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Drug Repurposing In Modern Drug Discovery: Role of *In Silico* Study

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ABSTRACT

Despite substantial pharmaceutical investments of approximately $50 billion annually, modern drug discovery yields only 20-25 new approvals, with traditional development requiring 12-15 years and success rates below 10%. Contemporary challenges, including high clinical failure rates, prolonged timelines, and limited preclinical predictive capacity, represent the current therapeutic debacle of de novo drug development. To address this critical scenario, drug repurposing is an appealing strategy for identifying novel therapeutic applications from existing approved drugs. However, traditional repurposing relies on serendipitous observations or resource-intensive screenings. In contrast, in silico drug repurposing is an emerging, hypothesis-driven approach leveraging big data, artificial intelligence, machine learning, multi-omics analysis, and network pharmacology to predict drug-target interactions and therapeutic efficacy cost-effectively. Additionally, repurposing approaches, including in silico techniques, reduce development timelines to 3-12 years with enhanced success rates of approximately 25%, with 30% of FDA-approved drugs originating from repurposing initiatives. Therefore, computational drug repurposing substantially improves therapeutic development efficiency while requiring rigorous experimental validation for clinical translation. Here, we will review in silico methodologies exploited for drug repurposing across oncology, infectious diseases, neurodegenerative disorders, metabolic disorders, and pandemic threats, alongside computational pharmacology assessment tools to address how the implementation of current in silico options can accelerate the robust drug repurposing opportunities.

DRUG REPURPOSING AND ITS STRATEGIC IMPORTANCE IN MODERN DRUG DISCOVERY

Drug repurposing, also defined as drug repositioning or reprofiling, represents an innovative pharmaceutical strategy that identifies novel therapeutic applications for existing approved or investigational drugs (Jarada et al., 2020). This approach has emerged as a transformative methodology in modern drug discovery, fundamentally altering traditional development paradigms. The strategy operates through four essential components: comprehensive pharmacological understanding, innovative formulation development, systematic biological evaluation, and robust clinical validation (Mittal & Mittal, 2021). In the context of *in silico* studies, this approach has gained particular significance in modern drug discovery through its integration with computational methods and molecular data analysis (Cha et al., 2018).

Comparative Advantages of Drug Repurposing in Modern Drug Development

The strategic value of drug repurposing becomes evident when compared to *de novo* drug discovery approaches. Contemporary data indicate that while traditional drug development requires investments of approximately $50 billion annually, 12-15 years with success rates below 10% and costs exceeding $1.2 billion,

repurposing pathways can achieve results within 3-12 years, boasting approximately 25% success rates (Gil & Martinez, 2021; Tafesse et al., 2020). This efficiency stems from the utilization of established safety profiles and pharmacokinetic data, streamlined regulatory pathways, reduced development costs and timelines, and enhanced success probabilities in clinical phases (Gil & Martinez, 2021).

Success and Challenges in Modern Therapeutics

The significance of drug repurposing is reflected in current therapeutic landscapes, with approximately 30% of FDA-approved drugs originating from repurposing initiatives (Pola et al., 2023). Successful approval requires demonstration of therapeutic efficacy and safety in new indications, building upon existing safety data to accelerate development timelines (R. Kumar et al., 2019).

However, modern drug repurposing faces significant challenges despite technological advances. Annual R&D (Research and Development) investments of approximately $50 billion yield only 20-25 new drug approvals (Vukicevic, 2016). Moreover, key challenges include high failure rates in clinical trials, increasing development costs, limited predictive capacity of preclinical models, extended development timelines, and complex regulatory requirements (Honkala et al., 2021; Sun et al., 2022).

The Role of *In Silico* Approaches

In silico drug repurposing has emerged as a transformative, cost-effective complement to experimental workflows, enabling rapid identification of new therapeutic uses for existing drugs across diverse disease areas (Cousins et al., 2024). The integration of computational methodologies has become crucial in modern drug repurposing. Advanced *in silico* techniques, including artificial intelligence and machine learning algorithms (Pan et al., 2023; Patel et al., 2023; Rajput et al., 2021), multi-omics data analysis (D. Y. Liu et al., 2025; F. Wang & Barrero, 2024), network-based targeting (Islam & Shibly, 2025; P. P. Liu et al., 2025; Mahmud et al., 2025), enable rapid screening of compound libraries, prediction of drug-target interactions, assessment of safety profiles, and ultimately guide decision-making for further downstream development. This computational approach significantly enhances the efficiency and success rate of further drug repurposing initiatives (Tiwari et al., 2023).

IN SILICO METHODOLOGIES AND COMPUTATIONAL FRAMEWORKS

Computational drug repurposing integrates structure and ligand-based virtual screening, multi-omics data integration, network analysis, and machine learning to prioritize existing compounds for new indications. These *in silico* approaches use molecular docking/dynamics, pharmacophore/QSAR modeling, expression analysis, network pharmacology, and target/bioactivity prediction to generate candidates that undergo ADME/toxicity assessment and subsequent *in vitro*, *in vivo*, and clinical validation (**Figure 1**).

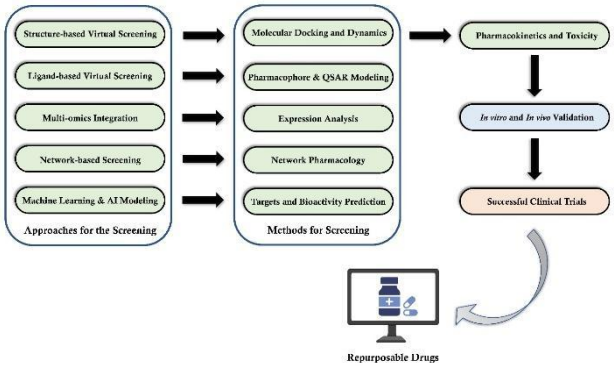

Figure 1. Flow diagram of drug screening approaches from *in silico* screening to subsequent downstream *in vitro*, *in vivo*, and clinical trials steps. Green boxes indicate *in silico* approaches, blue box indicates pre-clinical steps, and red box indicates clinical steps.

Virtual Screening: Structure-Based and Ligand-Based Strategies

Virtual screening (VS) encompasses both structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS). SBVS leverages three-dimensional target structures to evaluate candidate binding, while LBVS exploits chemical similarity, pharmacophore models, and quantitative structure–activity relationship (QSAR) models when structural information is absent or incomplete (Ananna et al., 2024; Muratov et al., 2020). LBVS is particularly useful for rapidly sifting among approved-drug libraries using fingerprint similarity, scaffold hopping, or ML-derived feature embeddings (Ripphausen et al., 2011). In repurposing, VS

pipelines often combine SBVS and LBVS outputs, applying consensus ranking, ensemble docking, or ML-based filtering to increase hit rates and reduce false positives before experimental testing (Ahmed et al., 2023).

Molecular Docking, Molecular Dynamics Simulation, and Structure-Based Screening

Structure-based methods anchored by molecular docking and binding-affinity prediction remain central to many repurposing workflows because they provide explicit, interpretable models of drug–target interactions (Cavalcante et al., 2024; Fan et al., 2019). Docking algorithms predict ligand poses within protein binding sites and estimate relative affinities; when combined with rescoring, free-energy methods, and molecular dynamics (MD) simulations, these approaches can prioritize compounds with plausible mechanistic effects (Vanhaelen et al., 2017). Strengths of structure-based screening include the ability to exploit high-resolution target structures, rationalize polypharmacologic interactions, and propose testable binding hypotheses. Limitations include sensitivity to protein conformational heterogeneity, inaccuracies in scoring functions, and dependency on available structural data; hybrid strategies that fuse docking with ML-based rescoring or MD-derived ensembles are increasingly used to mitigate these issues (Cavalcante et al., 2024).

Machine Learning and Artificial Intelligence Applications

Machine learning (ML) and artificial intelligence (AI) have become integral to modern repurposing, providing powerful tools for pattern recognition, feature extraction, and prediction across heterogeneous data types (Jordan & Mitchell, 2015; Tanoli et al., 2021). Applications include: supervised models for target prediction (Y. Zheng & Wu, 2021), ADMET profiling (Swanson et al., 2024) and biological activity prediction (Islam & Mahmud, 2025); deep learning for ligand and protein representation learning; graph neural networks for modeling molecular graphs and interaction networks; and generative models for proposing novel analogues or repositioning hypotheses (Ferreira & Andricopulo, 2019). AI augments traditional physics-based methods by improving scoring, imputing missing data, and enabling integrative analyses of omics and clinical records (Yetgin, 2025). However, key challenges are model interpretability, dataset bias, generalizability to unseen chemotypes, and the need for transparent validation against experimental benchmarks.

Network Pharmacology and Systems Biology Frameworks

Network pharmacology and systems biology offer complementary, systems-level perspectives that are essential for repurposing in complex diseases (Hopkins, 2008). By mapping drug–target–pathway–disease relationships within biological networks, these approaches identify indirect mechanisms, polypharmacologic opportunities, and context-dependent effects that single-target screens can miss (Lavecchia & Cerchia, 2016). Network-based methodologies include diffusion and proximity measures on protein–protein interaction (PPI) networks, community detection for module-driven repurposing, and central hubs identification (Islam & Mahmud, 2025). However, integration of network analysis with pathway enrichment, causal inference, and multi-omics promotes mechanistic interpretability and prioritization of candidate indications (Ahamed & Al Ashik, 2025; Islam & Shibly, 2025; P. P. Liu et al., 2025). Challenges include the limitations of network data to certain species types and contradictory target information from individual studies.

Integration of Clinical, Real-World, and Genomic Signature Data

Repurposing pipelines increasingly exploit clinical trial results, electronic health records (EHRs), adverse-event reporting, and population scale genomic/transcriptomic signatures to validate computational hypotheses and detect real-world drug–disease associations (Cousins et al., 2024). Signature-based repurposing matches disease-associated expression profiles with drug-induced transcriptional responses (Connectivity Map approaches), enabling identification of drugs that reverse disease signatures. Complementary analyses of EHRs and pharmacoepidemiologic data can reveal

off-label benefits or safety signals, and GWAS (Genome Wide Association Studies) data provide genetic evidence for target-disease causality, strengthening the translational rationale for repurposing (Khosravi et al., 2019). Challenges include confounding in observational data, heterogeneous data formats, and the need for robust causal inference frameworks (Mottini et al., 2019).

Databases, Cheminformatics Tools, and Computational Platforms

A rich ecosystem of public and proprietary resources underpins *in silico* repurposing: structural repositories (PDB), ligand and bioactivity databases (ChEMBL, DrugBank), transcriptomic atlases (LINCS/CMap), PPI and pathway databases (STRING, Reactome), and EHR/claims repositories for real-world evidence (Burley et al., 2023; Szklarczyk et al., 2023; Zdrazil et al., 2024). Cheminformatics toolkits (RDKit), docking suites (AutoDock, Glide), ML frameworks (TensorFlow, PyTorch), and integrated web platforms facilitate end-to-end repurposing workflows. **Table 1** represents the role of *in-silico* methods.

Table 1. Role of *in silico* methods in drug repurposing studies.

***In silico* Methods**	**Platforms/Databases**	**Role in Drug Repurposing**	**References**
Ligand-based Virtual Screening	LigandScout, Pharmit	Compares structural similarities between known drugs and ligands	(Al-Sanea et al., 2022)
Structure-based Virtual Screening	PyRx, SwissDock	Screens large drug libraries against target protein structures	(Bugnon et al., 2024; Xu et al., 2022)
Molecular Docking	AutoDock, AutoDock Vina, Schrödinger Glide, GOLD	Predicts binding pose, binding affinity, and interaction of approved drugs with new target proteins	(Eberhardt et al., 2021)
Molecular Dyamics (MD) Simulation	GROMACS, AMBER, DESMOND, NAMD	Simulates and validates the stability and behavior of drug-target complexes over time	(Yekeen et al., 2023)
Bioinformatics & Omics Integration	GEO, TCGA	Connects disease-associated genes, pathways, and drug targets using transcriptomics, proteomics, and interactome data.	(Clough & Barrett, 2016; Otasek et al., 2019; Szklarczyk et al., 2023)
Machine Learning / AI Models	DeepPurpose, ChemProp, TensorFlow, DeepChem	Predicts new drug–disease associations using large biological and chemical datasets using model development	(Abadi et al., 2016; Heid et al., 2023; Huang et al., 2021; Ramsundar, 2018)
Network-based Drug Repurposing	NetworkAnalyst, DrugBank, STITCH, STRING, Cytoscape	Analyzes drug-target-disease networks to uncover new mechanisms	(Knox et al., 2024; Kuhn et al., 2014; G. Zhou et al., 2019)
Drug Screening Databases	ZINC, ChEMBL, BindingDB	Provides ready-to-screen collections of approved or investigational drugs	(Gaulton et al., 2017)

PHARMACOLOGICAL AND TOXICOLOGICAL ASSESSMENT THROUGH *IN SILICO* TOOLS

The integration of computational approaches in drug repurposing has revolutionized the assessment of pharmacological and toxicological properties, enabling more efficient and cost-effective drug development processes. Approximately 90% of drugs fail to make it through the process due to improper AMDET profiling (Amorim et al., 2024).

ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) Prediction

Recent advances in machine learning platforms have significantly enhanced ADMET prediction capabilities. Modern platforms like ADMET-AI have achieved unprecedented accuracy in molecular predictions, processing up to one million molecules in just 3.1 hours (Swanson et al., 2024). The interpretable-ADMET platform represents another significant advancement, offering predictions for 59

ADMET-associated properties through 90 classification and 28 regression models (Wei et al., 2022). ADMETboost has demonstrated superior performance by ranking first in 18 out of 22 predictions (Tian et al., 2022). However, common tools, including pkCSM, SwissADME, and ADMETlab, also help evaluate the safety and pharmacokinetics of existing drugs before wet-lab testing (**Table 2**).

Table 2. Modern *in silico* tools for ADMET properties prediction.

***In silico* ADMET Prediction Platforms**	**Prediction Method**	**References**
ADMET-AI (https://admet.ai.greenstonebio.com)	GNN (Graph neural network) model	(Swanson et al., 2024)
ADMETlab 3.0 (https://admetlab3.scbdd.com)	DMPNN (Directed Message Passing Neural Network) architecture coupled with molecular descriptors	(Fu et al., 2024)
DeepPK (https://biosig.lab.uq.edu.au/deeppk/)	GNN (Graph Neural Networks) and graph-based signatures	(Myung et al., 2024)
ADMETboost (https://ai-druglab.smu.edu/admet)	Fingerprints and features-driven Tree-based extreme gradient boosting machine learning model	(Tian et al., 2022)
ADMETsar 2.0 (https://lmmd.ecust.edu.cn/admetsar2)	Molecular fingerprints-driven classical machine learning algorithms	(Yang et al., 2019)
SwissADME (https://www.swissadme.ch/)	Rule-based and descriptor-based classical machine-learning models	(Daina et al., 2017)
ProTox 3.0 (https://tox.charite.de/protox3/)	Molecular similarity and machine-learning algorithms	(Banerjee et al., 2024)

Pharmacokinetic and Pharmacodynamic Modelling

PK/PD modeling has emerged as a crucial bridge between preclinical and clinical research in drug repurposing. The PK/PD methodology encompasses the integration of existing drug data and *in vitro* pathogen information, dosage optimization through clinical PK considerations, correlation of drug pharmacokinetics with viral life cycle events, establishment of PK-clinical outcome relationships, and treatment effect assessment (Begley et al., 2021).

Mechanism-based PK-PD models have proven particularly valuable by distinguishing between drug-specific and biological system-specific parameters (Danhof et al., 2008). Additionally, these computational approaches facilitate the integration of diverse data types and enable more accurate inter-species scaling (Kang et al., 2024).

Drug-Drug Interaction Predictions

Machine learning approaches have achieved remarkable accuracy in predicting drug-drug interactions (DDIs). Notable achievements include the development of deep neural networks predicting 80 DDI types with 93.2% accuracy (Hou et al., 2019), drug interaction similarity clustering for 589 drugs (B. Zhou et al., 2015), and graph embedding approaches integrating drug-drug and protein-protein networks (Amiri Souri et al., 2023). This approach may prevent harmful and life-threatening adverse reactions by proactively identifying potential drug–drug interactions that are impractical to uncover through clinical testing alone.

Off-Target Effects and Polypharmacology Analysis

Strategies are needed to predict off-target protein interactions, which can help avoid adverse effects while identifying drug repurposing opportunities. Computational analysis of polypharmacology has revealed valuable insights into drug repurposing opportunities. The CANDO platform exemplifies systematic compound-proteome interaction screening capabilities (Sethi et al., 2015). Large-

scale studies have identified 2,923 potential cross-reactivity cases involving 140 unique drugs and 1,216 protein targets (Chartier et al., 2017). Therefore, systematic proteome-scale screening is essential to identify cross-reactivity risks and repurposing opportunities across drugs and protein targets.

Safety Profiling and Adverse Event Prediction

The identification, prediction, and mitigation of drug-related safety is necessary by detecting adverse events, assessing causality, and guiding safer use across diverse populations and real-world settings. Multiple computational strategies have emerged for safety profiling, including FAERS (FDA Adverse Event Reporting System) data mining (Morris et al., 2024), Mendelian randomization approaches (Walker et al., 2017), machine learning classifiers utilizing gene expression data (Z. Wang et al., 2016), and post-market safety analysis using AI-driven statistical approaches (Daluwatte et al., 2020). These complementary computational safety-profiling strategies can detect real-world adverse events, infer causality, predict mechanistic toxicity, and monitor long-term population-level risks that preclinical tests and clinical trials may miss.

Bioavailability and Formulation Optimization Studies

Recent studies have demonstrated significant advances in formulation optimization. Notable achievements include the development of solid self-nanoemulsifying drug delivery systems, increasing oral bioavailability, and the identification of formulation categories addressing poor solubility (Baek et al., 2024; Jug et al., 2024). These advances align with the four pillars of successful drug repurposing, outlined by pharmacological understanding, formulation optimization, biological assay evaluation, and clinical trial robustness (Mittal & Mittal, 2021). Modern data analysis tools such as Google Cloud Vertex AI (Sina et al., 2025) and Microsoft Azure AI (Vuppalapati et al., 2020) can be a rapid solution for automated bioavailability and formulation optimization using machine learning-driven approaches.

DISEASE-SPECIFIC APPLICATIONS AND THERAPEUTIC AREAS

The strategic deployment of *in silico* methodologies across diverse therapeutic domains has demonstrated the versatility and translational potential of computational drug repurposing. Computational approaches are being applied to address unmet medical needs across major disease categories, from complex malignancies to emerging infectious threats. **Figure 2** represents the drug repurposing opportunities in different disease types.

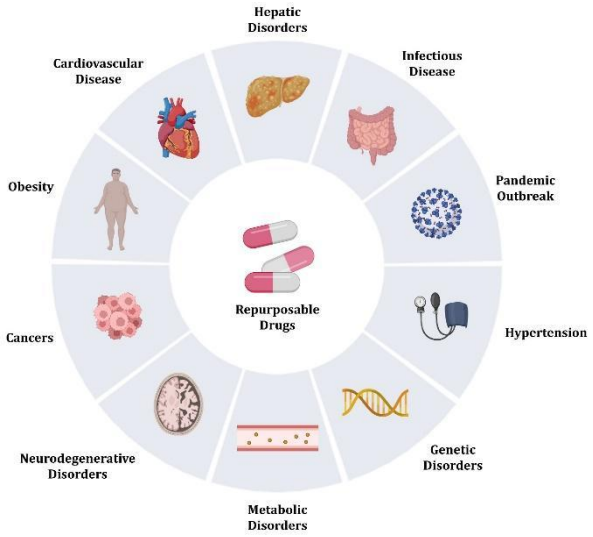

Figure 2. Drug repurposing opportunities in different disease types. Repurposable drugs can be applied to multiple clinical indications, such as hepatic, metabolic, infectious, cardiovascular, oncologic, neurodegenerative, genetic, and obesity-related disorders.

Cancer drug repurposing and precision oncology

Computational drug repurposing has emerged as a transformative strategy in oncology, leveraging molecular modeling, machine learning, and network-based approaches to identify novel therapeutic interventions for cancer treatment. A comprehensive analysis identified 238 studies employing *in silico* methods for cancer drug repurposing, with molecular modeling representing the most frequently utilized technique (Cavalcante et al., 2024). The computational toolkit encompasses virtual screening, molecular docking, molecular dynamics, network pharmacology, and artificial intelligence-driven prediction models that can

systematically evaluate drug-target interactions across the cancer proteome (Mottini et al., 2019).

These computational strategies have proven particularly valuable in precision oncology, where individual tumor molecular profiles can be matched against repurposed drug candidates to identify patient-specific therapeutic options. Moreover, computational approaches substantially expand the repertoire of actionable molecular targets, enabling personalized treatment strategies tailored to individual tumor characteristics (K.W. To & Cho, 2022). Furthermore, the integration of multi-omics data, including genomics, transcriptomics, and proteomics, with computational drug-target prediction platforms allows for the identification of vulnerabilities in specific cancer subtypes and the rational selection of repurposed agents that exploit these molecular dependencies (Mukherjee et al., 2024).

Infectious diseases: antibacterial, antiviral, and antiparasitic repurposing

The application of *in silico* drug repurposing to infectious diseases has accelerated dramatically, driven by the urgent need to combat emerging pathogens, drug-resistant organisms, and neglected tropical diseases (Hamid et al., 2024). Computational platforms have successfully identified repurposing candidates across diverse infectious disease contexts, including bacterial infections, viral diseases such as COVID-19 and dengue, and parasitic conditions, including malaria and tuberculosis (Hamid et al., 2024; Winkler, 2024; Zhang et al., 2025). These approaches could rapidly screen existing drug libraries against pathogen-specific targets, substantially reducing the time and cost associated with traditional antimicrobial development (W. Zheng et al., 2018).

Sophisticated computational workflows could integrate structural biology, cheminformatics, and systems pharmacology to predict drug-pathogen interactions and identify compounds with favorable therapeutic indices (N. Kumar et al., 2022). For antiviral applications specifically, researchers have employed computational methods to predict biological activities against viral proteins, analyze protein-drug interaction networks, and prioritize candidates based on predicted pharmacokinetic and safety profiles (Abdulaziz et al., 2022). These methodologies have proven particularly valuable in addressing the global challenge of antimicrobial resistance, where computational strategies can rapidly identify agents that circumvent established resistance mechanisms or that synergize with existing therapies (Upadhayay et al., 2023). This paradigm also offers a critical advantage in pandemic preparedness and response, enabling rapid computational screening against novel pathogen targets as genomic sequence data become available (Low et al., 2020; Vashisht et al., 2023; Zhang et al., 2025).

Neurodegenerative disorders: Alzheimer's, Parkinson's, and rare neurological diseases

In silico approaches have become indispensable tools for advancing therapeutic discovery in neurodegenerative diseases, where complex, multifactorial pathophysiology and the scarcity of disease-modifying treatments create substantial unmet medical needs. Computational methods enable researchers to systematically explore chemical space and identify compounds that interact with therapeutically relevant macromolecular targets implicated in neurodegeneration (Banjare et al., 2023; Haider et al., 2021).

The application of *in silico* techniques in Alzheimer's disease research encompasses computational screening against targets such as acetylcholinesterase, beta-secretase, and aggregation-prone proteins, including amyloid-beta and tau (Grcic et al., 2024; Vahid et al., 2024). Similarly, Parkinson's disease research has benefited from computational approaches targeting alpha-synuclein aggregation, monoamine oxidase enzymes, and neuroprotective pathways (Peña-Díaz et al., 2023; Siddiqui et al., 2023). Computational methods substantially reduce the experimental burden and cost of screening large compound libraries, while simultaneously enabling the prediction of ADMET properties that are critical for central nervous system penetration (Makhouri & Ghasemi, 2017). Recent advances in computational evaluation of drug candidates' affinity for macromolecular targets relevant to

neurodegeneration, demonstrating improved predictive accuracy and translational success (Cruz-Vicente et al., 2021).

Metabolic, genetic, hepatic, and cardiovascular diseases

In silico methodologies enable the systematic exploration of drug-disease interaction networks, pathway-level effects, and multi-target pharmacology that characterize many metabolic, genetic, hepatic, and cardiovascular conditions, along with hypertension and obesity (Hodos et al., 2016; Mullins et al., 2022; Sood et al., 2023; Wu et al., 2022).

Computational workflows applied to specifically metabolic and cardiovascular diseases integrate diverse data modalities, including disease-associated genetic variants, transcriptomic signatures, protein-protein interaction networks, and pharmacological databases. These integrated platforms can predict novel drug-target associations, identify mechanism-based repurposing candidates, and prioritize agents with favorable efficacy and safety profiles for specific patient subpopulations (El-Nikhely & El-Yazbi, 2024). For instance, Schubert et al. demonstrated computational screening approaches that identified existing drugs with previously unrecognized cardiovascular benefits, illustrating the potential to expand therapeutic options for conditions such as heart failure, atherosclerosis, and metabolic syndrome (Schubert et al., 2020).

Rare and orphan diseases: addressing unmet medical needs

In silico drug repurposing represents a critical strategy for addressing medical needs in rare and orphan diseases, where traditional pharmaceutical development models are often economically unfeasible due to limited patient populations. Computational approaches offer a pathway to accelerate therapeutic discovery by systematically exploring existing pharmacopeia for drugs that may be repurposed for rare disease indications, thereby leveraging established safety profiles and reducing development timelines (Roessler et al., 2021).

Structure-based computational methods, including drug-binding pocket matching and computational pharmacology, have been employed to systematically map potential drug-target interactions relevant to orphan diseases (Govindaraj et al., 2018). Additionally, Govindaraj et al. generated an extensive computational resource comprising 31,142 putative drug-target complexes linked to 980 orphan diseases, demonstrating the scalability of computational repurposing strategies (Govindaraj et al., 2018). These approaches integrate genomic and proteomic data from rare disease patients with computational target prediction platforms, enabling hypothesis-driven identification of repurposing candidates that address specific molecular pathophysiology.

Given that approximately 94% of rare diseases currently lack approved therapies, computational drug repurposing offers a pragmatic and scientifically rigorous approach to expanding therapeutic options for underserved patient populations (Roessler et al., 2021). However, successful translation will require collaborative frameworks that integrate computational discovery with patient advocacy, regulatory flexibility, and innovative clinical trial designs appropriate for small patient cohorts.

COVID-19 and pandemic response case studies

The COVID-19 pandemic catalyzed an unprecedented application of *in silico* drug repurposing methodologies, demonstrating the capacity of computational platforms to rapidly respond to emerging infectious disease threats. Within months of SARS-CoV-2 genome and structural protein data becoming available, researchers deployed comprehensive computational screening campaigns targeting viral proteins, including the spike glycoprotein, main protease (Mpro), RNA-dependent RNA polymerase, and other essential viral factors (Cavasotto & Di Filippo, 2021; Mushebenge et al., 2023).

These efforts identified multiple repurposing candidates, including remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, darunavir, arbidol, chloroquine, hydroxychloroquine, tocilizumab, and interferons, which were subsequently evaluated in preclinical models and clinical trials (Singh et al., 2020). Galindez et al. emphasized that *in silico* methods provided critical advantages during the pandemic response, including the ability to screen vast chemical

libraries *in silico* within weeks, predict drug-target interactions with mechanistic granularity, and prioritize candidates for resource-intensive experimental validation (Galindez et al., 2021). Therefore, these computational approaches enabled rapid prioritization of candidates based on predicted binding affinity, mechanism of action, and favorable ADMET properties, substantially accelerating the timeline from target identification to clinical evaluation in response to pandemic urgency.

INTEGRATION OF *IN SILICO* DRUG REPURPOSING WITH EXPERIMENTAL VALIDATION AND CLINICAL TRANSLATION

Computational predictions can be effectively bridged with *in vitro*, *in vivo*, and clinical evaluation through an integrative drug repurposing methodology that combines computational hypothesis generation with targeted experimental validation.

Wilkinson et al. elucidated that *in vitro* screening methodologies provide substantial advantages for validating computational predictions (Wilkinson & Pritchard, 2015), while Issa et al. delineated how high-performance computing infrastructures facilitate the generation of robust drug-target interaction hypotheses (Issa et al., 2013).

Guerra et al. and Barnwal et al. provide preclinical proof-of-concept for repurposing spironolactone and ponatinib, respectively. Guerra et al. showed spironolactone kills Schistosoma mansoni *in vitro* and, at clinically achievable oral doses, reduces worm burden and egg-related pathology in infected mice without overt toxicity (Guerra et al., 2019). Barnwal et al. identified ponatinib as a PD-L1 suppressor in cell-based assays and demonstrated that it lowers intratumoral PD-L1, increases CD8+ T-cell infiltration, and inhibits tumor growth in syngeneic mouse models at pharmacologically relevant exposures, supporting further clinical evaluation (Barnwal et al., 2023).

Additionally, the rapid global spread of SARS-CoV-2 prompted extensive drug-repurposing initiatives assessed across large platform trials and numerous smaller studies, identifying therapeutic benefit for agents including remdesivir, dexamethasone, tocilizumab, and baricitinib while refuting efficacy for others (hydroxychloroquine, lopinavir/ritonavir); by March 2021, 4,952 COVID-19 clinical trials had been registered across more than 100 countries (Chakraborty et al., 2021).

While virtual screening and molecular docking are valuable drug discovery tools, their limitations must be acknowledged. Computational methods frequently generate false positives where high docking scores fail to correlate with biological activity, exemplified by "activity cliffs", structurally similar compounds exhibiting dramatically different potencies (Shukla et al., 2025; Van Tilborg et al., 2022). These discrepancies arise from factors difficult to model computationally, including protein flexibility, solvent effects, entropic contributions, and limitations in scoring function accuracy. Consequently, experimental validation through biochemical and cellular assays is not a subsequent step but an indispensable step for eliminating false positives and confirming true hits. This integrated computational-experimental approach ensures that only compounds with genuine therapeutic potential advance through the drug development pipeline.

Therefore, despite the substantial utility of in silico approaches, these computational approaches necessitate rigorous validation through subsequent experimental and clinical evaluation protocols (Andrade, 2016). While demonstrating considerable promise, they currently function as complementary rather than replacement methodologies within established drug development paradigms.

CONCLUSIONS AND FUTURE PERSPECTIVES

In silico drug repurposing has emerged as a transformative paradigm in modern pharmaceutical development, offering substantial advantages over traditional *de novo* discovery approaches through reduced timelines, enhanced success rates, and cost-effective therapeutic identification. The integration of diverse computational methodologies, including structure-based and ligand-based virtual screening, molecular docking and dynamics simulations, machine learning and artificial intelligence algorithms,

network pharmacology, and multi-omics data integration, has demonstrated remarkable capability in predicting drug-target interactions and accelerating candidate prioritization across multiple therapeutic areas. These computational platforms have successfully addressed critical unmet medical needs in oncology, infectious diseases, neurodegenerative disorders, metabolic conditions, and pandemic response, with approximately 30% of FDA-approved drugs now originating from repurposing initiatives. As computational power increases and data availability expands, *in silico* drug repurposing will continue evolving from a complementary tool to an indispensable, hypothesis-driven engine driving pharmaceutical innovation in the era of precision medicine. Therefore, the future of *in silico* drug repurposing should lie in the synergistic integration of these complementary approaches into unified computational frameworks. Hybrid strategies that combine structure-based screening with machine learning-driven rescoring, deep learning-enhanced ligand representation with network-based polypharmacology analysis, and multi-omics signatures with systems biology modeling promise to overcome current limitations, including scoring function inaccuracies, dataset bias, and model interpretability challenges. Moreover, the incorporation of real-world clinical data, electronic health records, and population-scale genomic information with machine learning-based modeling will further strengthen translational predictions and enable personalized repurposing strategies tailored to individual patient molecular profiles.

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AUTHORS' CONTRIBUTIONS

K.M. Tanjida Islam: Conceptualization, Methodology, Data curation, Formal analysis, Validation, Writing- original draft, Review and editing.

CONFLICT OF INTERESTS

The author declared no conflicts of interest.

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Not applicable.

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