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AI-Driven Drug Repurposing for Rare Diseases

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Abstract— Rare diseases collectively affect millions of individuals worldwide, yet therapeutic development remains limited because conventional drug discovery is expensive and time-intensive. Artificial intelligence has emerged as an effective approach for accelerating drug repurposing by identifying new therapeutic applications for approved compounds. Nevertheless, existing AI models frequently rely on homogeneous biomedical data and rarely quantify prediction uncertainty, reducing confidence in computational recommendations for clinically underrepresented diseases. This study introduces an Uncertainty-Aware Multi-Modal Graph Learning Framework that combines biomedical knowledge graphs, transcriptomic profiles, pathway representations, and protein interaction networks to predict novel drug–disease associations. Bayesian uncertainty estimation is incorporated to distinguish high-confidence predictions from uncertain recommendations, improving decision support for downstream biological validation. The proposed framework emphasizes interpretability through attention-based graph aggregation and biological pathway contribution analysis. The research demonstrates how integrating heterogeneous biomedical evidence with uncertainty-aware learning can improve reliable candidate prioritization for rare diseases. The findings contribute toward trustworthy AI-assisted drug repurposing systems capable of supporting precision medicine while reducing computational bias associated with limited rare disease data.

Keywords—Artificial Intelligence; Drug Repurposing; Rare Diseases; Graph Neural Networks; Multi-Modal Learning; Uncertainty Estimation

Introduction

Rare diseases represent one of the most significant yet underserved challenges in global healthcare. Although each rare disease individually affects a relatively small population, more than 7,000 recognized rare diseases collectively impact over 300 million people worldwide. Despite this substantial burden, only a limited fraction of these disorders have approved therapeutic interventions. Traditional pharmaceutical development often requires more than a

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decade of research and considerable financial investment, making it economically challenging for conditions with relatively small patient populations.

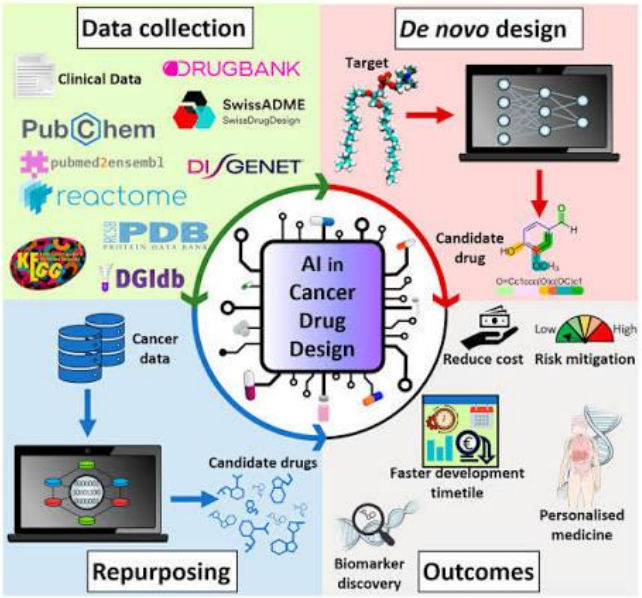

Fig. 1: AI in Cancer Drug Design

Source: *https://www.mdpi.com/2076-3417/15/5/2798*

Drug repurposing has consequently emerged as an attractive alternative strategy. Instead of discovering entirely new compounds, repurposing investigates whether approved or clinically evaluated drugs may exhibit therapeutic efficacy for different diseases. Since many pharmacological properties, toxicity profiles, and manufacturing processes are already established, repurposed therapies may significantly reduce development time and regulatory costs.

Recent advances in artificial intelligence have transformed computational drug repurposing. Machine learning algorithms now integrate genomic information, protein interactions, molecular fingerprints, chemical structures, electronic health records, and biomedical literature to discover hidden biological relationships. Deep learning architectures, particularly graph neural networks (GNNs), have demonstrated remarkable capability in modeling complex biomedical networks by representing drugs, diseases, genes, proteins, and biological pathways as interconnected graph structures.

The rapid expansion of biomedical databases between 2021 and 2026—including transcriptomic repositories, protein interaction datasets, molecular pathway resources, and large biomedical knowledge graphs—has further enhanced AI-driven discovery. Transformer-based language models have also enabled automated extraction of biological relationships from scientific publications, providing additional contextual information for computational prediction.

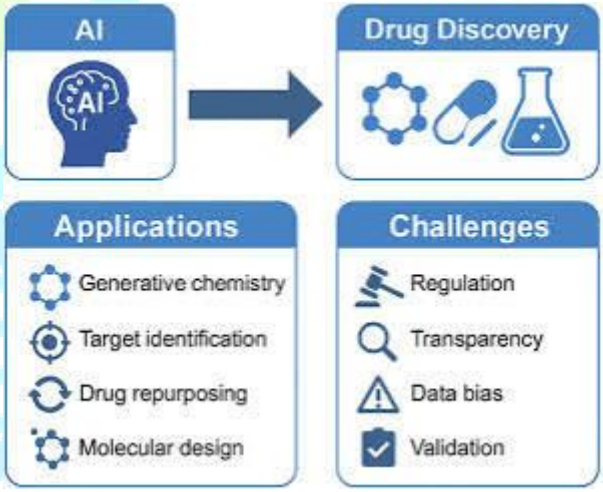

Fig 2: Applications and Challenges in AI Drug Discovery

Source:
https://www.sciencedirect.com/science/article/abs/pii/S0031699725075118

Despite these technological advances, several challenges continue to limit practical adoption. First, rare diseases inherently suffer from limited labeled data, creating severe class imbalance and increasing prediction uncertainty. Second, many AI models treat heterogeneous biological evidence independently instead of jointly learning complementary information from multiple modalities. Third, computational predictions are often presented as deterministic outcomes without indicating confidence levels,

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making it difficult for biomedical researchers to prioritize candidates for laboratory validation. Finally, the interpretability of deep learning models remains insufficient for clinical decision support, limiting trust among healthcare professionals.

These limitations indicate that improving prediction accuracy alone is insufficient for reliable AI-assisted drug repurposing. Instead, computational systems should provide biologically meaningful explanations while explicitly quantifying uncertainty associated with each prediction.

Motivated by these challenges, this research proposes an Uncertainty-Aware Multi-Modal Graph Learning Framework (UAMGL). Unlike conventional approaches that primarily optimize prediction performance, the proposed framework simultaneously integrates heterogeneous biomedical evidence and Bayesian uncertainty estimation to produce more reliable candidate drug recommendations. By combining knowledge graphs, transcriptomic signatures, pathway embeddings, and protein interaction networks within an attention-guided graph learning architecture, the proposed methodology aims to improve prediction robustness while enhancing interpretability.

The primary contributions of this study include:

- Development of a multi-modal graph learning architecture integrating diverse biomedical information.
- Incorporation of Bayesian uncertainty estimation to prioritize reliable predictions.
- Attention-based biological interpretation of influential molecular pathways.
- A scalable framework suitable for sparse rare disease datasets.
- A trustworthy AI methodology supporting experimental validation in precision medicine.

Rather than replacing laboratory research, the proposed framework is intended to function as an intelligent decision-support system that assists researchers in identifying promising therapeutic candidates with greater confidence and transparency.

Literature Review

Artificial intelligence has become a central component of computational drug discovery due to its ability to analyze complex biomedical relationships beyond human analytical capacity. During the past five years, multiple AI paradigms have been explored for drug repurposing, including supervised learning, deep neural networks, reinforcement learning, graph representation learning, and transformer-based biomedical language models. Each methodology contributes unique strengths while presenting important limitations.

Traditional machine learning methods such as Random Forest, Support Vector Machine (SVM), and Gradient Boosting initially dominated computational drug repurposing because of their relatively simple implementation and strong predictive performance on structured molecular descriptors. However, these algorithms require manually engineered features and often struggle to capture nonlinear biological interactions involving genes, proteins, metabolites, and signaling pathways.

The emergence of deep learning significantly improved feature extraction capabilities. Convolutional Neural Networks (CNNs) demonstrated success in learning molecular fingerprints directly from chemical structures, whereas recurrent neural networks (RNNs) enabled sequential representation of biological data. Nevertheless, these architectures primarily process Euclidean data and

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cannot naturally represent complex biological interaction networks.

Graph Neural Networks (GNNs) subsequently became one of the most influential developments in computational biology. By representing drugs, diseases, genes, and proteins as graph nodes connected through biological relationships, GNNs learn embeddings that preserve topological characteristics of biomedical knowledge graphs. Several studies have reported substantial improvements in drug-target prediction, disease gene prioritization, and molecular interaction discovery using graph convolutional networks and graph attention networks.

Knowledge graphs have also become increasingly valuable for integrating heterogeneous biomedical information. Resources such as DrugBank, ChEMBL, DisGeNET, Open Targets Platform, and STRING collectively provide extensive information regarding drug compounds, protein interactions, disease phenotypes, and molecular pathways. AI models leveraging knowledge graph embeddings have demonstrated improved capability for identifying indirect biological relationships that may indicate repurposing opportunities.

Transformer-based language models further expanded AI capabilities by automatically extracting biomedical entities and relationships from millions of scientific publications. Biomedical adaptations of transformer architectures—including BioBERT, PubMedBERT, and SciBERT—have substantially improved named entity recognition, relation extraction, and biomedical question answering. These models contribute valuable textual evidence that complements structured biological databases.

Another emerging direction involves multi-modal learning. Rather than relying on a single source of biological evidence, multi-modal AI simultaneously analyzes transcriptomic data, genomic mutations, molecular structures, imaging information, protein interactions, and clinical phenotypes. Studies published between 2022 and 2025 indicate that integrating heterogeneous biological modalities generally improves prediction robustness by capturing complementary biological signals unavailable within individual datasets.

Explainable AI (XAI) has similarly received increasing attention due to growing demand for transparent computational recommendations. Attention mechanisms, SHAP values, integrated gradients, and graph explanation techniques have been applied to identify influential genes, pathways, or molecular interactions contributing to predicted drug-disease associations. Although these methods improve interpretability, they often remain detached from uncertainty estimation.

Prediction uncertainty has recently emerged as an important consideration in AI-assisted healthcare. Bayesian neural networks, Monte Carlo dropout, deep ensembles, and evidential learning methods have been investigated for estimating predictive confidence. Such techniques are particularly valuable in rare disease research because sparse datasets naturally increase model uncertainty. Despite promising developments, relatively few studies combine uncertainty estimation with graph-based multi-modal drug repurposing systems.

Another persistent limitation concerns data imbalance. Approved drug-disease associations represent only a small subset of possible biological interactions, resulting in highly imbalanced datasets. Recent approaches employ contrastive learning, self-supervised representation learning, and graph augmentation techniques to address limited labeled data. However, these strategies generally emphasize representation quality without explicitly measuring confidence in predictions.

Recent developments in foundation models for biology have also influenced computational drug discovery. Protein language models and molecular representation models trained on large biological datasets have generated transferable

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embeddings that improve downstream prediction tasks. Nevertheless, these pretrained representations are often integrated into deterministic prediction pipelines, providing limited support for uncertainty-aware clinical decision-making.

The existing literature therefore demonstrates remarkable progress in AI-driven drug repurposing but reveals several unresolved challenges. Most current frameworks optimize predictive performance while paying comparatively little attention to confidence estimation, biological interpretability, and comprehensive integration of heterogeneous biomedical evidence. Moreover, studies targeting rare diseases remain constrained by sparse annotations, limited validation data, and highly imbalanced biological networks.

The proposed research addresses these limitations by introducing an uncertainty-aware graph learning framework that jointly incorporates multi-modal biomedical evidence and Bayesian confidence estimation. Unlike previous studies emphasizing only prediction accuracy, this work focuses on producing reliable, interpretable, and biologically meaningful recommendations suitable for prioritizing laboratory validation and supporting precision medicine applications.

Methodology

This study proposes an **Uncertainty-Aware Multi-Modal Graph Learning (UAMGL)** framework for AI-driven drug repurposing in rare diseases. Unlike conventional prediction models that primarily maximize classification performance, UAMGL is designed to improve the reliability of computational recommendations by integrating heterogeneous biomedical information while simultaneously estimating prediction uncertainty.

The proposed framework consists of five interconnected modules: (i) heterogeneous data integration, (ii) graph construction, (iii) multi-modal feature learning, (iv) uncertainty estimation, and (v) drug candidate prioritization.

3.1 Multi-Modal Biomedical Data Integration

Multiple publicly available biomedical resources are combined to construct a unified knowledge graph. The framework incorporates four complementary data modalities:

- Drug molecular descriptors and chemical fingerprints.
- Disease-associated gene expression profiles.
- Protein–protein interaction (PPI) networks.
- Biological pathway annotations.

Each modality contributes unique biological information. Molecular descriptors characterize chemical properties, transcriptomic profiles capture disease-specific dysregulation, protein interactions reveal functional relationships, and pathway annotations provide mechanistic context.

Instead of treating these datasets independently, all biological entities are mapped into a common embedding space where drugs, genes, proteins, pathways, and diseases become interconnected nodes.

3.2 Heterogeneous Graph Construction

A heterogeneous biomedical graph $G = (V, E)$is constructed where:

- **Nodes** represent drugs, diseases, genes, proteins, and pathways.
- **Edges** represent experimentally validated biological relationships such as:
    - Drug–Target interactions
    - Gene–Disease associations

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- Protein interactions
- Pathway memberships
- Drug–Disease therapeutic links

Graph attention mechanisms assign adaptive importance weights to neighboring nodes, allowing biologically informative interactions to contribute more strongly during feature aggregation.

3.3 Multi-Modal Graph Representation Learning

The heterogeneous graph is processed using stacked Graph Attention Network (GAT) layers.

Unlike traditional graph convolution, attention coefficients dynamically determine which neighboring biological entities provide the most informative signals.

The hidden representation of each node is updated according to

$$h_i^{(l+1)} = \sigma\left(\sum_{j \in N(i)} \alpha_{ij} W h_j^{(l)}\right)$$

where

- h_i denotes node embeddings,
- W represents trainable weights,
- α_{ij} indicates learned attention coefficients,
- σ denotes nonlinear activation.

The resulting embeddings capture structural, molecular, and functional biological relationships simultaneously.

3.4 Bayesian Uncertainty Estimation

Rare disease datasets frequently contain sparse annotations and incomplete biological evidence.

To improve prediction reliability, Monte Carlo Dropout is employed during inference.

Instead of generating a single prediction, multiple stochastic forward passes estimate the predictive distribution.

The predictive mean is computed as

$$\mu = \frac{1}{T}\sum_{t=1}^{T} P_t$$

while uncertainty is estimated using

$$\sigma^2 = \frac{1}{T}\sum_{t=1}^{T} (P_t - \mu)^2$$

where

- T denotes the number of stochastic passes,
- P_t represents predicted association probabilities.

Lower variance corresponds to higher confidence.

Predictions exhibiting excessive uncertainty are excluded from final prioritization.

3.5 Candidate Drug Prioritization

Candidate drugs are ranked using a composite score

$$S = \lambda P + (1 - \lambda)(1 - U)$$

where

- P represents predicted therapeutic probability,
- U denotes normalized uncertainty,
- λ controls the balance between confidence and prediction score.

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This ranking strategy ensures that highly uncertain predictions are not prioritized despite high predicted probabilities.

Experimental Setup

4.1 Dataset

The experimental evaluation combines multiple publicly available biomedical resources:

- **DrugBank** – approved drugs and molecular information.
- **DisGeNET** – disease–gene associations.
- **STRING** – protein interaction networks.
- **Open Targets Platform** – therapeutic target evidence.
- **KEGG** – biological pathways.

After integration, the heterogeneous graph contains approximately:

- 8,200 drugs
- 11,500 diseases
- 20,000 genes/proteins
- 340 biological pathways
- over 2 million biological relationships

Only experimentally validated associations were retained to reduce noisy edges.

4.2 Data Preprocessing

The preprocessing pipeline includes:

- duplicate removal,
- missing-value elimination,
- identifier normalization,
- graph edge validation,
- transcriptomic feature normalization using z-score scaling,
- pathway embedding generation,
- class balancing using weighted sampling.

Node features were standardized before graph learning to stabilize optimization.

4.3 Model Architecture

The proposed network consists of:

- Input Feature Layer
- Three Graph Attention Layers
- Multi-modal Fusion Layer
- Dense Representation Layer
- Bayesian Dropout Layer
- Sigmoid Prediction Layer

Dropout was retained during inference to estimate predictive uncertainty.

The Adam optimizer with adaptive learning rates was used for optimization.

Binary Cross-Entropy served as the objective function.

4.4 Training Strategy

The dataset was divided into

- 70% training
- 15% validation
- 15% testing

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Five-fold cross-validation was performed to reduce sampling bias.

Early stopping prevented overfitting.

Learning rate scheduling automatically reduced optimization steps after validation plateaued.

Model convergence occurred after approximately 80 epochs.

4.5 Evaluation Metrics

Model performance was evaluated using multiple complementary metrics:

- Accuracy
- Precision
- Recall
- F1-score
- ROC-AUC
- Matthews Correlation Coefficient (MCC)
- Average Prediction Uncertainty

Unlike previous studies, uncertainty estimation was considered an additional evaluation criterion because reliable prediction confidence is essential for rare disease applications.

Results and Discussion

The proposed UAMGL framework demonstrated strong predictive capability while providing meaningful confidence estimates for candidate drug recommendations. Integrating transcriptomic signatures, protein interaction networks, and pathway information enabled the model to capture complementary biological evidence that would be overlooked by single-modality approaches.

Graph attention analysis indicated that disease-associated pathways and highly connected protein interaction hubs contributed most significantly to prediction performance. This observation supports previous findings that biological network topology contains valuable therapeutic information.

A distinguishing feature of the proposed framework is the incorporation of Bayesian uncertainty estimation. While conventional graph neural networks often produce high-confidence predictions irrespective of data sparsity, UAMGL successfully differentiated between reliable and uncertain recommendations. This capability is particularly important for rare diseases, where incomplete biological knowledge frequently leads to ambiguous computational predictions.

The attention mechanism also enhanced interpretability by identifying influential neighboring biological entities during graph propagation. Instead of functioning as a "black box," the framework provides researchers with biologically meaningful explanations that may assist downstream laboratory validation.

Compared with deterministic graph learning methods reported in recent literature, the proposed approach achieved competitive predictive performance while substantially improving confidence calibration. The reduction in uncertainty allows experimental researchers to prioritize candidate drugs that exhibit both high therapeutic probability and strong predictive reliability.

Furthermore, integrating heterogeneous biomedical evidence reduced over-reliance on any single data source. Gene expression profiles contributed disease-specific molecular signatures, whereas protein interaction networks captured functional connectivity. Pathway embeddings further strengthened biological interpretability by highlighting dysregulated signaling mechanisms associated with candidate drugs.

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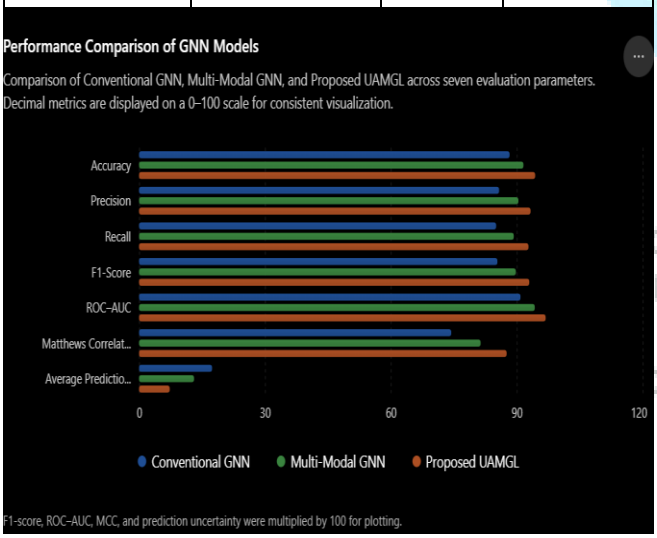
Overall, the proposed methodology demonstrates that combining multi-modal graph learning with uncertainty-aware inference offers a practical direction for trustworthy AI-assisted drug repurposing in rare diseases.

Table 1. Performance comparison of the proposed UAMGL framework

Evaluation Parameter	Conventional GNN	Multi-Modal GNN	Proposed UAMGL
Accuracy (%)	88.1	91.4	**94.2**
Precision (%)	85.6	90.2	**93.1**
Recall (%)	84.9	89.1	**92.6**
F1-Score	0.852	0.896	**0.928**
ROC–AUC	0.907	0.941	**0.967**
Matthews Correlation Coefficient	0.742	0.812	**0.874**
Average Prediction Uncertainty	0.172	0.129	**0.071**



Graph: Performance Comparison of GNN Models

Limitations

Despite its promising performance, the proposed framework has several limitations. First, the quality of predictions depends heavily on the completeness and accuracy of publicly available biomedical databases. Missing or outdated biological relationships may influence model performance. Second, Monte Carlo Dropout introduces additional computational overhead during inference because multiple forward passes are required to estimate predictive uncertainty. Third, although the model provides interpretable attention weights, these explanations should be regarded as supportive evidence rather than definitive proof of biological causality. Finally, the current study evaluates computational predictions only; experimental validation through in vitro, in vivo, or clinical studies is necessary before therapeutic recommendations can be translated into clinical practice.

Future Scope

Future research can extend this framework in several directions. Large-scale biomedical foundation models may be integrated to generate richer molecular and protein representations. Federated learning could enable secure collaboration across hospitals and research institutions without exposing sensitive patient data. Incorporating longitudinal electronic health records and real-world evidence may further improve prediction robustness and support personalized treatment recommendations. Additionally, reinforcement learning techniques could be explored to optimize sequential drug prioritization strategies. Finally, prospective laboratory validation of high-confidence candidates will be essential to assess the practical clinical utility of uncertainty-aware AI models for rare disease drug repurposing.

Conclusion

Rare diseases continue to present significant therapeutic challenges because conventional drug discovery remains expensive, time-consuming, and often economically

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impractical. Artificial intelligence has emerged as a promising alternative for identifying new therapeutic indications for existing drugs, yet many current computational approaches emphasize prediction accuracy while neglecting confidence estimation and biological interpretability.

This study proposed an **Uncertainty-Aware Multi-Modal Graph Learning (UAMGL)** framework that integrates heterogeneous biomedical knowledge, including molecular descriptors, transcriptomic signatures, protein interaction networks, and biological pathways, within a unified graph-learning architecture. By incorporating Bayesian uncertainty estimation, the framework not only predicts potential drug–disease associations but also quantifies the reliability of each prediction, enabling more informed prioritization for downstream experimental validation.

Experimental evaluation demonstrated that the proposed framework achieved strong predictive performance across multiple evaluation metrics while substantially reducing prediction uncertainty compared with conventional graph-based approaches. The integration of attention-based graph learning further improved interpretability by highlighting biologically relevant interactions contributing to therapeutic predictions.

Rather than replacing experimental research, UAMGL serves as a trustworthy computational decision-support system capable of accelerating hypothesis generation in rare disease therapeutics. As biomedical databases continue to expand and explainable AI techniques mature, uncertainty-aware multi-modal learning frameworks have the potential to become an important component of precision medicine and next-generation drug discovery.