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Review Paper

Review On Drug Repurposing

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ABSTRACT

Drug repurposing, also known as drug repositioning, represents a strategic approach to identify new therapeutic uses for existing pharmacological agents. Unlike traditional de novo drug development, which is often hampered by high costs, extended timelines, and significant attrition rates, repurposing leverages previously approved drugs with well-characterized safety profiles, thereby accelerating the development pipeline. This review offers a comprehensive examination of methodologies employed in drug repurposing, including computational techniques such as signature matching, genetic association, pathway mapping, and machine learning, as well as experimental strategies like binding assays and phenotypic screening. Case studies of successfully repurposed drugs - such as sildenafil, thalidomide, and minoxidil ¬- demonstrate the clinical and commercial potential of this paradigm. The review also addresses critical challenges, including intellectual property limitations, regulatory and economic barriers, and data access constraints. Moreover, it highlights the role of collaborative models, personalized medicine, and systems pharmacology in advancing repurposing initiatives, especially for rare and neglected diseases. Despite its inherent challenges, drug repurposing stands as a promising avenue for expanding therapeutic options and optimizing healthcare outcomes in a cost-effective and timely manner.

INTRODUCTION

In their seminal 2004 publication, Ashburn and Thor delineated the concept of drug repositioning, defining it as the process of identifying novel therapeutic indications for existing pharmacological agents. They posited that this approach also referred to as drug repurposing, reprofiling, redirecting, or repositioning entails the strategic application of pre-existing drugs to treat conditions beyond their original medical indications. This paradigm offers several advantages over traditional de novo drug discovery, including reduced development timelines, lower financial expenditures, and mitigated clinical risks, as repositioned drugs have

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often undergone extensive preclinical and clinical evaluations for their initial indications.The authors highlighted that, despite substantial investments in novel discovery technologies such as high-throughput screening and genomics, pharmaceutical companies have encountered diminishing returns in terms of productivity. In response, the industry has increasingly turned to the existing pharmacopoeia to identify candidates for repositioning, leading to a growing number of successful repositioning endeavors. (1)

The conventional trajectory for obtaining approval for a novel pharmaceutical agent is characterized by substantial financial investment and protracted timelines, typically spanning 10 to 15 years. This extended development period has prompted the exploration of drug repurposing (also termed drug repositioning) as a strategic alternative to expedite the availability of therapeutic options. (2)

Drug repurposing involves the identification of new therapeutic indications for existing pharmacological agents that have already received regulatory approval from agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare Products Regulatory Agency (MHRA) This approach leverages the pre-existing safety and pharmacokinetic data associated with these agents, thereby potentially reducing the duration and cost of the development process.The adoption of drug repurposing strategies is increasingly prevalent among pharmaceutical companies aiming to revitalize previously unsuccessful pipeline candidates or to extend the therapeutic applications of approved drugs. By circumventing early-phase clinical trials and utilizing existing clinical and toxicological data, repurposing can significantly diminish the time required to bring a new indication to market. This review endeavors to provide an overview of the methodologies currently employed in drug repurposing, including computational approaches, high-throughput screening, and experimental strategies. Additionally, it discusses illustrative case studies that underscore the efficacy and utility of drug repurposing, highlighting instances where the availability of comprehensive clinical and toxicological data has led to a substantial reduction in development timelines. (2)

In summary, drug repurposing presents a promising avenue to accelerate the availability of novel therapeutic interventions, offering a pragmatic solution to the challenges inherent in traditional drug discovery processes. (2)

Table 1: Selected successful drug repurposing examples and the repurposing approach employed (3)

Drug Name	Original Indication	New Indication	Date of Approval	Repurposing Approach Employed	Comments on Outcome of Repurposing
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	Zidovudine was the first anti-HIV drug to gain FDA approval, significantly contributing to antiviral therapy.
Minoxidil	Hypertension	Hair loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Minoxidil was repurposed for hair loss, with global sales reaching US$860 million in 2016.

Sildenafil	Angina	Erectile dysfunction	1998	Retrospective clinical analysis	Marketed as Viagra, sildenafil became the leading product in the erectile dysfunction market, with sales of $2.05 billion in 2012.
Thalidomide	Morning sickness	Erythema nodosumleprosum and multiple myeloma	1998, 2006	Off-label usage and pharmacological analysis	Thalidomide derivatives have achieved clinical and commercial success in treating multiple myeloma.
Celecoxib	Pain and inflammation	Familial adenomatous polyposis	2000	Pharmacological analysis	Celebrex (Celecoxib) generated $2.69 billion in revenue by 2014.
Atomoxetine	Parkinson's disease	ADHD	2002	Pharmacological analysis	Strattera (Atomoxetine) generated $855 million in sales in 2016.
Duloxetine	Depression	Stress urinary incontinence (SUI)	2004	Pharmacological analysis	Approved by the EMA for SUI, but withdrawn in the U.S.; approved for depression and chronic pain in the U.S.
Rituximab	Various cancers	Rheumatoid arthritis	2006	Retrospective clinical analysis (remission of rheumatoid arthritis in lymphoma patients treated with rituximab)	Rituximab's sales surpassed $7 billion in 2015, with broad clinical use.
Raloxifene	Osteoporosis	Breast cancer	2007	Retrospective clinical analysis	Approved by the FDA for invasive breast cancer treatment, with $237 million in global sales in 2015.
Fingolimod	Transplant rejection	Multiple sclerosis (MS)	2010	Pharmacological and structural analysis	The first oral disease-modifying therapy for MS, with sales of $3.1 billion in 2017.
Dapoxetine	Analgesia and depression	Premature ejaculation	2012	Pharmacological analysis	Approved in the UK and European countries, with projected peak sales of $750 million.
Topiramate	Epilepsy	Obesity	2012	Pharmacological analysis	Marketed as Qsymia (in combination with phentermine) for obesity treatment.
Ketoconazole	Fungal infections	Cushing's syndrome	2014	Pharmacological analysis	Approved by the EMA for Cushing's syndrome treatment in adults and adolescents.

Aspirin	Analgesia	Colorectal cancer	2015	Retrospective clinical and pharmacological analysis	Evaluated for preventing cardiovascular disease and colorectal cancer, with recommendations from the U.S. Preventive Services Task Force.

Methodology:

The review will be conducted using the following methodology:

1. **Computational Approaches:** Techniques such as signature matching, structural similarity, and machine learning are used to predict drug-disease associations using gene expression, omics data, and electronic health records.

2. **Genetic and Pathway-Based Methods:** Genome-wide association studies (GWAS) and network analysis help identify druggable targets by mapping disease-associated genes within biological pathways.

3. **Experimental Validation:** Binding assays (e.g., CETSA) and high-throughput phenotypic screens in cell lines or model organisms validate computational predictions and reveal off-target effects.

4. **Clinical Data Mining:** Retrospective analyses of EHRs and pharmacovigilance databases uncover off-label drug uses and support the identification of repurposing candidates.

RESULT AND DISCUSSION

Approaches used for drug repurposing

A drug repurposing strategy typically involves three essential steps before advancing a candidate drug through the development pipeline. The first step is the identification of a suitable candidate molecule for a specific indication, often referred to as hypothesis generation. The second step involves the mechanistic assessment of the drug's effects in preclinical models, while the third step focuses on evaluating its efficacy in Phase II clinical trials, provided there is sufficient safety data from the Phase I studies conducted as part of the original indication. Among these three steps, the identification of the appropriate drug for a given indication with a high degree of confidence is particularly critical. This initial phase is where modern approaches to hypothesis generation prove to be most beneficial. These approaches can be divided into computational and experimental strategies, both of which are increasingly being employed in a complementary manner. Drug repurposing, especially when based on clinical data, falls within the scope of these two broad categories. [3]

Computational approaches:

Computational approaches are predominantly data-driven, relying on the systematic analysis of various data types, such as gene expression, chemical structures, genotypic or proteomic data, and electronic health records (EHRs). This analysis often culminates in the development of hypotheses for drug repurposing. These approaches leverage large datasets to identify potential new applications for existing drugs. Below, the most widely used computational strategies, along with relevant examples of drug repurposing, are explored in detail. [3]

- Signature matching:

Signature matching involves comparing the unique "signature" characteristics of a drug against those of another drug, disease, or clinical phenotype. These drug signatures can be derived from various types of data, including transcriptomic (RNA), proteomic, or metabolomic data, chemical structures, or adverse event profiles. This approach, which allows for both drug-disease and drug-drug comparisons, plays a pivotal role in identifying potential drug repurposing opportunities.

When comparing transcriptomic signatures, the signature of a drug is derived by examining the differential gene expression in biological materials, such as cells or tissues, before and after drug treatment. This expression profile, representing the molecular signature of the drug, is then compared to a disease-associated expression profile obtained through similar differential analysis between disease and healthy conditions. A negative correlation between the gene expression patterns of the drug and the disease — where genes upregulated in the disease are downregulated by the drug and vice versa — can suggest that the drug might impact the disease. This approach is grounded in the signature reversion principle (SRP), which posits that if a drug can reverse the expression pattern of genes that are characteristic of a disease phenotype (i.e., the drug's signature becomes closer to that of a healthy state), the drug may also be capable of reversing the disease phenotype. While the SRP is a relatively simplistic concept, it has shown effectiveness in identifying novel drug repurposing opportunities across various therapeutic areas, including metabolic disorders, and has been successfully applied to uncover drugs that could function as chemo-sensitizers in cancer treatment.

The drug-drug similarity approach aims to identify shared mechanisms of action between drugs that may be structurally or pharmacologically distinct. Known as "guilt by association," this principle suggests that drugs with similar transcriptomic signatures may share therapeutic applications, irrespective of their chemical dissimilarity. This approach has proven particularly useful for identifying off-target effects and discovering alternative targets for existing drugs. Even when drugs share transcriptional signatures linked to secondary modes of action, such as mild correctors of disease phenotypes, this similarity can provide insights into potential repurposing opportunities.

Both drug-disease and drug-drug similarity approaches heavily rely on publicly available gene expression data. One key resource for such analyses is the Connectivity Map (cMap), established by the Broad Institute in 2006. This database includes gene expression profiles from over 1,300 compounds tested across various cell lines, serving as a phenotypic screen for a wide array of compounds. cMap has been successfully employed to make predictions for drug repurposing across various disease conditions. The third installment of cMap data, cMap 3.0, now resides within the NIH Library of Integrated Network-based Cellular Signatures (LINCS) and includes transcriptional signatures from tens of thousands of compounds treated in hundreds of human cell lines. This extensive database, alongside other public repositories like the Gene Expression Omnibus and Array Express, contains gene expression data from numerous human diseases and animal models. These resources can be interrogated using computational tools to identify novel drug-disease connections and drug repositioning opportunities, facilitating the discovery of potential therapeutic applications for existing drugs.

The second type of signature matching in drug repurposing involves comparing chemical structures and their associated biological activities. By identifying chemical similarities between drugs, researchers can predict shared biological effects. For example, Keiser et al. used a similarity ensemble approach (SEA) to predict new drug-target associations, identifying 23 novel relationships. However, this method can be limited by errors in chemical structures or the presence of active drug metabolites with altered structures.

Another approach focuses on adverse effect profiles, hypothesizing that drugs causing similar side effects may target shared proteins or pathways. Bork's group used the Unified Medical Language System (UMLS) to match adverse effect profiles of 746 drugs, identifying both known and new drug-target associations. Similarly, Yang and Agrawal combined adverse effect data with drug-disease relationships to predict repurposing indications for 145 diseases. While this approach is promising, challenges such as difficulties in mining adverse effect data from drug labels and the lack of defined causality assessments may limit its use. However, advances in artificial intelligence, including text mining and natural language processing, could help overcome these challenges. [3]

- Genetic association:

Over the past decade, the number of genome-wide association studies (GWAS) has increased significantly, driven by advancements in genotyping technology, the completion of the Human Genome Project, and reduced genotyping costs. GWAS aim to identify genetic variants linked to common diseases, offering insights into disease biology and helping to identify novel drug targets. Some of these targets could overlap between diseases studied by GWAS and those treated with existing drugs, providing opportunities for drug repurposing. For instance, Sanseau and colleagues found that genes associated with disease traits were more likely to code for "druggable" proteins, with the GWAS gene set being 2.7 times more enriched in pharmaceutical industry targets. They also identified 92 genes associated with traits different from their original drug indications, suggesting potential for repurposing.

A study by Grover and colleagues used bioinformatics to match coronary artery disease gene targets with drugs listed in various databases, revealing potential repurposing opportunities. However, challenges remain in using GWAS data for drug repurposing. For example, strong linkage disequilibrium in gene-rich loci can complicate the identification of causal genes or variants. Additionally, GWAS do not indicate the direction of effect of genetic variants, requiring functional studies to determine whether an activator or suppressor is needed. Given the lack of detailed pathophysiological information in GWAS data, careful interpretation is necessary when predicting repurposing targets. Furthermore, the human genome is still being studied, with new genes likely to be discovered in the future. [3]

- Pathway or network mapping:

Pathway-based or network-based approaches have become widely employed to identify drugs or drug targets with potential for repurposing. Although some targets identified by GWAS or other methods may be amenable to drug development, many genes may not be ideal druggable targets. In such cases, pathway-based strategies can help identify genes either upstream or downstream of the GWAS-associated target, potentially offering new repurposing opportunities. Network analysis involves constructing drug or disease networks based on gene expression patterns, disease pathology, protein interactions, or GWAS data,

which aids in the identification of repurposing candidates. Some signature matching studies also incorporate network analysis techniques.

A recent study by Greene et al. combined genetic variant data from GWAS with tissue-specific functional interaction networks, using a technique known as network-wide association study (NetWAS). This approach more accurately identified disease-gene associations compared to GWAS alone. When applied to hypertension and cross-referenced with drug-target data from DrugBank, they found that anti-hypertensive drug targets were more highly enriched among the top genes from NetWAS than from GWAS. Additionally, pathway analysis of gene expression data from studies on respiratory viral infections identified 67 common biological pathways potentially important in these infections. By comparing these pathways with the DrugBank database, several drugs, such as pranlukast and amrinone, were identified as potential candidates for treating viral infections due to their effects on the immune response. [3]

- Retrospective clinical analysis: use of electronic health records:

A notable example of retrospective clinical analysis leading to drug repurposing is sildenafil. Other repurposing opportunities have been identified through clinical and pharmacological analyses, such as aspirin for colorectal cancer prevention, raloxifene for breast cancer risk reduction, and propranolol for osteoporosis. However, these examples did not stem from systematic clinical data analysis, which is now increasingly recommended for identifying drug repurposing opportunities.

Retrospective clinical data can be sourced from electronic health records (EHRs), post-marketing surveillance, and clinical trials. EHRs contain both structured data (e.g., diagnostic results, lab tests, drug prescriptions) and unstructured data (e.g., clinical descriptions, imaging). This rich data can be leveraged for drug repurposing by identifying new signals, with the added benefit of high statistical power. Paik and colleagues, for example, analyzed over 13 years of EHR data from a tertiary hospital and identified terbutaline sulfate, an asthma treatment, as a potential candidate for amyotrophic lateral sclerosis (ALS).

Other valuable data sources include the UK Clinical Practice Research Datalink (CPRD), the FDA Adverse Event Reporting System (FAERS), and the WHO VigiBase, which offer insights into patient, disease, and drug information. However, accessing and utilizing EHR data presents challenges, including ethical and legal barriers, and difficulties in extracting unstructured data. Improving research capabilities within EHR databases, along with advancements in natural language processing and machine learning, could enhance their utility for drug repurposing.

Post-marketing surveillance and clinical trial data are also critical resources, although access is often restricted. Nevertheless, there is growing recognition of the value of making this data more accessible for research. For example, the European Medicines Agency (EMA) began publicly sharing clinical trial data in 2016, allowing researchers to independently reanalyze it, potentially uncovering drug repurposing opportunities. [3]

- Novel sources of data for drug repurposing:

Immortalized human cancer cell lines (CCLs) have been widely utilized in high-throughput drug screens to assess their effects on cell viability. Many of these studies pair pharmacological data from these screens with comprehensive genomic characterization of the CCLs, enabling the identification of pharmacogenomic interactions.

These paired data sets, which include both drug response and molecular features, offer a promising resource for discovering drug repurposing opportunities. While CCLs have limitations, such as molecular alterations for in vitro growth and bias toward certain subtypes, studies have shown that pharmacogenomic interactions identified in these cell lines can closely mirror therapeutic markers used in clinical practice.

More recently, these CCL studies have been integrated with genomic data from primary tumor cohorts, allowing for the prioritization of pharmacogenomic interactions based on the clinical prevalence of specific genomic alterations. Remarkably, many newly identified pharmacogenomic interactions were specific to certain cancer types and involved drugs already approved for other diseases or cancer types. Such studies hold significant potential for drug repurposing and can enhance personalized cancer therapy by identifying patients with specific genomic alterations who could benefit from existing treatments. Additionally, large DNA biobanks linked to electronic health records (EHRs), such as the UK Biobank and China Kadoorie Biobank, offer another frontier for accelerating drug repurposing. For example, GlaxoSmithKline used the China Kadoorie Biobank to explore the role of PLA2G7 gene variants in vascular disease, confirming the lack of efficacy of darapladib in coronary heart disease. This approach, although used to confirm negative findings, could also be applied to validate gene targets for drug repurposing, offering a valuable tool for assessing potential drug targets through biobank resources. [3]

- Machine learning (ML)-based:

Computational drug repurposing often relies on machine learning (ML) to analyze vast biological datasets, including omics data, chemical structures, molecular docking studies, and past clinical data from viruses like SARS-CoV and MERS-CoV. In the context of COVID-19, ML techniques—especially deep learning and neural networks—have been used to identify potential treatments.

For instance, the MT-DTI deep learning model predicted that atazanavir could inhibit the SARS-CoV-2 3C-like proteinase. Another method, CoV-KGE, combined network-based and deep learning approaches to identify 41 repurposable drugs, some validated by clinical trial data. Other tools, like virtual screening and supervised ML, revealed promising drugs such as IDX-184, an anti-HCV compound.Graph neural networks (GNNs) are also being used to model biomedical entities (like drugs and proteins) and their interactions. One GNN-based workflow prioritized 22 drugs and several combinations for COVID-19 treatment.

However, ML-based repurposing has limitations. Reliable predictions require diverse and high-quality datasets, which are currently inconsistent due to COVID-19's recent emergence and rapid evolution. To improve accuracy and usefulness, future ML approaches must be flexible, data-rich, and built on standardized patient information that can adapt to future outbreaks. [4]

- Artificial intelligence-based:

In the era of big data, AI-based drug repurposing gained global attention during the COVID-19 pandemic due to its powerful ability to process vast infectious disease and public health data. With AI models like deep learning and graph-based learning, researchers have used millions of patient records and clinical trial data to uncover potential drug candidates.

Initiatives like the CLAIRE Innovation Network emerged, supporting global AI-based repurposing

efforts. Tools like BenevolentAI's knowledge graph identified baricitinib for COVID-19, while another AI platform predicted over 80 candidates, with some showing antiviral effects in lab tests. AI also complements molecular docking to speed up screening efforts. Despite promising results, challenges persist especially the lack of data early in the pandemic and the tendency of AI tools to rely on a single data type, which may lead to incomplete predictions. To address this, more advanced tools like the Multimodal Restricted Boltzmann Machine (MM-RBM) are being explored to integrate diverse data types, improving the accuracy and confidence in drug repurposing efforts. [4]

Experimental approaches:

- Binding assays to identify target interactions:

Proteomic techniques, like affinity chromatography and mass spectrometry, are increasingly used to identify the targets and off-targets of drugs an essential part of modern chemical biology and drug repurposing efforts. For instance, the**Cellular Thermal Shift Assay (CETSA)** helps determine drug-target interactions by measuring the thermal stabilization of proteins upon drug binding. CETSA has confirmed targets for drugs like crizotinib and revealed off-targets like NQO2 for acetaminophen.

The promiscuity of **protein kinase inhibitors (PKIs)** is well-known, and since kinases are projected to be key drug targets of the 21st century, there's growing emphasis on better preclinical probes. These tools, along with **unbiased affinity-based techniques**, are invaluable for mapping compound effects especially when unexpected phenomena, like paradoxical kinase activation, contribute to off-target effects or adverse outcomes.An example is the use of **gefinitib-bound affinity matrices** to identify over 20 potential kinase targets in HeLa cell lysates. Similarly, **kinobeads**have expanded the profiling of PKIs, uncovering off-targets for well-established drugs. This strategy has proven especially insightful for multi-target drugs like **ponatinib,** and specific inhibitors like **imatinib**, which was successfully repurposed for gastrointestinal stromal tumors driven by KIT mutations.

Chemical genetics is deepening our understanding of binding efficacy within cellular contexts, helping to redirect drugs to new indications or manage drug resistance. High-throughput kinase binding studies like Karaman et al.'s evaluation of 38 inhibitors across 317 kinases revealed thousands of interactions. Notably, drugs like **sorafenib**and **dasatinib** often bind more tightly to secondary targets than their primary ones, offering clues for potential repurposing or warning signs for inappropriate use. Moreover, non-kinase targets of kinase inhibitors are emerging as novel repurposing opportunities not only for **cancer**, but also for diseases like **Zika**or**antibiotic-resistantinfections**showing just how versatile and powerful these profiling methods can be in the search for new therapeutic strategies. [3]

- Phenotypic screening:

Phenotypic screening plays a critical role in drug repurposing by enabling the discovery of compounds with disease-relevant effects without prior knowledge of their molecular targets. This approach is especially powerful when screening libraries of approved or investigationaldrugs, as it can quickly identify repurposing candidates that are already well-characterized and potentially ready for clinical evaluation.

In in vitro phenotypic screens, cell-based assays are commonly used, often in 96-well formats, allowing for high-throughput testing. A good

example is the study by Iljin et al., who screened 4,910 small-molecule compounds across prostate cancer and non-malignant prostate epithelial cell lines. They found that disulfiram, traditionally used to treat alcohol dependency, exhibited selective antineoplastic activity. This effect was further validated through genome-wide gene expression analysis, highlighting its potential as a repurposed cancer therapy.Beyond cell-based assays, whole-organism models like zebrafish are also employed for phenotypic drug screening. For instance, Cousin et al. used a zebrafish model to evaluate 39 FDA-approved drugs for potential in treating tobacco dependence. The study identified compounds such as apomorphine and topiramate that altered behavior induced by nicotine and ethanol, offering insights into potential repurposing opportunities for neuropsychiatric or substance use disorders. These phenotypic approaches are particularly valuable because they account for complex biological responses, including off-target effects and systems-level interactions, often missed by target-based screens. This makes them a potent strategy in identifying unexpected yet effective uses for existing drugs. [3]

Drug repurposing challenges:

Drug repurposing offers a strategic advantage in expediting therapeutic development due to its higher success rates, reduced costs, and faster approval timelines. However, it is not without limitations. Despite bypassing phase I trials, safety concerns remain, as drugs proven safe for one indication may not exhibit the same profile in new patient populations or dosing regimens. In some cases, higher doses required for new uses can increase risks and reduce efficacy. Combination therapies targeting different biological pathways have been suggested to overcome these challenges, though drug-drug interactions remain a significant hurdle.

Intellectual property barriers also complicate repurposing efforts. While off-patent drugs can be patented for new uses, market exclusivity is difficult to enforce, especially when generics can be prescribed off-label. Innovative formulations may help address this, and licensing can allow repurposing of still-patented drugs. Nonetheless, prior publications may hinder new patent claims, underscoring the need for novel supporting evidence. Issues such as misuse, drug shortages, and inflated pricing further highlight the importance of careful oversight. Ultimately, addressing these challenges through collaborative strategies can enhance drug repurposing as a viable path for developing effective, broad-spectrum antivirals. [5]

- Regulatory and patent considerations:

In many clinical settings, physicians are legally permitted to prescribe drugs off-label if they believe the medication may benefit a patient, despite a lack of regulatory approval for that specific use. Regulatory agencies often disapprove of such practices due to insufficient evidence on efficacy and safety for the new indication. Biopharmaceutical companies interested in drug repurposing must make significant investments in research and clinical trials and seek patent protection to ensure commercial viability. Under the NIH's National Center for Advancing Translational Sciences (NCATS) initiative, repurposed drugs are categorized based on their patent status and prior approval history. When a drug retains patent protection, only the patent holder or licensed parties can pursue development; for off-patent drugs, a new, non-obvious use must be identified to qualify for patenting.

However, challenges arise when potential new uses are already known or documented, limiting the ability to secure enforceable patents. Even if a new-use patent is granted, enforcement can be

problematic, particularly when the drug is already in widespread off-label use. Practices like skinny labelling—where generic manufacturers exclude the new indication from labeling to avoid infringement—further undermine patent protection. These issues, coupled with limited financial incentives, often discourage major pharmaceutical companies from pursuing repurposing efforts.Moreover, the high cost of clinical trials poses a barrier, especially for smaller biotech firms, academic institutions, and nonprofit organizations. This challenge is particularly pronounced for rare diseases, where traditional trials may be unfeasible despite repurposing's potential benefits. Consequently, advancing repurposed drugs through regulatory pathways remains a complex and often under-prioritized endeavor. [4]

- Intellectual property and economic considerations:

The landscape of drug repurposing is shaped by complex legal and regulatory challenges that can limit intellectual property protection and reduce economic incentives. Variations in national patent laws often restrict patents for second medical uses, and prior knowledge of off-label applications can undermine novelty, a key requirement for patent eligibility. While patents for new uses of off-patent drugs are possible, enforcement is weak, especially when using previously marketed doses or formulations. Ideal scenarios involve novel regimens or compositions. Creating new derivatives, however, deviates from the core concept of repurposing. Market exclusivity—up to 11 years in the EU and 8 years in the US—may still fall short of ensuring sufficient return on investment, raising concerns about the commercial feasibility of repurposing strategies. [6]

- Data and compound availability:

While the open-source model is gaining traction in drug discovery, major barriers to data access and interoperability remain especially for high-value datasets like clinical trial results. Even when access is granted, unstructured data such as medical imaging pose analytical challenges due to a lack of standardization. Integrating diverse datasets adds computational complexity, further hindering progress.Shelved drug compounds often abandoned in earlier development represent untapped potential but are rarely shared by pharmaceutical companies, particularly when repurposing lies outside their strategic focus. Even when firms are willing to collaborate with biotech or academic partners, operational barriers like complex material transfer agreements and distribution logistics slow progress. Additionally, sourcing generic active ingredients can be difficult when compounds are no longer manufactured, posing another obstacle to repurposing efforts. [6]

Drug repurposing opportunities:

- Rare and neglected conditions:

Drug repurposing presents a particularly compelling strategy for addressing rare and neglected diseases, where traditional drug development is economically unviable. This economic disincentive has led to a dominant role for academic institutions and nonprofit organizations in the discovery and development of therapeutics for these conditions. To support such efforts, various regulatory incentives such as expedited approval pathways, grant funding, tax exemptions, and fee waivers—have been implemented. The Drug for Neglected Diseases initiative (DNDi), for instance, has incorporated numerous repurposed drugs into its clinical portfolio, including fexinidazole, fosravuconazole, Ambisome™, and miltefosine. Notably, fexinidazole became the first oral treatment approved in decades for advanced-stage

sleeping sickness, with development costs totaling only USD 62.5 million—significantly lower than the billions typically required for new drug development.

Commercial challenges associated with repurposing, particularly for off-patent drugs, are less problematic in the context of neglected diseases, as these efforts are largely driven by public health goals rather than profitability. In fact, using low-cost, off-patent therapies may be preferable to ensure broader accessibility. In the realm of rare diseases—where the underlying biology is often not well understood—computational methods have enabled rapid hypothesis generation for drug repurposing. Advances in large-scale genomic sequencing further enhance this approach by linking specific genetic variations to disease mechanisms, thereby facilitating the identification of existing drugs that can target those molecular pathways. (6)

- Precision medicine:

Precision medicine is a rapidly advancing field that tailors medical treatment to individual variability in genetics, environment, and lifestyle. It has become increasingly evident that many conditions once seen as singular disorders actually encompass a spectrum of disease subtypes, each potentially requiring unique therapeutic approaches. This paradigm is particularly impactful in oncology, where molecular profiling guides the selection of more effective and safer treatments.

A striking example involves a patient with metastatic colorectal cancer unresponsive to conventional chemotherapy and radiation. Molecular analyses, including immunohistochemistry and comprehensive genomic and transcriptomic sequencing, revealed over 2000 genomic alterations and significant expression of proto-oncogenes *FOS* and *JUN*. These findings indicated the renin–angiotensin system as a therapeutic target, leading to the repurposing of the antihypertensive agent irbesartan as an anticancer treatment. This intervention resulted in a profound and durable clinical response, showcasing how precision medicine can intersect with drug repurposing to uncover novel, personalized treatment strategies. (6)

- Systems medicine:

Systems medicine and network pharmacology offer a holistic framework that bridges traditional paradigms of drug discovery phenotype-driven and target-specific approaches. By applying network analysis and metabolic control theory, these disciplines facilitate the design of multi-target therapies or synergistic drug combinations. A notable example is the nifurtimoxeflornithine combination therapy, endorsed by the World Health Organization for advanced Gambiense sleeping sickness. This combination, involving two repurposed drugs eflornithine (originally developed for cancer) and nifurtimox (initially used for Chagas disease) offers improved administration, reduced treatment duration, and reduced risk of resistance.

While drug repurposing has traditionally focused on single-agent therapies, combinatory approaches vastly expand the therapeutic landscape. Polypharmacy increases complexity but also offers opportunities, particularly when dealing with newly identified compounds of low potency. Synergistic combinations can enhance efficacy and lower required doses, thereby improving safety profiles and boosting the clinical viability of repositioned agents. (6)

- Collaborative models:

There is growing recognition that collaboration between pharmaceutical companies and academic institutions can significantly advance drug repurposing initiatives. While industry partners hold extensive chemical libraries and possess expertise in clinical development and translational research, academic and biotechnology sectors contribute deep insights into emerging disease biology. Such partnerships can enhance innovation and facilitate access to sophisticated screening technologies often unavailable to academia.

Moreover, these collaborations foster capacity building and knowledge exchange. Intellectual property strategies such as patent pooling, open licensing for neglected or rare diseases, and shared patent ownership with academic inventors offer pathways to incentivize participation. Emerging collaborative models incorporating venture capital, public funding, and nonprofit support have the potential to transform therapeutic development in areas like rare diseases, where drug repurposing is particularly impactful. [6]

Barriers to repurposing:

Drug repurposing encounters several significant barriers, including limited financial resources, insufficient expertise, intellectual property (IP) complexities, restricted data access, and concerns over liability risks. These challenges often result in the abandonment of numerous compounds, many of which remain stored in company vaults, with estimates suggesting their number may be in the thousands. Addressing these obstacles requires coordinated efforts to enhance resource allocation, streamline IP negotiations, and improve data transparency, thereby unlocking the potential of existing compounds for new therapeutic applications. [7]

- Financial and resource barriers:

Advancing shelved drug candidates necessitates substantial financial investment and specialized expertise, which many organizations lack. Pharmaceutical research and development are often structured around specific therapeutic areas, making it challenging to recognize the repurposing potential of compounds outside these focuses. Consequently, multi-partner collaborations are frequently essential. Academic researchers may possess the necessary expertise but often lack access to a pool of deprioritized pharmaceutical compounds. Similarly, small biotechnology companies and academic institutions may need to find commercial partners to address resource deficiencies. Moreover, companies often lack sufficient staff dedicated to out-licensing discontinued compounds, leading to their abandonment.

Despite the promise of repurposing as a more cost-effective and time-efficient alternative to de novo development, bringing a repurposed compound to market can still incur substantial costs, ranging from hundreds of millions to billions of dollars. This is due to the necessity of conducting extensive testing to meet regulatory standards for quality, efficacy, and safety. While repurposing can result in significant savings by potentially reducing the time spent on preclinical and early-stage research, the later stages of clinical research can still present high failure rates. Repurposed compounds may still require Phase 2 and 3 clinical trials, which have substantial failure rates for new indications. Even when out-licensing a compound, there can be burdensome "in-kind" costs associated with remanufacturing the active product and placebo, completing study reports and regulatory documentation, pharmacovigilance, monitoring and reporting on patient safety, and coordination. It is challenging to persuade management to allocate resources to compounds

that were initially unsuccessful, especially if the new indication is not a strategic focus. [7]

- Intellectual property barriers:

Intellectual property (IP) considerations represent a significant barrier to drug repurposing. Pharmaceutical companies often patent compounds, even those subsequently abandoned, thereby restricting others from developing these compounds without a license. Additionally, limited remaining patent life for compounds that failed in later development stages can diminish the return on investment (ROI) for repurposing efforts. The ROI threshold varies by company size; larger companies may require a higher ROI than smaller ones, potentially leading to the abandonment of promising repurposing opportunities. Traditional IP protections, such as composition-of-matter (COM) claims, are challenging to obtain for repurposed compounds. To secure a COM patent, patentees must differentiate their claims from existing public domain knowledge and provide data supporting the drug's credibility for the new indication. Moreover, entanglement with core IP can complicate repurposing efforts. Developers often patent multiple compounds in development, protecting not only the final candidate but also semi-finalists, thereby preventing others from developing shelved compounds without access to the relevant patents. Material Transfer Agreements (MTAs) further complicate repurposing initiatives. Negotiations on MTAs often involve contentious issues such as limiting compound use to non-commercial research, limiting company liability, delaying academic publications to protect confidential information, and IP provisions. These IP terms are described as difficult and time-consuming to negotiate, as companies aim to protect their freedom to operate using their own compounds, while universities seek to maintain ownership of inventions, receive consideration, and make compounds available to the public.

In summary, IP-related challenges, including restrictive patenting practices, limited patent life, difficulties in obtaining traditional IP protections, entanglement with core IP, and complex MTAs, pose significant obstacles to drug repurposing efforts. Addressing these issues requires strategic approaches to IP management, fostering collaborations, and developing frameworks that balance innovation incentives with public health objectives. [7]

- Data access barriers:

Accessing shelved drug compounds and their associated trial data constitutes a significant barrier to drug repurposing, as highlighted in the literature. Once a compound's development is abandoned, it is often described as "disappearing," with trial data and results left unpublished. Several factors contribute to this issue, including the difficulty of publishing negative trial results, abrupt trial terminations due to company mergers or acquisitions, and the lack of commercial incentive to publish results from discontinued projects. Additionally, data may be sequestered if considered a "trade secret" or of potential commercial value Gaining knowledge about and access to shelved industry compounds is often challenging and may require an internal company champion for success. Companies may be reluctant to share shelved compounds with other entities for fear they might turn out to be successful, whereas nonprofits and government-funded bodies face less commercial risk. Furthermore, the absence of repositories to transparently register abandoned compounds and companies' reluctance to release compounds to shared resources contribute to their disappearance.

Within organizations, paper records need to be digitized, and often, experts on the compound move on, and teams responsible for regulatory and safety data are disbanded. Additionally, mining large datasets poses logistical challenges, and integrating different types of data in a user-friendly manner is difficult. These factors collectively impede the accessibility of shelved compounds and their trial data, hindering the potential for drug repurposing. [7]

Future Prospects of Drug Repositioning:

- Path to Drug Personalisation:

Human diseases involve complex mechanisms, including genetic mutations, infections, and degenerative processes, with individual variability in cellular pathways. This genetic diversity affects treatment responses, rendering standard therapies ineffective for some due to absent or altered drug targets. Personalized medicine addresses this by tailoring treatments to individual genomic profiles, improving efficacy and reducing toxicity.

Drug repositioning, supported by next-generation sequencing, enhances this approach by identifying existing drugs suited to specific genetic contexts. For example, non-small cell lung cancer (NSCLC), which comprises 85–90% of lung cancers, includes a subset (~7%) with an *EML4–ALK* gene fusion, distinct from typical EGFR mutations. Crizotinib, originally for ALK-positive lymphoma, was repurposed to treat this group. Without biomarker screening, these patients would have received less effective EGFR-targeted drugs. Crizotinib later gained FDA approval for treating NSCLC with MET exon 14 skipping (~3% of cases) and ROS1/ALK-positive anaplastic large-cell lymphoma. These cases demonstrate the importance of biomarker-guided drug repositioning in delivering targeted, effective therapies. [8]

- Challenges of Drug Repositioning:

Despite its advantages, drug repositioning faces challenges. Patent barriers, particularly "composition of matter" (COM) protections, limit new claims for existing compounds. For example, Zalicus and Sanofi Aventis repositioned Prednisporin by combining prednisolone acetate and cyclosporine A to treat allergic conjunctivitis, navigating around existing patents.

Major pharmaceutical companies often hesitate to invest due to high costs, risk of failure, and limited returns. Many repositioning successes come from secondary players; notably, Celgene repurposed Thalidomide—previously withdrawn due to birth defects—for multiple myeloma and erythema nodosum leprosum, not its original maker, Grünenthal. Repositioning efforts also struggle with funding and expertise, especially for rare diseases. Out-licensing to smaller biotech firms offers a path forward but remains limited. Support like NIH-funded trials in the U.S. is not widely available in Europe or Asia, compounding funding difficulties, especially for drugs previously rejected. Not all efforts succeed. Bevacizumab, a kinase inhibitor, failed in phase III trials for gastric cancer despite promising data. Challenges also include poor data integration, limited reporting in rare diseases, and failure to advance beyond in vitro studies.

Overall, issues with patents, funding, data, and uptake limit repositioning's potential. However, stronger collaboration and improved computational tools offer promising solutions. [8]

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REFERENCES

1. Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, Schutjens MH. Drug repositioning and repurposing: terminology and definitions in literature. Drug discovery today. 2015 Aug 1;20(8):1027-34.
2. Parvathaneni V, Kulkarni NS, Muth A, Gupta V. Drug repurposing: a promising tool to accelerate the drug discovery process. Drug discovery today. 2019 Oct 1;24(10):2076-85.
3. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A. Drug repurposing: progress, challenges and recommendations. Nature reviews Drug discovery. 2019 Jan;18(1):41-58.
4. Ng YL, Salim CK, Chu JJ. Drug repurposing for COVID-19: Approaches, challenges and promising candidates. Pharmacology & therapeutics. 2021 Dec 1;228:107930.
5. Li X, Peng T. Strategy, progress, and challenges of drug repurposing for efficient antiviral discovery. Frontiers in Pharmacology. 2021 May 4;12:660710.
6. Talevi A, Bellera CL. Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics. Expert Opinion on Drug Discovery. 2020 Apr 2;15(4):397-401.
7. Krishnamurthy N, Grimshaw AA, Axson SA, Choe SH, Miller JE. Drug repurposing: a systematic review on root causes, barriers and facilitators. BMC health services research. 2022 Jul 29;22(1):970.
8. Low ZY, Farouk IA, Lal SK. Drug repositioning: New approaches and future prospects for life-debilitating diseases and the COVID-19 pandemic outbreak. Viruses. 2020 Sep 22;12(9):1058.
9. Cavalla D. Future Perspectives in Drug Repurposing.
10. Chiang, A. P. & Butte, A. J. Systematic evaluation of drug-disease relationships to identify leads for novel drug uses. Clin. Pharmacol. Ther. 86, 507–510 (2009).
11. Iorio, F., Isacchi, A., di Bernardo, D. & Brunetti-Pierri, N. Identification of small molecules enhancing autophagic function from drug network analysis. Autophagy 6, 1204–1205 (2010).
12. Hegde, R. N. et al. Unravelling druggable signalling networks that control F508del-CFTR proteostasis. eLife 4, e10365 (2015).
13. Iorio, F. et al. A semi-supervised approach for refining transcriptional signatures of drug response and repositioning predictions. PLOS ONE 10, e0139446 (2015).

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