	Drug–target–disease link prediction	Literature/connectivity bias
GNNs	Graph representation learning	Complex DTI and disease-network prediction	Shortcut learning and leakage
Foundation models	Cross-disease transfer/zero-shot prediction	Rare and untreated diseases	Limited prospective validation
Generative AI	Hypothesis generation	Candidate prioritization	Can reproduce literature bias or unsupported claims

Figure 1. Conceptual model of AI-enabled drug repurposing

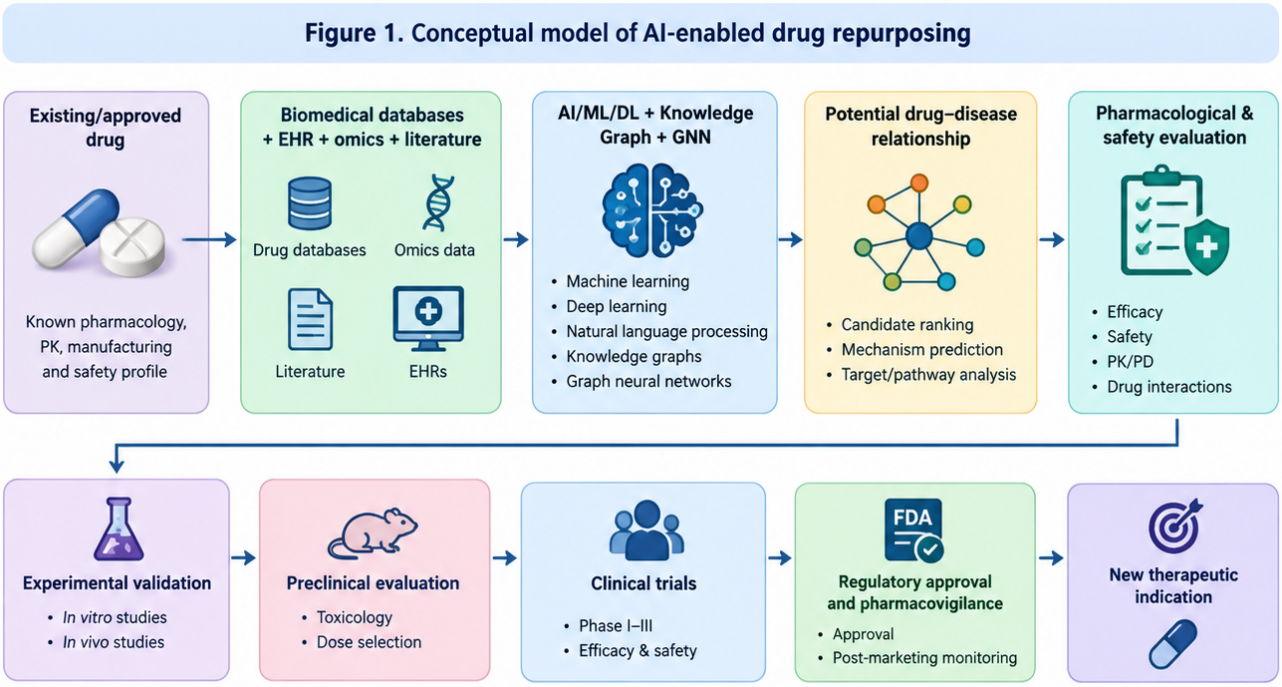


Figure 1 illustrates the proposed translational workflow from an existing drug and heterogeneous biomedical data through AI-based candidate ranking, pharmacological assessment, experimental validation, clinical trials and regulatory evaluation.

Figure 2. Role of the pharmacist in AI-enabled drug repurposing

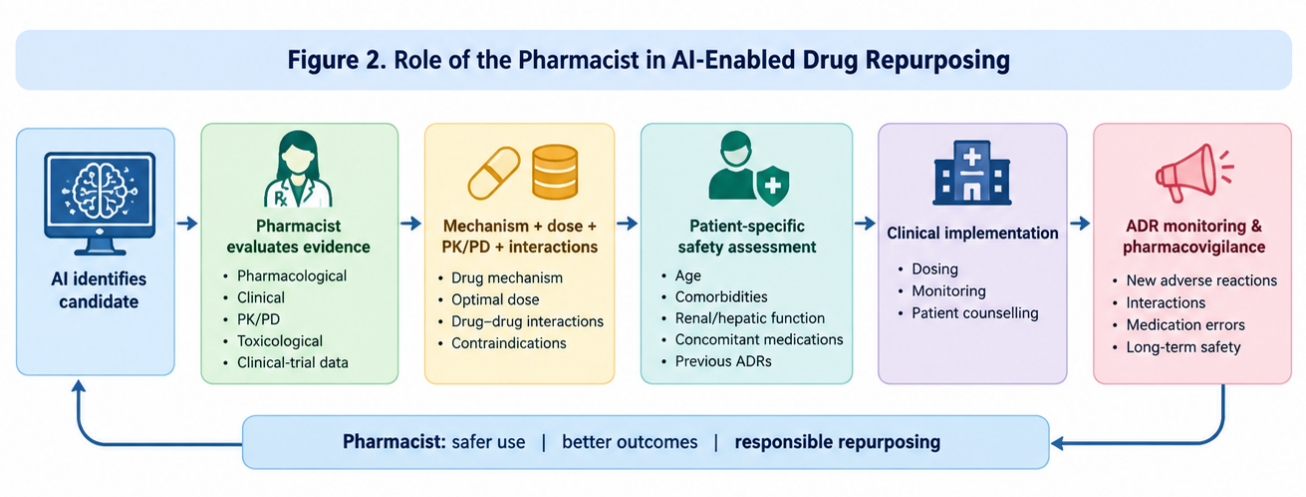


Figure 2 emphasizes pharmacist-led evidence appraisal, PK/PD and interaction assessment, patient-specific safety evaluation, clinical implementation and pharmacovigilance.

15. References

1. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov. 2004;3(8):673-683. doi:10.1038/nrd1468.
2. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1):41-58. doi:10.1038/nrd.2018.168.
3. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463-477. doi:10.1038/s41573-019-0024-5.
4. Ghandikota SK, Jegga AG. Application of artificial intelligence and machine learning in drug repurposing. Prog Mol Biol Transl Sci. 2024;205:171-211. doi:10.1016/bs.pmbts.2024.03.030.
5. Wan Z, Sun X, Li Y, Chu T, Hao X, Cao Y, et al. Applications of artificial intelligence in drug repurposing. Adv Sci (Weinh). 2025;12(14):e2411325. doi:10.1002/advs.202411325.
6. Wei S, Sasi C, Piepenbrock J, Huynen MA, 't Hoen PAC. The use of knowledge graphs for drug repurposing: from classical machine learning algorithms to graph neural networks. Comput Biol Med. 2025;196(Pt C):110873. doi:10.1016/j.compbiomed.2025.110873.
7. de la Fuente J, Serrano G, Veleiro U, Casals M, Vera L, Pizurica M, et al. Towards a more inductive world for drug repurposing approaches. Nat Mach Intell. 2025;7(3):495-508. doi:10.1038/s42256-025-00987-y.
8. Réda C, Vie JJ, Wolkenhauer O. Comprehensive evaluation of pure and hybrid collaborative filtering in drug repurposing. Sci Rep. 2025;15(1):2711. doi:10.1038/s41598-025-85927-x.
9. Bakhtiari N, Safaei AA, Ebadi MJ. Drug repurposing using machine learning and deep learning: a systematic literature review. Curr Comput Aided Drug Des. 2026;22. doi:10.2174/0115734099434707260517095301.
10. Santos R, et al. Knowledge graphs and their applications in drug discovery. Expert Opin Drug Discov. 2021;16(9). doi:10.1080/17460441.2021.1910673.
11. Huang K, Chandak P, Wang Q, Havaldar S, Vaid A, Leskovec J, et al. A foundation model for clinician-centered drug repurposing. Nat Med. 2024;30(12):3601-3613. doi:10.1038/s41591-024-03233-x.
12. Brière G, Stosskopf T, Loire B, Baudot A. Benchmarking the impact of data leakage on the performance of knowledge graph embedding models for biomedical link prediction. Bioinformatics. 2026;42(8):btag608. doi:10.1093/bioinformatics/btag608.
13. Fawzy MP, Nafie MS, Nabih NW, Diab MK, Babker A, Mohamed H, et al. Reprogramming cancer therapeutics through artificial intelligence-guided drug repurposing: computational innovation, experimental validation, and translational challenges. Artif Intell Life Sci. 2026;9:100168. doi:10.1016/j.ailsci.2026.100168.
14. Peterson JF, Feng Q, Malin BA, et al. Leveraging generative AI to prioritize drug repurposing candidates for Alzheimer's disease with real-world clinical validation. NPJ Digit Med. 2024;7:46. doi:10.1038/s41746-024-01038-3.
15. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020;395(10223):e30-e31. doi:10.1016/S0140-6736(20)30304-4.
16. Stebbing J, Krishnan V, de Bono S, Ottaviani S, Casalini G, Richardson PJ, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med. 2020;12(8):e12697. doi:10.15252/emmm.202012697.
17. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med. 2021;384(9):795-807. doi:10.1056/NEJMoa2031994.
18. Tambuyzer E, Vandendriessche B, Austin CP, et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. Nat Rev Drug Discov. 2020;19(2):93-111. doi:10.1038/s41573-019-0049-9.
19. Farha MA, Brown ED. Drug repurposing for antimicrobial discovery. Nat Microbiol. 2019;4:565-577. doi:10.1038/s41564-019-0357-1.

20. U.S. Food and Drug Administration. Drug Repurposing [Internet]. Silver Spring (MD): FDA; 2026 [cited 2026 Oct 18]. Available from: https://www.fda.gov/drugs/resources-drugs/drug-repurposing.
21. U.S. Food and Drug Administration. Drug Repurposing for Unmet Medical Needs; Request for Information. Fed Regist. 2026;91:25897-25899. Docket No. FDA-2026-N-4492.
22. U.S. Food and Drug Administration. New Drug Application (NDA) [Internet]. Silver Spring (MD): FDA; 2026 [cited 2026 Oct 18]. Available from: https://www.fda.gov/drugs/types-applications/new-drug-application-nda.
23. U.S. Food and Drug Administration. Determining Whether to Submit an ANDA or a 505(b)(2) Application: Draft Guidance for Industry. Silver Spring (MD): FDA; 2026.
24. U.S. Food and Drug Administration. Frequently Asked Questions on Patents and Exclusivity [Internet]. Silver Spring (MD): FDA; 2026 [cited 2026 Oct 18].
25. Breckenridge A, Jacob R. Overcoming the legal and regulatory barriers to drug repurposing. Nat Rev Drug Discov. 2019;18:1-2. doi:10.1038/nrd.2018.92.
26. Fu Z, Yang Y, Chung MK, Cheng F. Artificial intelligence to guide repurposing of drugs. Annu Rev Med. 2026;77(1):381-398. doi:10.1146/annurev-med-050224-122802.
27. Zielińska A, Fornalik M, Szczepaniak M, et al. Artificial intelligence in drug research and development: a review of methods and applications in drug repurposing. Brief Bioinform. 2026;27(3):bbag203. doi:10.1093/bib/bbag203.
28. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1):41-58. doi:10.1038/nrd.2018.168.
29. Schneider P, Walters WP, Plowright AT, Sieroka N, Listgarten J, Goodnow RA Jr, et al. Reconsidering drug design in the age of artificial intelligence. Nat Rev Drug Discov. 2020;19(5):353-364. doi:10.1038/s41573-019-0050-3.
30. Cousins HC, Nayar G, Altman RB. Applications of machine learning and artificial intelligence in drug discovery and development: drug repositioning. Drug Discov Today. 2026. [Bibliographic details should be verified against the final indexed record before journal submission].
31. Ghandikota SK, Jegga AG. Artificial intelligence and machine learning in drug repurposing. Prog Mol Biol Transl Sci. 2024;205:171-211. doi:10.1016/bs.pmbts.2024.03.030.
32. Wan Z, et al. Applications of knowledge graphs in drug repositioning: from classical machine learning to graph neural networks. Comput Biol Med. 2025;110873. doi:10.1016/j.compbiomed.2025.110873.
33. U.S. Food and Drug Administration. Drug Repositioning. Silver Spring (MD): FDA; 2026.
34. U.S. Food and Drug Administration. Criteria and Considerations for Drug Repositioning. Silver Spring (MD): FDA; 2026.
35. Krishnamoorthy M, Sjoding MW, Wiens J. Off-label use of artificial intelligence models in medicine. Nat Med. 2024;30:1525-1527.