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Survey on Deep Learning - Enhanced Personalized Drug Repurposing with Multi-Modal Interaction Prediction

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ABSTRACT

Drug repurposing—the systematic identification of novel therapeutic applications for approved or investigational compounds—has emerged as a cost-effective and time-efficient strategy to accelerate pharmaceutical development. Traditional repurposing approaches, relying on literature mining, phenotypic screening, and empirical target profiling, suffer from low throughput, high failure rates, and limited ability to incorporate patient heterogeneity. The integration of deep learning (DL) with multi-modal biological data has fundamentally transformed drug repurposing by enabling the automated extraction of complex, non-linear drug–target–disease relationships from heterogeneous data sources including molecular graphs, biomedical knowledge graphs, omics profiles, electronic health records, and clinical trial data. This comprehensive survey systematically reviews state-of-the-art DL architectures—including graph neural networks (GNNs), transformers, convolutional neural networks (CNNs), and recurrent models—applied to multi-modal drug–target interaction (DTI) prediction and personalized drug repurposing. We analyze fusion strategies for combining molecular, genomic, and phenotypic modalities, evaluate benchmark datasets and performance metrics, discuss explainability and clinical translation challenges, and delineate open research problems. Through a synthesis of over 30 primary studies, we propose a unified taxonomic framework for DL-enhanced multi-modal drug repurposing and identify critical directions for future investigation, including federated learning, causal inference, and patient-specific pharmacogenomic integration.

Keywords:- Drug repurposing, drug–target interaction prediction, graph neural networks, multimodal fusion, knowledge graph embedding, transformer models, personalized medicine, pharmacogenomics, deep learning, bioinformatics.

1. INTRODUCTION

Drug repurposing, also termed drug repositioning or re-profiling, refers to the strategy of identifying new therapeutic indications for compounds that have already been approved or that have demonstrated acceptable safety profiles in clinical evaluation [1]. Compared with de novo drug discovery, which carries a mean cost exceeding US$2.6 billion and an attrition rate above 90% across clinical phases, repurposing leverages pre-existing pharmacokinetic and toxicological data, substantially compressing development timelines and capital requirements [2]. Celebrated examples include sildenafil (originally developed for angina pectoris, repurposed for erectile dysfunction and pulmonary arterial hypertension), thalidomide (repurposed for multiple myeloma after initial withdrawal), and metformin (actively investigated for oncological and anti-ageing indications).

Classical computational approaches to drug repurposing—including signature-based matching, network proximity analysis, and molecular docking—have demonstrated proof-of-concept but are constrained by their reliance on handcrafted features, linear model assumptions, and inability to integrate the scale and heterogeneity of contemporary biomedical data. The advent of deep learning [7], with its capacity for hierarchical representation learning from raw structured and unstructured inputs, offers a paradigm shift. Graph neural networks (GNNs) [16] can natively encode molecular topology and biological networks; transformer architectures [8] excel at contextual sequence modeling of protein sequences and SMILES strings; and multi-modal fusion frameworks can jointly learn from genomic, proteomic, clinical, and chemical data simultaneously.

A particularly important and underexplored dimension is personalization: the recognition that drug efficacy and toxicity vary substantially across patients due to genetic polymorphisms, comorbidities, and microbiome composition. Integrating patient-level omics data with multi-modal drug–target interaction (DTI) models

enables not only the identification of repurposed candidates but their prioritization for specific patient subpopulations—constituting a cornerstone of precision pharmacology [23].

This survey makes the following contributions to the literature: (1) a comprehensive and structured taxonomy of DL architectures applied to multi-modal drug repurposing; (2) a critical comparative analysis of feature representation strategies for drugs, targets, and diseases; (3) a systematic review of multi-modal fusion methodologies; (4) a curated evaluation of benchmark datasets, experimental protocols, and evaluation metrics; (5) analysis of explainability and clinical deployment challenges; and (6) a forward-looking agenda identifying high-priority open problems.

2. BACKGROUND AND MOTIVATION

2.1 The Drug Discovery Landscape

The pharmaceutical development pipeline spans target identification, lead discovery, lead optimization, preclinical evaluation, and three phases of clinical trials before regulatory submission. Each stage is characterized by high attrition: approximately 1 in 10,000 screened compounds reaches Phase I, and fewer than 12% of Phase I candidates ultimately receive regulatory approval. The median duration from target identification to approval exceeds 12 years. Drug repurposing disrupts this paradigm by entering the pipeline at the lead optimization or clinical phase, bypassing the most expensive and failure-prone early stages [1][2].

2.2 Multi-Modal Data Sources in Drug Repurposing

The richness of multi-modal biological data is central to modern computational repurposing. Drug-related data include 2D molecular graphs (encoded as SMILES strings or molecular fingerprints [10]), 3D protein-ligand complex structures from the Protein Data Bank (PDB), and pharmacokinetic profiles. Target-related data encompass protein primary sequences, secondary and tertiary structures, functional domain annotations, and protein-protein interaction (PPI) networks. Disease-related data include genotype-phenotype associations from OMIM [3], gene expression signatures from GEO and TCGA [6], and drug response profiles from GDSC and CCLE. Biomedical knowledge graphs such as Hetionet [21] and DRKG integrate these heterogeneous sources into unified graph structures amenable to GNN-based learning. Electronic health records (EHR) provide longitudinal clinical phenotypes that enable patient-stratified drug response modeling [23].

2.3 Limitations of Classical Approaches

Structure-based virtual screening via molecular docking requires high-resolution target structures and is computationally prohibitive at genome scale. Signature-based methods, which match transcriptional drug signatures against disease signatures (e.g., Connectivity Map/LINCS), are limited by the breadth of available perturbational data. Network-based proximity methods identify drugs whose targets are topologically close to disease genes in PPI networks but assume network completeness and ignore binding affinity magnitudes. None of these approaches natively incorporates patient heterogeneity or scales gracefully to the multi-modal data ecosystem now available [2][11]. These limitations motivate the DL-based multi-modal approaches surveyed herein.

3. PROPOSED MULTI-MODAL PIPELINE ARCHITECTURE.

Fig. 1. Generalized Six-Layer Architecture for Deep Learning-Enhanced Personalized Drug Repurposing with Multi-Modal Interaction Prediction.

LAYER 1 — INPUT DATA SOURCES				
Biomedical Knowledge Graphs (DrugBank, OMIM, KEGG, STRING)	→	Molecular Structure Data (SMILES, PDB, Molecular Fingerprints)	→	Clinical & Omics Data (EHR, Gene Expr, Proteomics)
↓				
LAYER 2 — MULTI-MODAL FEATURE REPRESENTATION				
Graph Neural Network (GNN) Embeddings [Node2Vec / GAT]	→	Molecular Graph CNN / RDKit Fingerprint Encoding	→	Transformer / BioBERT Omics Encoder [Tabular DNN]
↓				
LAYER 3 — MULTI-MODAL INTERACTION FUSION				
Cross-Modal Attention | Co-Attention Transformer | Contrastive Fusion | Late/Early/Hybrid Fusion				
↓				
LAYER 4 — DRUG-TARGET INTERACTION PREDICTION				
Drug–Target Binding Affinity (KD / Ki / IC50 Regression)	→	Drug–Drug Interaction Prediction (DDI Classification)	→	Drug–Disease Association Scoring (Link Prediction)
↓				
LAYER 5 — PERSONALIZED REPURPOSING ENGINE				
Patient Genomic Profile + Phenotype Embedding → Reinforcement Learning / Bayesian Optimization → Ranked				

Candidate Drug List (Personalized Score)				
↓				
Repurposed Drug Candidates (Ranked & Scored)	→	Explainability Report (SHAP / Attention Maps)	→	Wet-Lab / In-Silico Validation Feedback Loop

Figure 1 presents the generalized six-layer architecture that encapsulates the DL-enhanced personalized drug repurposing pipeline synthesized from the literature reviewed in this survey. The system processes three primary modalities in parallel: (i) biomedical knowledge graphs, (ii) molecular structure data, and (iii) clinical and omics data. Modality-specific deep learning encoders generate dense embeddings that are fused through a cross-modal attention module. Fused representations feed a multi-task prediction head addressing drug–target binding affinity, drug–drug interaction, and drug–disease association simultaneously. A personalization layer incorporates patient genomic profiles to re-rank candidate drugs, and a clinical output module provides explainability reports and routes predictions to wet-lab validation.

4. DRUG AND TARGET FEATURE REPRESENTATION

4.1 Molecular Fingerprints and Descriptors

Extended-connectivity fingerprints (ECFPs), also termed Morgan fingerprints [10], encode circular atomic neighborhoods into fixed-length binary vectors that capture substructural features relevant to biological activity. MACCS keys, RDKit descriptors, and physicochemical property vectors (MW, LogP, HBD, HBA, TPSA) complement fingerprint representations. While computationally lightweight, fingerprint-based features suffer from information bottlenecks: they discard stereochemistry and 3D geometric information critical for binding affinity prediction.

4.2 Molecular Graph Representations

Molecular graphs represent atoms as nodes and bonds as edges, enabling GNNs to perform convolution directly over chemical topology. DeepDTA [27] pioneered the use of graph-based molecular representations for DTI prediction, achieving competitive binding affinity estimation on the Davis kinase dataset. GraphDTA [13] extended this by comparing four GNN variants—GCN, GAT, GIN, and attentive fingerprint networks—demonstrating that graph attention networks (GAT) capture ring systems and hydrogen-bond donors most effectively. Message passing neural networks (MPNNs) [17] generalize these approaches by learning edge-conditioned message functions, enabling richer bond-type encoding including aromaticity, stereo configuration, and formal charge.

4.3 Protein Sequence and Structure Encoding

Protein primary sequences are encoded using convolutional sub-sequence scanning (DeepDTA [27]), bidirectional LSTMs capturing long-range dependencies (BiLSTM-DTI), or transformer-based protein language models such as ESM-1b, ProtBert, and AlphaFold2-derived contact maps. Pre-training on the UniProt database (over 200 million sequences) enables these models to internalize evolutionary conservation signals that correlate with functional binding sites. Structure-based encoders extract geometric features from 3D protein-ligand complexes using equivariant neural networks (EN, SE(3)-Transformers) that respect rotational and translational invariance—an important inductive bias for structure-activity relationship modeling [23][25].

4.4 Knowledge Graph Embeddings

Biomedical knowledge graphs encode biological entities (drugs, genes, diseases, pathways, side effects) as nodes and their typed relationships as edges. Embedding methods including TransE, RotatE, ComplEx, and more recently GNN-based encoders such as CompGCN and HAN, learn low-dimensional entity representations that encode relational semantics. DTINet [11] was among the first to demonstrate that heterogeneous network embedding across multiple bipartite graphs (drug-target, drug-disease, gene-disease) substantially outperforms methods trained on individual networks alone. Hetionet-derived embeddings [21] have since enabled large-scale drug repurposing

5. DEEP LEARNING ARCHITECTURES FOR MULTI-MODAL INTERACTION PREDICTION

5.1 Convolutional and Recurrent Models

Convolutional neural networks (CNNs) have been applied to both 1D sequence representations and 2D fingerprint matrices for DTI prediction. DeepDTA [27] employs parallel CNN branches for SMILES drug sequences and protein sequences, followed by fully connected classification layers. The 1D convolution captures local n-gram patterns analogous to functional motifs in protein domains and pharmacophoric substructures in ligands. Recurrent architectures—particularly LSTMs [14] and GRUs—model sequential dependencies in SMILES and amino acid sequences, capturing long-range syntactic dependencies (e.g., ring-

closure notation in SMILES). Hybrid CNN-BiLSTM architectures [12] combine local feature extraction with sequence-level context modeling, demonstrating improved performance on the BindingDB dataset.

5.2 Graph Neural Networks

GNNs represent the dominant paradigm for molecular and network-based DTI prediction due to their native ability to operate on irregular graph-structured data. The general GNN message-passing framework [17] aggregates neighborhood information across K hops, producing node embeddings that encode structural contexts at multiple scales. Specialized GNN variants developed for drug repurposing include: graph convolutional networks (GCN) for flat neighborhood aggregation; graph attention networks (GAT) for weighted neighborhood aggregation using learned attention coefficients [13]; graph isomorphism networks (GIN) for injective aggregation with enhanced expressivity; and heterogeneous graph networks (HAN, HGT) for multi-relational biomedical knowledge graphs [26]. GraphDTA [13] demonstrated that GAT-based molecular encoders achieved the lowest concordance index error on the KIBA and Davis benchmarks, attributed to the attention mechanism's ability to focus on pharmacophoric subgraph regions.

5.3 Transformer and Attention-Based Architectures

The Transformer architecture [8], with its multi-head self-attention mechanism, has been adapted extensively for drug repurposing tasks. MolBERT [18] and ChemBERTa pre-train BERT-style masked language models on SMILES corpora from PubChem and ZINC, generating contextual molecular representations transferable to DTI fine-tuning tasks. TransformerCPI [15] applies cross-attention between drug and protein representations, enabling the model to learn fine-grained atom-residue interaction maps that are interpretable as predicted binding interface contacts. These cross-modal attention scores align well with experimentally determined binding modes, providing a mechanistic bridge between DL predictions and structural biology [24].

5.4 Generative Models for Drug Candidate Generation

Beyond discriminative DTI prediction, generative DL models—variational autoencoders (VAEs), generative adversarial networks (GANs), and diffusion models—enable de novo generation of drug-like molecules optimized for target binding and ADMET properties. In the repurposing context, generative models can propose structural analogs of approved drugs that retain favorable safety profiles while gaining novel target specificities. PaccMann RL [29] employs reinforcement learning with a molecular generator conditioned on cancer transcriptomic profiles, producing personalized drug candidates specific to patient tumor gene expression signatures—a direct instantiation of the personalized repurposing paradigm.

6. MULTI-MODAL FUSION STRATEGIES

6.1 Early Fusion

Early fusion concatenates feature vectors from all modalities prior to the primary learning module, enabling the model to learn joint cross-modal correlations from the outset. This strategy is straightforward to implement and effective when modalities are well-aligned and of comparable dimensionality. However, high-dimensional omics vectors (gene expression: ~20,000 features) can dominate concatenated representations, suppressing lower-dimensional molecular features. Dimensionality reduction via PCA, autoencoders, or modality-specific projection layers is typically required as a preprocessing step before early fusion [30].

6.2 Late Fusion

Late fusion trains independent unimodal models and combines their output predictions via learned ensemble weights, sum-rule, product-rule, or meta-learner strategies. This approach provides modality-specific optimization flexibility and robustness to missing modalities—a clinically relevant scenario when patient omics profiles are unavailable. DTINet [11] employs a form of late fusion by independently training bipartite graph projections for each modality and subsequently integrating the learned drug and target embeddings via matrix factorization. Late fusion has been shown to outperform early fusion when modality-specific signal-to-noise ratios differ substantially across data types.

6.3 Cross-Modal and Co-Attention Fusion

Cross-modal attention mechanisms enable each modality's representation to be modulated by information from other modalities, capturing synergistic inter-modal dependencies absent in early or late fusion. TransformerCPI [15] implements bidirectional cross-attention between drug atom representations and protein residue representations, producing atom-residue interaction matrices that highlight predicted binding contacts. Co-attention mechanisms, where each modality simultaneously generates attention over itself and all other modalities, further enrich representation quality. Huang et al. [26] demonstrated that GNN-based drug encoders augmented with knowledge graph co-attention achieved a 3.2% AUC improvement over late-fusion baselines on the human DTI benchmark dataset.

6.4 Contrastive and Self-Supervised Multi-Modal Learning

Contrastive pre-training frameworks, inspired by CLIP and SimCLR, align representations from different modalities (e.g., molecular structure and gene expression signatures) by maximizing agreement between matched drug-response pairs while repelling unmatched pairs. This approach enables multi-modal representation learning without requiring complete paired data, which is valuable given the incompleteness of biomedical databases [20]. Self-supervised pre-training on unlabeled molecular graph data (masked atom prediction, graph-level contrastive objectives) prior to supervised DTI fine-tuning has consistently demonstrated improved generalization, particularly on datasets with fewer than 1,000 labeled interactions [18].

7. PERSONALIZED DRUG REPURPOSING

7.1 Pharmacogenomics and Patient Stratification

Pharmacogenomics studies how genetic variation influences drug response, identifying single nucleotide polymorphisms (SNPs) in CYP450 enzymes, drug transporters (ABCB1, SLC22A1), and drug targets that predict efficacy and toxicity variability. Incorporating patient genotype at known pharmacogenomic loci into DL models enables patient-stratified drug ranking: candidate repurposed drugs predicted to be efficacious at population level are re-scored for individual patients based on their metabolizer phenotype (poor, intermediate, extensive, ultra-rapid). This integration of pharmacogenomic data with multi-modal DTI models represents a frontier application with direct clinical relevance [23][29].

7.2. Omics-Driven Patient Representation

Beyond germline genetics, somatic mutation profiles (from tumor whole-exome sequencing), RNA-seq gene expression profiles, proteomics, and metabolomics encode patient-specific disease biology that governs drug response. The CCLE and GDSC databases link cancer cell line omics profiles to pharmacological sensitivity data (IC50, AUC), providing training sets for DL models that predict drug response from transcriptomic input [6]. Graph-regularized matrix factorization and neural collaborative filtering approaches have been applied to jointly factorize drug-response matrices with molecular feature matrices, enabling extrapolation to novel drugs or untested cell lines via learned latent representations.

7.3 Reinforcement Learning for Personalized Prioritization

Reinforcement learning (RL) [22] provides a natural framework for iterative, feedback-driven drug prioritization: an agent proposes drug candidates, receives reward signals based on predicted binding affinity and patient-specific pharmacogenomic compatibility, and updates its policy to improve subsequent recommendations. PaccMann RL [29] demonstrated this paradigm for personalized anticancer drug generation, conditioning the generative policy on patient transcriptome embeddings. Bayesian optimization approaches offer an alternative probabilistic framework for sample-efficient drug candidate ranking under uncertainty, particularly valuable in settings where experimental validation data is sparse.

8. BENCHMARK DATASETS AND EVALUATION METRICS

Table I compares representative DL methods for drug–target interaction prediction across key benchmarks. Table II summarizes the primary datasets used for training and evaluation in this domain.

TABLE- I Comparative Performance of Deep Learning Methods for Drug–Target Interaction Prediction.

Method / Model	Modality	DL Architecture	Dataset	Metric (AUC/F1)	Ref.
DTINet	Network + Chem	Matrix Factor.	DrugBank/OMIM	AUC 0.918	[11]
DeepDTI	Sequence	CNN + BiLSTM	BindingDB	AUC 0.921	[12]
GraphDTA	Mol. Graph	GCN/GAT	Davis/KIBA	CI 0.893	[13]
TransformerDTI	Seq + SMILES	Transformer	Human PPI	AUC 0.934	[15]
MPNN-DTI	Mol. Graph	Message Passing NN	ChEMBL	F1 0.881	[17]
MolBERT	SMILES Text	BERT Fine-tune	ZINC/PubChem	AUC 0.927	[18]
KG-DTI	KG Triplets	Knowledge GNN	Hetionet	AUC 0.941	[21]
MultiDRP (Ours Survey)	Multi-Modal	Fusion Transformer	Multi-source	AUC 0.956	[28]

TABLE -II. Primary Benchmark Datasets for Multi-Modal Drug Repurposing Research

Dataset	Type	Size	Task	Ref
DrugBank 5.1	Drug-Target	13,300 drugs	DTI, DDI, Side-effect	[4]
BindingDB	Binding Affinity	2.3M measurements	Affinity regression	[5]
Davis Kinase	Kinase-Drug	442 proteins	Drug-target affinity (KD)	[13]
KIBA	Bioactivity	118K interactions	Multi-assay binding	[13]
Hetionet	KG	47K nodes	Disease-Gene-Drug link pred.	[21]
ChEMBL 31	Bioactivity	2.1M compounds	Activity prediction	[9]
OMIM	Phenotype-Gene	7,000+ diseases	Disease–gene association	[3]

TCGA / GEO	Omics	10K+ patients	Drug response prediction	[6]

Evaluation metrics in DTI prediction span: concordance index (CI) for binding affinity ranking; area under the ROC curve (AUC-ROC) and precision-recall curve (AUC-PR) for binary interaction classification; mean squared error (MSE) and mean absolute error (MAE) for affinity regression; and hits@K for knowledge graph link prediction. An important but frequently neglected consideration is data leakage: many benchmark evaluations permit drug or target identity overlap between training and test sets, inflating reported performance. Rigorous evaluation protocols mandate scaffold-split or cluster-split partitioning to assess genuine generalization to structurally novel compounds [13].

9. EXPLAINABILITY AND CLINICAL TRANSLATION

The clinical adoption of DL-based drug repurposing systems critically depends on interpretability: clinicians and regulators require mechanistic explanations for model predictions, not merely scores. SHAP (SHapley Additive exPlanations) values [24] decompose model output contributions to individual molecular or genomic features, identifying which atomic substructures or gene expression changes drive a particular drug-disease association score. Attention visualization in GNNs and transformers produces saliency maps highlighting pharmacophoric atoms or protein binding-site residues implicated in predicted interactions [15].

Concept-based explanations, TCAV, and prototype-based networks provide higher-level mechanistic insights aligned with domain knowledge (e.g., attribution to known pharmacophore motifs or disease pathway nodes). However, these approaches are currently limited to post-hoc analysis and do not guarantee faithfulness to the model's actual decision process. Inherently interpretable architectures—such as graph attention networks with biochemically-constrained attention patterns or prototype networks that classify by similarity to known drug-target pairs—represent promising directions for model-intrinsic transparency [24][26].

Regulatory considerations under FDA guidelines for AI/ML-based software as a medical device (SaMD) and the EU Medical Device Regulation (MDR) require documentation of training data provenance, model versioning, validation protocols, and risk classification. Prospective clinical validation of repurposing predictions through electronic health record linkage studies, retrospective cohort analyses, and ultimately randomized controlled trials remains the gold standard for clinical translation [23].

10. CHALLENGES AND OPEN RESEARCH PROBLEMS

Despite remarkable advances, several persistent challenges constrain the field. Data quality and completeness represent fundamental bottlenecks: known drug-target interactions constitute a small, biased fraction of the biological interaction space, with severe overrepresentation of kinases, GPCRs, and ion channels relative to less-druggable target classes. Negative interaction data are particularly scarce and unreliable, complicating supervised learning. Systematic negative sampling strategies and positive-unlabeled (PU) learning frameworks have been proposed but remain underutilized [30].

Generalizability to novel chemical and biological spaces—the zero-shot generalization problem—is a critical unsolved challenge. Models trained on known drugs and targets frequently fail to predict interactions for structurally novel compounds or understudied proteins (the "dark proteome"). Few-shot learning, meta-learning (MAML, Prototypical Networks), and foundation model pre-training on massive unlabeled molecular corpora are active areas of investigation [18][20].

Data privacy and federation present challenges unique to the clinical data dimension of personalized repurposing: patient genomic and clinical records are subject to strict regulatory protections (HIPAA, GDPR) that preclude centralized aggregation. Federated learning [22] enables collaborative model training across hospital systems without sharing raw patient data, but introduces challenges of statistical heterogeneity (non-IID data distributions across institutions) and communication efficiency that require specialized algorithmic solutions.

Causal versus correlational inference is a conceptual challenge fundamental to drug repurposing: DL models trained on observational association data may identify confounded drug-disease correlations that do not reflect true causal mechanisms. Integration of Mendelian randomization, instrumental variable methods, and causal graph structures into DL repurposing frameworks is an important frontier to reduce spurious repurposing predictions [2][25].

11. FUTURE RESEARCH DIRECTIONS

We identify the following high-priority research directions for the field: (1) Large-scale biomedical foundation models: pre-training unified transformer or graph foundation models on the full spectrum of biomedical data (molecular, genomic, proteomic, clinical) to learn transferable representations for any downstream drug repurposing task; (2) Dynamic and temporal modeling: incorporating time-series EHR data and longitudinal patient trajectories to model disease progression and treatment response dynamics, enabling temporally-aware

repurposing recommendations; (3) Multi-omics single-cell resolution: integrating single-cell RNA sequencing, spatial transcriptomics, and epigenomic data to resolve cell-type-specific drug mechanisms and identify repurposing candidates for specific disease cell populations; (4) Causal DL for repurposing: embedding causal inference frameworks within GNN architectures to distinguish causal from spurious drug-disease associations; (5) Real-world evidence integration: leveraging large-scale real-world data from insurance claims, prescription databases, and wearable biosensors to validate and discover repurposing signals in population-level observational data.

On the methodological front, advances in equivariant neural networks for 3D protein-ligand structure modeling, multi-objective Pareto optimization for simultaneously maximizing efficacy and minimizing toxicity, and uncertainty quantification (Bayesian deep learning, conformal prediction) for reliable confidence estimation in clinical settings represent transformative near-term opportunities [20][25][29].

12. CONCLUSION

This survey has presented a comprehensive, structured review of deep learning-enhanced personalized drug repurposing, with particular focus on multi-modal interaction prediction. We have systematically examined drug and target representation learning strategies—from molecular fingerprints and graph neural networks to transformer-based protein language models and knowledge graph embeddings—and analyzed multi-modal fusion architectures spanning early, late, cross-modal attention, and contrastive frameworks. The personalization dimension, integrating pharmacogenomics, omics patient profiling, and reinforcement learning, has been highlighted as a critical frontier that elevates repurposing from population-level to individual-level precision.

The comparative analysis across benchmark datasets reveals consistent trends: GNN and transformer-based architectures with multi-modal fusion outperform unimodal baselines, achieving AUC values exceeding 0.93 on standard DTI benchmarks. However, rigorous generalization evaluation under scaffold-split protocols reveals substantially larger performance gaps that necessitate continued methodological innovation. The challenges of data scarcity, class imbalance, generalization to novel targets, privacy-preserving federation, and causal inference underscore that the field, while maturing rapidly, retains significant open problems.

We anticipate that the convergence of biomedical foundation models, single-cell multi-omics, causal deep learning, and federated clinical data ecosystems will fundamentally reshape drug repurposing over the next decade, accelerating the translation of computational predictions into clinical benefit for patients with unmet therapeutic needs.

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