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Intelligent Drug Repurposing: Integrating Multi-Omics Data, Machine Learning and Clinical Evidence

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Abstract

Drug repurposing has emerged as an important strategy for identifying new therapeutic applications for existing drugs, potentially reducing the time, cost and risks associated with conventional drug development. However, traditional repurposing approaches frequently rely on individual data sources and may fail to capture the complex molecular mechanisms underlying disease and treatment response. The integration of multi-omics data, machine learning and clinical evidence offers a more comprehensive framework for intelligent drug repurposing. This paper examines how genomic, transcriptomic, proteomic, metabolomic and epigenomic information can be combined with machine-learning models and real-world clinical evidence to identify, prioritise and validate new drug–disease associations. A conceptual framework is proposed that integrates molecular signatures, drug–target relationships, biological pathways, electronic health records, clinical trials and pharmacovigilance data. Particular attention is given to knowledge graphs, graph neural networks, representation learning, causal inference, network medicine and multimodal learning. Applications across oncology, infectious diseases, neurological disorders, rare diseases and chronic conditions are discussed. The paper also examines major challenges, including heterogeneous data quality, missing information, population bias, confounding, interpretability, data privacy and the distinction between statistical association and causal therapeutic benefit. The analysis suggests that intelligent drug repurposing should be implemented as a staged discovery pipeline in which computational predictions are progressively evaluated through molecular evidence, retrospective clinical analyses, prospective trials and pharmacovigilance. The convergence of multi-omics, artificial intelligence and clinical evidence could transform drug repurposing from largely hypothesis-driven screening into a data-integrated and continuously learning therapeutic discovery process.

Keywords: Drug Repurposing, Multi-Omics, Machine Learning, Clinical Evidence, Precision Medicine, Network Medicine, Drug–Disease Associations, Pharmacogenomics, Artificial Intelligence, Therapeutic Discovery.

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1. Introduction

Developing a new medicine is a lengthy and expensive process.

Traditional drug development commonly involves:

1. Target identification.
2. Lead discovery.
3. Preclinical testing.
4. Clinical trials.
5. Regulatory evaluation.
6. Post-market monitoring.

Drug repurposing provides an alternative strategy.

Instead of developing a completely new compound, researchers investigate whether an existing drug can be used to treat another disease or condition.

This approach can potentially reduce development time because information regarding an existing drug's pharmacology, safety and manufacturing may already be available.

However, identifying useful repurposing opportunities is difficult.

A drug may influence:

- Multiple molecular targets.
- Several biological pathways.
- Different tissues.
- Multiple downstream phenotypes.

Similarly, diseases involve interconnected molecular mechanisms rather than isolated targets.

Multi-omics data and machine learning provide an opportunity to analyse these relationships systematically.

2. Drug Repurposing

Drug repurposing, also called drug repositioning, involves identifying new therapeutic applications for existing drugs.

Potential repurposing candidates can include:

- Approved medicines.
- Investigational compounds.
- Failed clinical candidates.
- Drugs discontinued for one indication.

The fundamental hypothesis is:

A drug developed for one biological condition may influence mechanisms relevant to another disease.

3. Conventional Repurposing Approaches

Traditional approaches include:

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Target-Based Repurposing
Identifying drugs that affect a biological target associated with another disease.

Phenotype-Based Repurposing
Identifying drugs that produce a phenotype similar to the desired therapeutic effect.

Literature-Based Repurposing
Searching published evidence for potential drug–disease relationships.

Clinical Observation
Identifying unexpected therapeutic effects during clinical use.
AI can integrate these approaches into a unified analytical framework.

4. The Role of Multi-Omics
Diseases are complex biological systems.
Different omics layers provide different information.

Omics Layer	Information
Genomics	Genetic variation
Epigenomics	Regulatory modifications
Transcriptomics	Gene expression
Proteomics	Protein abundance and activity
Metabolomics	Metabolic states
Pharmacogenomics	Genetic influence on drug response

Integrating these layers can provide a more comprehensive representation of disease biology.

5. Genomic Data
Genomic information can identify genetic variants associated with disease.
Examples include:

- Risk variants.
- Disease-associated genes.
- Pathogenic mutations.
- Pharmacogenetic markers.

Genetic evidence can help identify potential therapeutic targets.

6. Transcriptomic Data

Transcriptomics measures RNA expression patterns.

Disease-associated expression signatures can be compared with drug-induced expression signatures.

A conceptual repurposing strategy is:

Disease Signature

Versus

Drug Signature

If a drug reverses a disease-associated molecular pattern, it may represent a candidate for further investigation.

7. Proteomics

Proteomic data provide information about proteins and their functional states.

This is important because many drugs directly or indirectly influence proteins.

Proteomic analysis can help identify:

- Drug targets.
- Signalling pathways.
- Biomarkers.
- Mechanisms of resistance.

8. Metabolomics

Metabolomics provides information about cellular metabolic states.

Metabolic abnormalities are important in many diseases, including:

- Cancer.
- Diabetes.
- Cardiovascular disorders.
- Neurological diseases.

Drug-induced metabolic changes can therefore provide repurposing signals.

9. Epigenomics

Epigenetic regulation influences gene expression without changing the underlying DNA sequence.

Drug effects on:

- DNA methylation.
- Histone modification.
- Chromatin accessibility

may reveal mechanisms relevant to diseases beyond the original indication.

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10. Multi-Omics Integration

The central challenge is combining heterogeneous data.

A conceptual representation is:

Genomics

•

Transcriptomics

•

Proteomics

•

Metabolomics

•

Clinical Data

↓

Integrated Disease Representation

This representation can then be used for computational drug discovery.

11. Machine Learning for Drug Repurposing

Machine learning can identify complex relationships between:

- Drugs.
- Targets.
- Genes.
- Diseases.
- Pathways.
- Clinical outcomes.

Models can rank candidate drug–disease associations based on available evidence.

12. Supervised Learning

Supervised models can learn from known drug–disease relationships.

Possible features include:

- Chemical structure.
- Target information.
- Gene expression.
- Disease similarity.
- Clinical outcomes.

The trained model can then predict previously unobserved relationships.

13. Unsupervised Learning

Unsupervised approaches can identify hidden patterns without requiring predefined labels.

Applications include:

- Patient clustering.
- Disease subtyping.
- Molecular phenotype discovery.
- Drug similarity analysis.

This can reveal repurposing opportunities that are difficult to identify using predefined categories.

14. Deep Learning

Deep learning can process high-dimensional biological information.

Applications include:

- Molecular representation learning.
- Drug–target prediction.
- Disease classification.
- Multi-omics integration.
- Patient outcome prediction.

15. Graph Neural Networks

Drug repurposing naturally forms a graph problem.

A graph may contain:

Drugs → Targets → Genes → Pathways → Diseases

Graph neural networks can learn representations from these interconnected relationships.

16. Knowledge Graphs

A biomedical knowledge graph can integrate information from:

- Scientific literature.
- Drug databases.
- Gene databases.
- Clinical studies.
- Molecular interaction networks.

For example:

Drug A → targets → Protein B

Protein B → regulates → Pathway C

Pathway C → associated with → Disease D

This can reveal indirect drug–disease relationships.

17. Network Medicine

Network medicine views disease as a perturbation of interconnected biological networks.

A disease may involve:

- Multiple genes.

- Multiple proteins.
- Several pathways.

A drug may influence multiple nodes within this network.
Repurposing therefore becomes a network-matching problem.

18. Drug–Disease Similarity

AI can compare diseases based on:

- Gene signatures.
- Molecular pathways.
- Clinical phenotypes.
- Expression patterns.

Drugs can similarly be represented using their molecular and pharmacological profiles.
The model can then identify drugs whose profiles align with disease mechanisms.

19. Disease Signature Reversal

One important computational strategy is to identify compounds that reverse disease-associated molecular signatures.
Conceptually:

Disease Expression Pattern
↓
Drug Treatment
↓
Opposing Expression Pattern
↓
Potential Therapeutic Effect

This approach can generate candidate repurposing hypotheses.

20. Clinical Evidence

Computational predictions alone are insufficient.
Clinical evidence is essential for evaluating whether a drug actually produces meaningful therapeutic outcomes.
Relevant evidence includes:

- Clinical trials.
- Electronic health records.
- Observational studies.
- Real-world evidence.
- Pharmacovigilance databases.

21. Electronic Health Records

Electronic health records can reveal patterns of drug exposure and clinical outcomes.
For example:

Patients receiving Drug X

Versus

Comparable patients not receiving Drug X

Researchers can examine differences in:

- Disease progression.
- Hospitalisation.
- Mortality.
- Biomarkers.
- Adverse events.

However, observational associations can be strongly affected by confounding.

22. Real-World Evidence

Real-world data can provide information from routine healthcare environments.
Potential sources include:

- EHRs.
- Claims databases.
- Registries.
- Pharmacy data.
- Patient-generated data.

These sources can complement controlled clinical trials.

23. Causal Inference

A major challenge is determining whether a drug actually caused an observed outcome.
For example:

Drug Exposure → Improved Outcome

may appear to be associated because patients receiving the drug differ systematically from other patients.
Causal inference methods can help address:

- Confounding.
- Selection bias.
- Treatment assignment differences.

24. Pharmacovigilance

Repurposing requires careful safety assessment.

Pharmacovigilance systems can identify:

- Adverse drug reactions.
- Unexpected toxicities.
- Drug interactions.
- Population-specific risks.

Safety evidence should therefore be integrated into repurposing models.

25. Clinical Trial Data

Clinical trials provide stronger evidence than many observational studies.
Machine learning can analyse trial information to identify:

- Successful indications.
- Failed endpoints.
- Patient subgroups.
- Safety signals.

Historical trial data may contain valuable information for new repurposing hypotheses.

26. Precision Drug Repurposing

Not every patient responds identically to a drug.
Multi-omics information can identify subgroups with distinct molecular characteristics.
This supports:

Drug → Disease Subtype → Patient Subgroup
rather than simply:
Drug → Disease

27. Oncology Applications

Cancer is particularly suitable for intelligent repurposing because tumours contain complex molecular signatures.
AI can integrate:

- Genomic mutations.
- Gene expression.
- Protein signalling.
- Tumour phenotype.
- Treatment response.

Potential candidates can then be prioritised for experimental and clinical evaluation.

28. Rare Disease Applications

Rare diseases frequently suffer from limited therapeutic options.
Computational methods can connect:

- Rare genetic variants.

- Disease pathways.
- Existing drug targets.

This may identify candidate therapies for diseases with limited commercial incentives for conventional drug development.

29. Neurological Diseases

Neurological disorders involve complex molecular and network-level mechanisms.
Multi-omics and machine learning can support investigation of:

- Neuroinflammation.
- Protein aggregation.
- Synaptic dysfunction.
- Metabolic abnormalities.

These mechanisms may reveal opportunities for repurposing existing medicines.

30. Infectious Diseases

Drug repurposing can be valuable when rapid therapeutic options are required.
AI systems can analyse:

- Host pathways.
- Pathogen proteins.
- Drug targets.
- Clinical outcomes.

However, computational predictions should be carefully validated before clinical adoption.

31. Chronic Diseases

Conditions such as:

- Diabetes.
- Cardiovascular disease.
- Chronic inflammatory disorders.

often involve multiple interacting biological pathways.
Multi-omics models may help identify drugs capable of influencing several disease mechanisms.

32. Patient Stratification

Machine learning can divide patients into molecularly meaningful groups.
For example:

Patient Data
↓
Molecular Clustering
↓
Disease Subtype

↓

Drug Response Prediction

This can support precision repurposing.

33. Multi-Modal Learning

Future systems may combine:

- Molecular data.
- Clinical notes.
- Medical images.
- Laboratory measurements.
- Drug information.

Multimodal AI can potentially produce more comprehensive representations of patients and therapies.

34. Natural Language Processing

Scientific literature contains enormous amounts of drug–disease information.

NLP systems can extract:

- Drug names.
- Targets.
- Diseases.
- Molecular mechanisms.
- Clinical outcomes.

This information can populate knowledge graphs and machine-learning datasets.

35. Literature Mining

AI-assisted literature mining can identify relationships that may be missed by conventional keyword searches.

For example, a system can connect:

Drug → Molecular Target → Biological Pathway → Disease Mechanism

across thousands of publications.

36. Proposed Intelligent Repurposing Framework

The proposed framework includes nine stages:

1. Data collection.
2. Multi-omics integration.
3. Drug representation.
4. Disease representation.
5. Machine-learning prediction.

6. Network-based prioritisation.
7. Clinical evidence evaluation.
8. Safety assessment.
9. Experimental and clinical validation.

37. Conceptual Architecture

Multi-Omics Data
↓
Disease Molecular Signature
•
Drug Molecular/Pharmacological Profile
↓
AI-Based Representation Learning
↓
Knowledge Graph + Network Analysis
↓
Candidate Drug Ranking
↓
Clinical Evidence Integration
↓
Safety & Causal Evaluation
↓
Experimental Validation
↓
Clinical Trial

38. Candidate Ranking

A repurposing system can assign candidates a composite score.
For example:
Repurposing Score = Molecular Evidence + Network Evidence + Clinical Evidence + Safety Evidence
The exact weighting should be determined using validated methodology rather than arbitrary scoring.

39. Explainable AI

Clinical researchers need to understand why a drug is recommended.
An explainable model might identify:

- Relevant molecular targets.
- Disease pathways.
- Supporting omics evidence.

- Previous clinical observations.
- Predicted therapeutic mechanisms.

This increases trust and facilitates scientific review.

40. Model Validation

Models should be evaluated using:

- Retrospective validation.
- Independent datasets.
- External cohorts.
- Prospective validation.

Performance metrics may include:

Metric	Purpose
AUROC	Classification performance
AUPRC	Imbalanced classification
Precision	Candidate reliability
Recall	Candidate coverage
F1-score	Balanced performance
Calibration	Reliability of predicted probabilities
External validation	Generalisation

41. Data Integration Challenges

Multi-omics datasets often differ in:

- Scale.
- Measurement technology.
- Sample size.
- Missingness.
- Biological context.

Effective integration requires careful preprocessing and harmonisation.

42. Batch Effects

Different laboratories or technologies can produce systematic differences.

These batch effects may create artificial patterns.

AI models must distinguish:

Biological Signal
from
Technical Variation

43. Data Bias
Clinical datasets may underrepresent particular populations.
Potential biases can arise from:

- Age.
- Sex.
- Geography.
- Healthcare access.
- Socioeconomic characteristics.

Models trained on biased data may produce unequal predictions.

44. Privacy and Data Governance
Clinical and genomic data are highly sensitive.
Responsible systems require:

- Secure data storage.
- Controlled access.
- De-identification.
- Appropriate consent.
- Governance frameworks.

Federated learning may provide one potential strategy for distributed model training without centralising all patient data.

45. Causal versus Predictive Models
A model that predicts treatment response is not necessarily explaining why the treatment works.
This distinction is critical.

Prediction
asks:
Who is likely to benefit?

Causal inference
asks:
What would happen if this patient received the drug instead of another treatment?
Both perspectives are valuable but should not be conflated.

46. Regulatory Considerations

Repurposed therapies still require appropriate evidence of:

- Efficacy.
- Safety.
- Appropriate dosing.
- Patient selection.
- Drug interactions.

AI-generated predictions cannot substitute for required clinical evidence.

47. Economic Impact

Successful repurposing can potentially reduce:

- Early discovery costs.
- Development time.
- Molecular screening requirements.

It can also increase the value of existing pharmacological knowledge.

However, economic incentives for repurposing may vary depending on:

- Patent status.
- Market size.
- Regulatory requirements.
- Clinical development costs.

48. Proposed Research Questions

1. How can multi-omics datasets be integrated effectively for drug repurposing?
2. Which machine-learning architectures provide the most reliable drug–disease predictions?
3. Can knowledge graphs improve interpretability and candidate prioritisation?
4. How can causal inference distinguish genuine treatment effects from observational associations?
5. Can patient-specific multi-omics profiles improve repurposing precision?
6. How can pharmacovigilance data be integrated into AI-based repurposing models?
7. Can foundation models improve multimodal biomedical representation?
8. How can federated learning support privacy-preserving repurposing research?
9. What evidence threshold should be required before computational candidates enter clinical testing?
10. Can intelligent repurposing reduce the cost and duration of therapeutic development?

49. Future Research Directions

Future research should focus on:

- Multi-omics foundation models.
- Drug–disease knowledge graphs.
- Graph neural networks.

- Causal machine learning.
- Patient-specific drug response prediction.
- Federated biomedical AI.
- AI-assisted clinical trial design.
- Real-world evidence integration.
- Pharmacovigilance intelligence.
- Autonomous hypothesis generation.

50. Discussion

Intelligent drug repurposing represents a transition from isolated computational prediction toward evidence-integrated therapeutic discovery.

Traditional approaches may examine one source at a time.

A future system could simultaneously analyse:

Molecular Evidence

-

Pharmacological Evidence

-

Clinical Evidence

-

Safety Evidence

to determine whether a repurposing hypothesis deserves further investigation.

The critical principle is that AI should function as a candidate prioritisation and evidence-integration system, not as an autonomous clinical decision-maker.

51. From Drug-Centred to Patient-Centred Repurposing

Conventional repurposing asks:

Can Drug X treat Disease Y?

Intelligent precision repurposing asks:

Which patients with Disease Y are most likely to benefit from Drug X, through which biological mechanism, and under what clinical conditions?

This is a more sophisticated and clinically relevant question.

52. Closed-Loop Therapeutic Discovery

A future intelligent repurposing ecosystem could operate as:

Multi-Omics Data

↓

AI Hypothesis Generation

↓

Drug Candidate Ranking

↓

Clinical Evidence Analysis

↓

Experimental Validation

↓

Clinical Evaluation

↓

Real-World Monitoring

↓

Model Updating

This creates a continuously learning therapeutic discovery system.

53. Conclusion

Intelligent drug repurposing represents a promising convergence of multi-omics, artificial intelligence, network medicine and clinical evidence.

The integration of genomics, transcriptomics, proteomics, metabolomics and epigenomics provides a richer understanding of disease mechanisms and drug activity. Machine learning can then analyse these high-dimensional datasets to identify hidden relationships between drugs, biological pathways and disease phenotypes.

However, computational prediction alone cannot establish therapeutic efficacy.

The strongest repurposing framework therefore combines:

Multi-Omics → Machine Learning → Biological Networks → Clinical Evidence → Safety Assessment → Experimental Validation → Clinical Trials

Such an approach can move drug repurposing beyond simple drug–disease matching toward mechanism-aware, patient-specific and evidence-driven therapeutic discovery.

Future advances in multimodal foundation models, causal AI, biomedical knowledge graphs and real-world evidence could further accelerate this transformation. If developed with rigorous validation, transparency and appropriate clinical governance, intelligent drug repurposing could help identify new therapeutic opportunities while making more effective use of existing pharmaceutical knowledge.

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