Chapter- Eleven

Drug Repurposing: Strategies, Methodologies, and Emerging Therapeutic Innovations

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Abstract

Drug repurposing, also referred to as drug repositioning or therapeutic switching, is a strategic approach aimed at identifying novel therapeutic indications for existing drugs, including approved, investigational, or discontinued molecules. Conventional drug discovery is associated with prolonged development timelines, high research and development costs, and significant failure rates, particularly during late-stage clinical trials. Drug repurposing addresses these challenges by leveraging prior knowledge of pharmacokinetics, safety, toxicity, and manufacturing processes, thereby substantially reducing development time and economic burden. The present chapter provides a structured and comprehensive overview of drug repurposing based on well-established strategies and methodologies. The introduction outlines the rationale and growing importance of repurposing in modern pharmaceutical sciences. The methods section, derived from established conceptual frameworks, describes on-target and off-target repurposing strategies, experimental and in-silico approaches, methodological classifications, and key databases used in the repurposing process. Recent advances, including artificial intelligence, network pharmacology, and multi-omics integration, are incorporated to reflect current trends. This chapter emphasizes drug repurposing as a rational, efficient, and sustainable approach to accelerate therapeutic innovation and address unmet medical needs.

Keywords: *Drug repurposing; Drug repositioning; On-target repurposing; Off-target repurposing; In-silico drug discovery; Pharmaceutical sciences.*

Introduction

The process of drug discovery and development is widely recognized as one of the most complex, time-consuming, and resource-intensive undertakings in pharmaceutical sciences. Despite remarkable advances in molecular biology, medicinal chemistry, genomics, and high-throughput screening technologies, the overall productivity of conventional drug discovery pipelines has declined over the past few decades. On average, the development of a new chemical entity from target identification to market approval requires approximately 10–15 years and is associated with an estimated cost exceeding one billion US dollars [1,2]. Furthermore, only a small fraction of candidate molecules entering clinical trials ultimately receive regulatory approval, with the highest attrition rates observed during Phase II and Phase III clinical studies due to lack of efficacy or unexpected safety concerns.

These challenges have prompted both the pharmaceutical industry and academic research institutions to explore alternative strategies capable of reducing development

timelines, minimising financial risk, and improving success rates. Among these strategies, drug repurposing—also referred to as drug repositioning or therapeutic switching—has emerged as a particularly attractive and pragmatic approach. Drug repurposing involves the identification of new therapeutic indications for existing drugs, including approved drugs, investigational compounds, and molecules that were discontinued during development for reasons unrelated to safety [3]. By leveraging existing knowledge of pharmacokinetics, toxicology, formulation, and clinical safety, drug repurposing significantly reduces uncertainty in the development process.

The conceptual basis of drug repurposing aligns strongly with the principles of rational drug design and translational research. Unlike de novo drug discovery, which begins with limited biological and chemical information, repurposing efforts start with compounds that already possess well-characterized physicochemical properties and human exposure data. This advantage not only shortens development timelines but also enhances the probability of regulatory success [4]. Consequently, drug repurposing has gained increasing attention as a cost-effective and efficient strategy to address unmet medical needs, particularly in therapeutic areas characterised by high failure rates.

Historically, many successful examples of drug repurposing were discovered serendipitously through clinical observation rather than systematic investigation. A classic example is aspirin, initially developed as an analgesic and anti-inflammatory agent, which was later repurposed for cardiovascular disease prevention due to its antiplatelet activity and is currently being explored for potential anticancer applications [5]. Similarly, minoxidil, originally approved as an oral antihypertensive agent, was repositioned for the treatment of androgenic alopecia following observations of increased hair growth in patients receiving the drug [6]. These examples, which are also highlighted in foundational teaching frameworks, clearly demonstrate the translational potential of repurposing strategies.

While early repurposing discoveries relied largely on chance, contemporary drug repurposing has evolved into a structured and hypothesis-driven discipline. Advances in bioinformatics, cheminformatics, systems biology, and computational chemistry have enabled systematic identification of drug–target and drug–disease relationships [7]. The availability of large-scale biomedical databases containing chemical, biological, genomic, and clinical information has further facilitated data-driven repurposing efforts. Resources such as DrugBank, ChEMBL, PubChem, ClinicalTrials.gov, KEGG, and OMIM provide curated datasets that support comprehensive analysis of drug properties, molecular targets, biological pathways, and clinical outcomes [8–10].

The growing importance of drug repurposing is also driven by the increasing burden of complex and multifactorial diseases. Chronic conditions such as cancer, neurodegenerative disorders, metabolic diseases, and cardiovascular disorders involve multiple molecular pathways, making them particularly challenging targets for single-target drugs developed through traditional approaches. Drug repurposing offers the opportunity to identify multi-target drugs or drugs with pleiotropic effects that may be better suited for such complex disease states [11]. In addition, repurposing plays a critical role in the management of rare and neglected diseases, where limited commercial incentives often restrict investment in de novo drug development.

Global health emergencies have further highlighted the strategic value of drug repurposing. During outbreaks of emerging infectious diseases, including the COVID-19 pandemic, repurposing strategies enabled rapid evaluation of approved drugs and clinical candidates for antiviral and host-directed therapeutic effects [12]. Although not all repurposed candidates demonstrated clinical efficacy, these efforts underscored the ability of repurposing frameworks to generate rapid therapeutic hypotheses in crises. As a result,

regulatory agencies and funding bodies have increasingly recognised drug repurposing as a vital component of emergency preparedness and response strategies.

Recent advances in artificial intelligence (AI) and machine learning (ML) have further transformed the landscape of drug repurposing. AI-driven models integrate chemical structures, bioactivity data, transcriptomic signatures, and clinical records to predict novel drug–disease associations with improved accuracy [13–15]. Network pharmacology approaches complement these methods by modelling diseases as perturbations of complex biological networks rather than isolated targets. Together, these technologies have shifted drug repurposing from a largely empirical practice to a data-intensive and predictive science.
In addition to scientific and technological drivers, regulatory and economic factors have contributed to the growing adoption of drug repurposing. Regulatory pathways such as the United States Food and Drug Administration (FDA) 505(b)(2) application allow sponsors to rely partly on existing data for previously approved drugs, thereby reducing the scope of additional studies required for new indications [16]. Similar regulatory mechanisms exist within the European Medicines Agency framework. These pathways provide a structured route for the clinical development and approval of repurposed drugs, further enhancing their commercial and translational feasibility.

Taken together, these factors position drug repurposing as a central strategy in modern pharmaceutical sciences. The systematic integration of experimental validation, computational modelling, and regulatory support has transformed repurposing into a mature and impactful discipline. This chapter builds upon established conceptual frameworks—commonly used in pharmaceutical education and research—to present a structured overview of drug repurposing strategies, methodologies, and outcomes. By combining foundational principles with recent advances reported between 2020 and 2025, the chapter aims to provide a comprehensive understanding of drug repurposing as a sustainable and innovative pathway for drug development.

Methods

The methodology of drug repurposing is based on a structured and systematic framework designed to identify new therapeutic indications for existing drug molecules. Unlike conventional drug discovery, which begins with target identification followed by lead optimisation and extensive preclinical testing, drug repurposing methodologies leverage prior knowledge of drug safety, pharmacokinetics, pharmacodynamics, and clinical usage. This significantly reduces development time, cost, and uncertainty while improving translational success [17,18]. The methodological framework adopted in this chapter is derived from established educational and research models in pharmaceutical sciences and integrates strategic classification, experimental validation, in-silico prediction, methodological orientation, and data-driven integration.

Strategic Classification of Drug Repurposing

Drug repurposing strategies are broadly classified into on-target and off-target repurposing. This classification provides a mechanistic foundation for understanding how existing drugs can be redirected toward new therapeutic applications and is widely accepted in repurposing research frameworks [19,20].

On-target drug repurposing involves applying the known pharmacological mechanism of a drug to a new disease indication that involves the same molecular target. In this approach,

the biological target remains unchanged, while the clinical application differs. On-target repurposing is particularly effective when a target plays a role in multiple disease pathways or physiological processes. Because the mechanism of action is already well characterised, on-target repurposing generally requires fewer additional mechanistic studies and is associated with higher regulatory acceptance [21].

In contrast, off-target drug repurposing identifies novel therapeutic effects mediated through biological targets or pathways different from the drug's original mechanism of action. Off-target effects may arise from secondary binding interactions, modulation of signalling cascades, or pleiotropic biological responses. While off-target repurposing often leads to unexpected therapeutic opportunities, it typically requires more extensive validation to ensure safety and efficacy in the new indication [22].

Experimental Approaches in Drug Repurposing

Experimental or activity-based repurposing approaches rely on biological assays to identify new pharmacological activities of existing drugs without prior assumptions regarding molecular targets. These approaches are particularly useful for uncovering complex or multi-target effects and are well-suited for diseases with poorly understood molecular mechanisms [23].

Target-Based Screening

Target-based screening evaluates interactions between approved or investigational drugs and specific disease-relevant molecular targets, such as enzymes, receptors, ion channels, or transporters. This approach is hypothesis-driven and is most effective when the target has been well validated in disease pathophysiology. High-throughput biochemical assays are commonly employed to screen drug libraries against selected targets, enabling rapid identification of potential repurposing candidates [24].

Cell-Based and Phenotypic Screening

Cell-based and phenotypic screening approaches assess the effects of drugs on cellular functions without prior knowledge of specific molecular targets. These assays capture integrated biological responses, including alterations in cell morphology, proliferation, differentiation, apoptosis, and intracellular signaling. Phenotypic screening is particularly valuable for identifying off-target effects and drugs with pleiotropic activity, making it highly relevant for oncology, neurological disorders, and infectious diseases [25,26].

In Vivo Models

Animal models play a critical role in validating repurposing candidates identified through in vitro or computational approaches. In vivo studies provide essential information on pharmacokinetics, pharmacodynamics, tissue distribution, efficacy, and toxicity within a whole-organism context. Although resource-intensive, animal models remain indispensable for assessing translational relevance before clinical evaluation [27].

Clinical and Observational Studies

Clinical observations and retrospective analyses of patient data represent an important experimental approach in drug repurposing. Unexpected therapeutic benefits observed during routine clinical use often generate repurposing hypotheses. Increasing availability of real-world evidence from electronic health records, insurance databases, and patient registries has further strengthened the role of observational studies in repurposing research [28].

In-Silico Approaches in Drug Repurposing
In-silico drug repurposing employs computational tools to predict drug–target and drug–disease associations. These approaches offer significant advantages in terms of speed, scalability, and cost-effectiveness and have become central to modern repurposing pipelines [29].

Molecular Docking and Virtual Screening
Molecular docking predicts the binding orientation and affinity of drugs to molecular targets using three-dimensional structural information. Virtual screening enables rapid evaluation of large drug libraries against disease-associated targets, allowing prioritisation of candidates for experimental validation. These techniques are widely used in early-stage repurposing studies [30].

Ligand-Based Similarity Approaches
Ligand-based methods identify repurposing candidates based on chemical similarity to known active compounds. These approaches assume that structurally similar molecules may exhibit similar biological activities and are particularly useful when target structural data are unavailable [31].

Network Pharmacology
Network pharmacology models biological systems as interconnected networks of genes, proteins, pathways, and diseases. This approach recognises that drugs often exert therapeutic effects through the modulation of multiple targets rather than single molecular entities. Network-based analysis is especially relevant for complex and multifactorial diseases such as cancer, neurodegenerative disorders, and metabolic syndromes [32].

Artificial Intelligence and Machine Learning
Recent advances in artificial intelligence and machine learning have significantly enhanced in-silico drug repurposing. AI-driven models integrate chemical structures, bioactivity data, transcriptomic profiles, and clinical information to predict novel drug–disease associations. Deep learning and graph-based approaches have demonstrated improved predictive accuracy and translational relevance in repurposing studies published between 2020 and 2025 [33–35].

Methodological Orientation of Drug Repurposing
Drug repurposing methodologies can also be categorised based on their primary orientation, as given in Table 2:

Drug-Oriented Approaches
Drug-oriented approaches focus on intrinsic properties of drugs, including chemical structure, known pharmacological activities, adverse effect profiles, and pharmacokinetic characteristics. Side-effect similarity analysis and chemical fingerprinting are commonly employed techniques in this category [36].

Target-Oriented Approaches
Target-oriented approaches prioritise disease-relevant molecular targets and identify existing drugs capable of modulating these targets. These methods are particularly effective when disease biology is well understood, and suitable targets have been validated [37].

Disease-Oriented Approaches
Disease-oriented approaches integrate genomic, proteomic, metabolomic, and transcriptomic data to identify drugs capable of reversing disease-specific molecular signatures. Signature matching between disease states and drug-induced gene expression profiles is a widely used strategy within this framework [38,39].

Databases and Data Resources Supporting Drug Repurposing
The effectiveness of drug repurposing methodologies is strongly supported by the availability of comprehensive biomedical databases. Resources such as DrugBank, ChEMBL, PubChem, ClinicalTrials.gov, KEGG, and OMIM provide curated information on drug properties, molecular targets, biological pathways, and clinical outcomes [40–43]. Integration of these databases enables systematic data mining, hypothesis generation, and validation across both experimental and computational repurposing studies.

Integration of Hybrid Repurposing Approaches
Modern drug repurposing increasingly relies on hybrid approaches that combine in-silico prediction with experimental validation. Computational methods are used to prioritise candidates, which are subsequently evaluated through in vitro assays, animal models, and clinical studies. This iterative workflow enhances efficiency, reduces false-positive rates, and improves translational success [44,45].

Results

Comparative Outcomes of Drug Repurposing versus Conventional Drug Development
Comparative analysis of outcomes from traditional drug development and drug repurposing demonstrates clear advantages of repurposing strategies in terms of development timeline, cost efficiency, and probability of success. Conventional drug discovery follows a linear and resource-intensive process involving target identification, lead optimisation, preclinical testing, and multiple phases of clinical trials, with high attrition rates particularly during Phase II and Phase III clinical evaluation [46]. In contrast, drug repurposing leverages existing knowledge of drug safety, pharmacokinetics, formulation, and manufacturing, allowing several early-stage development steps to be bypassed.

Reported outcomes from academic and industrial repurposing programs indicate that development timelines can be reduced to approximately 3–6 years, compared with more than a decade for de novo drug discovery [47]. Financial investment is correspondingly lower, and the availability of prior clinical data reduces the likelihood of late-stage failure. These comparative outcomes strongly support the role of drug repurposing as an efficient and pragmatic alternative to traditional drug development pipelines, as per Table 2.

Outcomes of Experimental Drug Repurposing Approaches
Experimental repurposing approaches have produced significant outcomes across multiple therapeutic areas. Target-based screening has successfully identified existing drugs capable of modulating disease-relevant molecular targets, particularly in oncology, infectious diseases, and inflammatory disorders [48]. In several cases, approved drugs demonstrated inhibitory or modulatory effects on targets that were not initially associated with their original therapeutic indication.

Cell-based and phenotypic screening approaches have yielded particularly impactful results by identifying off-target and pleiotropic drug effects. These assays capture integrated biological responses and have led to the discovery of drugs capable of modulating complex

cellular processes such as apoptosis, autophagy, immune signalling, and metabolic regulation [49]. Phenotypic screening outcomes have been especially valuable in diseases with poorly understood molecular mechanisms, where target-centric approaches alone are insufficient.
In vivo validation studies further confirmed the translational relevance of repurposed drugs identified through in vitro screening. Animal models demonstrated improved efficacy and acceptable safety profiles for several repurposing candidates, supporting their progression toward clinical evaluation [50]. Collectively, these experimental outcomes highlight the robustness and translational potential of activity-based repurposing methodologies.

Outcomes of In-Silico Drug Repurposing Approaches
In-silico repurposing approaches have generated substantial outcomes by enabling rapid and cost-effective identification of candidate drugs for new indications. Molecular docking and virtual screening studies have successfully prioritised approved drugs with high binding affinity toward disease-associated targets, many of which were subsequently validated experimentally [51]. Ligand-based similarity approaches further supported the identification of drugs with shared pharmacological properties and potential therapeutic overlap.

Network pharmacology-based repurposing has produced outcomes of particular significance for complex and multifactorial diseases. By modelling diseases as perturbations of interconnected biological networks, network-based approaches identified drugs capable of modulating multiple targets and pathways simultaneously [52]. Such outcomes are especially relevant for cancer, neurodegenerative disorders, and metabolic diseases, where single-target interventions often prove insufficient.

Computational repurposing played a critical role during global health emergencies, including the COVID-19 pandemic. Large-scale virtual screening of approved drug libraries enabled rapid prioritisation of antiviral and host-directed therapeutic candidates, demonstrating the practical utility of in-silico repurposing as a rapid response strategy [53]. Although not all candidates demonstrated clinical efficacy, these outcomes underscored the speed and scalability of computational repurposing pipelines.

Case Study Outcomes: Aspirin
Aspirin represents one of the most well-documented and successful examples of drug repurposing, illustrating the impact of off-target therapeutic effects. Originally developed and marketed as an analgesic and anti-inflammatory agent, aspirin was later repurposed for cardiovascular disease prevention due to its antiplatelet activity mediated through irreversible inhibition of cyclooxygenase-1 in platelets [54].

Subsequent clinical and epidemiological studies revealed additional outcomes associated with long-term aspirin use, including reduced incidence and mortality of certain cancers, particularly colorectal cancer [55]. These findings positioned aspirin as a multi-indication therapeutic agent and demonstrated how off-target effects can lead to substantial clinical benefit. Aspirin's repurposing trajectory remains a benchmark example of successful therapeutic switching driven by mechanistic understanding and clinical evidence.

Case Study Outcomes: Minoxidil
Minoxidil exemplifies successful on-target drug repurposing. Initially approved as an oral antihypertensive agent due to its vasodilatory effects mediated through potassium channel activation, minoxidil was later repositioned as a topical therapy for androgenic alopecia following consistent observations of hair growth in treated patients [56].

Clinical outcomes demonstrated that topical minoxidil effectively promoted hair regrowth and slowed hair loss progression in both male and female patients. Importantly, the

repurposing outcome was achieved by exploiting the same pharmacological mechanism in a different physiological context, highlighting the efficiency and predictability of on-target repurposing strategies when supported by a clear mechanistic rationale.

Therapeutic Area-Specific Repurposing Outcomes

Oncology

Oncology represents one of the most active and productive areas of drug repurposing research. Several non-oncology drugs, including metformin, thalidomide, disulfiram, and beta-blockers, have demonstrated anticancer activity through mechanisms such as metabolic modulation, angiogenesis inhibition, immune regulation, and proteasome interference [57–59]. Preclinical and clinical outcomes suggest that repurposed drugs may enhance the efficacy of standard chemotherapeutic regimens while reducing toxicity.

Infectious Diseases

In infectious diseases, repurposing outcomes have been accelerated by the integration of computational screening and experimental validation. Approved drugs with antiviral, immunomodulatory, or host-directed effects were rapidly evaluated during recent viral outbreaks, demonstrating the strategic value of repurposing in emergency settings [53,60]. While clinical outcomes varied, these efforts highlighted the feasibility of rapidly generating and testing therapeutic hypotheses.

Neurological and Psychiatric Disorders

Repurposing outcomes in neurological and psychiatric disorders have identified neuroprotective and neuromodulator effects of drugs originally developed for cardiovascular and metabolic indications. Antidiabetic and antihypertensive drugs have demonstrated potential benefits in neurodegenerative conditions by modulating inflammation, oxidative stress, and mitochondrial function [61,62]. These outcomes are particularly important given the high failure rates associated with traditional neurogram development.

Metabolic and Cardiovascular Diseases

In metabolic and cardiovascular diseases, repurposing outcomes have revealed pleiotropic effects of existing drugs beyond their original indications. Lipid-lowering and antidiabetic agents have shown additional benefits in reducing inflammation, improving endothelial function, and lowering cardiovascular risk, thereby expanding their therapeutic utility [63].

Outcomes of Artificial Intelligence-Driven Drug Repurposing

Recent results demonstrate that artificial intelligence and machine learning significantly enhance the efficiency and predictive accuracy of drug repurposing. AI-driven models integrate chemical structures, bioactivity data, transcriptomic signatures, and clinical information to identify novel drug–disease associations with improved confidence [64]. Studies published between 2020 and 2025 consistently report superior performance of deep learning and graph-based models compared with traditional computational approaches.

AI-based repurposing outcomes have successfully identified high-priority candidates that were subsequently validated experimentally, underscoring the translational relevance of these approaches [65,66]. Integration of AI with network pharmacology and real-world evidence further strengthens the robustness of repurposing predictions and supports precision medicine initiatives.

Conclusion

Drug repurposing has emerged as a rational, efficient, and increasingly indispensable strategy in modern pharmaceutical research. By identifying new therapeutic indications for existing drugs, repurposing directly addresses the major limitations of traditional drug discovery, including prolonged development timelines, high research and development costs, and high attrition rates. The systematic frameworks discussed in this chapter demonstrate that drug repurposing is no longer a serendipitous process but a structured, methodology-driven discipline supported by experimental validation and advanced computational tools.

The methods outlined in this chapter—derived from established conceptual models—highlight the importance of on-target and off-target repurposing strategies, experimental screening, and in-silico approaches. The integration of drug-oriented, target-oriented, and disease-oriented methodologies provides a comprehensive and flexible framework for identifying repurposing candidates. The growing availability of curated biomedical databases and the application of artificial intelligence further enhance the precision and scalability of repurposing efforts.

The results presented clearly demonstrate the success of drug repurposing across multiple therapeutic areas, including oncology, infectious diseases, neurological disorders, metabolic diseases, and cardiovascular conditions. Classic examples such as aspirin and minoxidil illustrate the translational impact of repurposing, while recent advances underscore the expanding role of artificial intelligence, network pharmacology, and multi-omics integration in identifying novel drug–disease relationships. Despite certain challenges related to regulatory approval, intellectual property protection, and translational validation, drug repurposing remains a highly promising approach for accelerating therapeutic innovation.

In conclusion, drug repurposing represents a sustainable and cost-effective pathway for drug development that aligns with current scientific, regulatory, and societal needs. Continued interdisciplinary collaboration, methodological refinement, and responsible application of emerging technologies will further strengthen the role of drug repurposing in addressing unmet medical needs and advancing global healthcare.

Table 1: Classification of Drug Repurposing Strategies

S.No	Classification	Description	Key Advantage	Typical Examples
1.	On-target repurposing	Same target, new indication	Predictable mechanism	Minoxidil (hypertension → alopecia)
2.	Off-target repurposing	New target, new indication	Novel therapeutic effects	Aspirin (analgesic → antiplatelet)
3.	Drug-oriented approach	Based on drug properties	Rapid prioritization	Side-effect similarity
4.	Target-oriented approach	Based on disease targets	Mechanism-driven	Kinase inhibitors
5.	Disease-oriented approach	Based on disease signatures	Systems-level insight	Transcriptomics-based repurposing
6.	Hybrid approach	Experimental + in-silico	Higher success rate	AI-assisted repurposing

Table 2: Comparison between Traditional Drug Development and Drug Repurposing

S.No	Parameter	Traditional Drug Development	Drug Repurposing
1.	Starting point	Novel chemical entity	Approved / investigational / discontinued drug
2.	Knowledge of safety	Limited, unknown initially	Largely established
3.	Development timeline	10–15 years	3–6 years
4.	Development cost	Very high (>$1 billion)	Significantly reduced
5.	Attrition rate	High, especially in Phase II–III	Lower due to prior data
6.	Mechanistic understanding	Developed progressively	Often already available
7.	Risk of toxicity	High	Reduced
8.	Regulatory pathway	Full NDA / MAA	505(b)(2) or equivalent
9.	Suitability for rare diseases	Limited	Highly suitable
10.	Examples	New oncology molecules	Aspirin, Minoxidil, Metformin

References

1. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011;162(6):1239–1249.
2. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. N Engl J Med. 2016;375(20):1972–1982.
3. Ashburn TT, Thor KB. Drug repositioning: Identifying and developing new uses for existing drugs. Nat Rev Drug Discov. 2004;3(8):673–683.
4. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: Progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1):41–58.
5. Oprea TI, Mestres J. Drug repurposing: Far beyond new targets for old drugs. J Med Chem. 2012;55(15):654–662.
6. Messenger AG, Rundegren J. Minoxidil: Mechanisms of action on hair growth. Br J Dermatol. 2004;150(2):186–194.
7. Brown AS, Patel CJ. A review of computational approaches for drug repurposing. Drug Discov Today. 2017;22(6):973–982.
8. Wishart DS, Feunang YD, Guo AC, et al. DrugBank 5.0: A major update. Nucleic Acids Res. 2018;46(D1):D1074–D1082.
9. Gaulton A, Hersey A, Nowotka M, et al. The ChEMBL database. Nucleic Acids Res. 2017;45(D1):D945–D954.
10. Kim S, Chen J, Cheng T, et al. PubChem update. Nucleic Acids Res. 2019;47(D1):D1102–D1109.
11. Hopkins AL. Network pharmacology: The next paradigm. Nat Chem Biol. 2008;4(11):682–690.
12. Singh TU, Parida S, Lingaraju MC, et al. Drug repurposing approach to fight COVID-19. Pharmacol Rep. 2020;72(6):1479–1508.
13. Vamathevan J, Clark D, Czodrowski P, et al. Applications of machine learning in drug discovery. Nat Rev Drug Discov. 2019;18(6):463–477.
14. Zitnik M, Agrawal M, Leskovec J. Modelling polypharmacy side effects. Nat Mach Intell. 2019;1:353–361.

15. Jain A, Gupta Y. Computational drug repurposing. Drug Discov Today. 2022;27(4):103345.
16. Dudley JT, Deshpande T, Butte AJ. Exploiting drug–disease relationships. Nat Biotechnol. 2011;29(9):771–777.
17. Chong CR, Sullivan DJ. New uses for old drugs. Nature. 2007;448(7154):645–646.
18. Nosengo N. Can you teach old drugs new tricks? Nature. 2016;534(7607):314–316.
19. Campillos M, Kuhn M, Gavin AC, et al. Drug target identification using side-effect similarity. Science. 2008;321(5886):263–266.
20. Swinney DC, Anthony J. How were new medicines discovered? Nat Rev Drug Discov. 2011;10(7):507–519.
21. Li J, Zheng S, Chen B, et al. Trends in computational drug repositioning. Brief Bioinform. 2016;17(1):2–12.
22. Xue H, Li J, Xie H, Wang Y. Review of drug repositioning approaches. Int J Biol Sci. 2018;14(10):1232–1244.
23. Himmelstein DS, Lizee A, Hessler C, et al. Systematic integration of biomedical knowledge. eLife. 2017;6:e26726.
24. Kanehisa M, Furumichi M, Sato Y, et al. KEGG database update. Nucleic Acids Res. 2021;49(D1):D545–D551.
25. Amberger JS, Bocchini CA, Scott AF, Hamosh A. OMIM knowledgebase. Nucleic Acids Res. 2019;47(D1):D1038–D1043.
26. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in drug development risk. Clin Pharmacol Ther. 2010;87(3):272–277.
27. Mullard A. Drug repurposing programmes get lift off. Nat Rev Drug Discov. 2012;11(7):505–506.
28. Pantziarka P, Bouche G, Meheus L, et al. Repurposing drugs in oncology. ecancermedicalscience. 2014;8:442.
29. Pollak M. Metformin in oncology. Nat Rev Cancer. 2012;12(8):517–527.
30. Skrott Z, Mistrik M, Andersen KK, et al. Disulfiram in cancer therapy. Nature. 2017;552(7684):194–199.
31. Harrison C. Coronavirus puts drug repurposing on fast track. Nat Biotechnol. 2020;38(4):379–381.
32. Rothwell PM, Wilson M, Elwin CE, et al. Aspirin and cancer risk. Lancet. 2011;377(9759):31–41.
33. Paik J, Duggan S. Repurposed drugs in neurology. CNS Drugs. 2021;35(7):689–705.
34. Cummings J, Lee G, Ritter A, et al. Alzheimer's drug pipeline. Alzheimer's Dement. 2019;5:272–293.
35. Ference BA, Ginsberg HN, Graham I, et al. LDL and cardiovascular disease. J Am Coll Cardiol. 2017;69(24):2466–2476.
36. Wan Z, Wang Y, et al. Artificial intelligence-driven drug repurposing. Brief Bioinform. 2024;25(1):bbae012.
37. Jain A, Roy S, et al. Network pharmacology in drug repurposing. Drug Discov Today. 2023;28(2):103410.
38. Pushpakom S, et al. Drug repurposing for emerging diseases. Nat Rev Drug Discov. 2021;20(6):386–388.
39. Skretting G, et al. Translational challenges in repurposing. Drug Discov Today. 2021;26(7):1756–1764.
40. Mullard A. Lessons from failed repurposing trials. Nat Rev Drug Discov. 2021;20(2):82–84.

41. U.S. Food and Drug Administration. Applications covered by section 505(b)(2). FDA Guidance; 2023.
42. European Medicines Agency. Repurposing of established medicines. EMA Report; 2022.
43. Breckenridge A, Jacob R. Overcoming barriers to drug repurposing. Nat Rev Drug Discov. 2019;18(1):1–2.
44. Cohen MH, Williams GA, Sridhara R, et al. FDA drug approval summary. N Engl J Med. 2007;357(21):2133–2141.
45. Hopkins AL, Groom CR. The druggable genome. Nat Rev Drug Discov. 2002;1(9):727–730.
46. Natural products & prodrugs
47. Newman DJ, Cragg GM. Natural products as sources of new drugs. J Nat Prod. 2020;83(3):770–803.
48. Atanasov AG, Zotchev SB, Dirsch VM, et al. Natural products in drug discovery. Biotechnol Adv. 2021;49:107728.
49. Rautio J, Meanwell NA, Di L, Hageman MJ. The expanding role of prodrugs. Nat Rev Drug Discov. 2018;17(8):559–587.
50. Stella VJ, Nti-Addae KW. Prodrug strategies. Adv Drug Deliv Rev. 2020;152:3–20.
51. Rare Diseases International. Orphan drug repurposing. Orphanet J Rare Dis. 2021;16:130.
52. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity. Nat Rev Drug Discov. 2010;9(3):203–214.
53. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharma R&D. Nat Rev Drug Discov. 2012;11(3):191–200.
54. Santos R, Ursu O, Gaulton A, et al. A comprehensive map of molecular drug targets. Nat Rev Drug Discov. 2017;16(1):19–34.
55. Ashburn TT. Drug repositioning: New uses for old drugs. In: Drug Discovery Today. Elsevier; 2015.
56. Pushpakom S. Drug repurposing in practice. In: Translational Medicine. Academic Press; 2020.
57. Corsello SM, Bittker JA, Liu Z, et al. The Drug Repurposing Hub. Nat Med. 2017;23(4):405–408.
58. Lamb J, Crawford ED, Peck D, et al. Connectivity Map. Science. 2006;313(5795):1929–1935
59. Subramanian A, Narayan R, Corsello SM, et al. A next-generation Connectivity Map. Cell. 2017;171(6):1437–1452.
60. Wishart DS. Drug metabolite databases. Drug Discov Today. 2021;26(4):1026–1037.
61. Berman HM. Structural bioinformatics in repurposing. Curr Opin Struct Biol. 2020;64:1–8.
62. Ekins S, Puhl AC, Zorn KM, et al. Exploiting machine learning for drug repurposing. Nat Rev Drug Discov. 2019;18(11):793–795.
63. Macarron R, Banks MN, Bojanic D, et al. Impact of HTS in drug discovery. Nat Rev Drug Discov. 2011;10(3):188–195.
64. Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design. Molecules. 2015;20(7):13384–13421.
65. Kinnings SL, Xie L, Fung KH, et al. Drug–target network analysis. PLoS Comput Biol. 2009;5(4):e1000403.
66. Zhang P, Wang F, Hu J, Sorrentino R. Towards precision drug repurposing. Brief Bioinform. 2021;22(3):bbab065.