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The Drug Reboot: Finding New Life in Old Formulations

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Abstract: Drug repurposing, also known as drug repositioning, is a strategic approach aimed at discovering new therapeutic uses for existing drugs, whether they are currently on the market or have been withdrawn. This method effectively identifies and develops pharmaceutical compounds with new pharmacological or therapeutic activities. In recent years, many major pharmaceutical companies have adopted drug repositioning strategies within their research and development programs to explore new indications by targeting novel biological mechanisms. This approach can save time and costs while maintaining high effectiveness and reducing the risk of failure. By maximizing the therapeutic value of existing drugs, it enhances the likelihood of success. Repositioning drugs offers a valuable alternative to traditional drug discovery, which is often expensive, labor-intensive, and time-consuming. Drug repurposing builds on the established safety profiles of existing compounds, employing a combination of computational methods (in silico) and experimental techniques to uncover new applications. This emerging methodology aims to redirect medications that have already been safely tested in humans to address rare, hard-to-treat disorders and neglected diseases. Overall, drug repurposing represents a promising avenue for maximizing the potential of existing therapies and addressing unmet medical needs.

Keywords: drug repositioning; *in silico*-based method; activity-based method; patent concerns; organizational hurdles; real-world data (RWD).

1. Introduction

In addition to drug repurposing, other names for this practice include drug reprofiling, repositioning, rescue, and recycling. Drug repositioning may define the technique of identifying novel therapeutic applications for drugs, whether drugs that were initially unsuccessful, experimental, commercially available, FDA-approved, or pro-drugs. This process involves repurposing these compounds to address conditions other than their intended uses. It also identifies new therapeutic uses for drugs that have been previously approved, discontinued, abandoned, or explored experimentally [1-4]. Conventional drug development is known for its high costs, risks, time-consuming nature, and labor-intensive process. By reducing the extended development time, higher failure rate, and high financial cost associated with standard drug discovery programs, the revolutionary drug repositioning strategy may be used instead. Besides saving an average of 5 to 7 years in the drug formulation period, it also reduces the chances of failure, estimated to be as high as 45%, solely because of safety or harmfulness problems for most conventional drug research programs [5,6]. Drug repositioning has certainly been extremely successful over these past years. Today, roughly one-third of newly approved treatments are repositioned drugs, accounting for approximately 25% of

annual revenues in pharmaceuticals [7]. Repurposed pharmaceuticals account for approximately 30% of FDA-approved medications and biologics (including vaccines) in the United States. Pharmaceutical companies predicted that the market for repurposed drugs would reach $24.4 billion in 2015 and $31.3 billion in 2020, correspondingly. The initial discovery of repositioning drugs is a coincidental finding or observation that is believed to be traced back to the 1920s. Following almost a hundred years of research and progress, additional methods are devised to expedite the drug repositioning process. Notable and effective medications resulting from this method include methotrexate, aspirin, valproic acid, minoxidil, and sildenafil. For example, sildenafil, initially developed for treating angina pectoris and hypertension, is now widely used for erectile dysfunction [8].

2. Significance of Drug Repurposing

Despite specifically identifying the mechanism of action, repurposing can help discover novel drugs based on their phenotypic advantages. Preclinical animal models can be used to evaluate this directly, and research and clinical applications can benefit more from these findings. It might move right forward to phase II clinical trials. Repurposed medications carry a little risk of failure [9]. Table 1 represents the differentiation between drug repurposing and traditional drug discovery [10-15].

Table 1. Primary differences between traditional drug discovery and drug repurposing.

Aspect	Traditional Drug Discovery	Drug Repurposing
Stages	1. Discovery and Preclinical Studies 2. Safety Evaluation 3. Clinical Testing 4. FDA Review Process 5. Post-Market Safety Surveillance	1. Identifying Existing Compounds 2. Acquiring the Compounds 3. Development and Testing 4. FDA Post-Market Monitoring
Investment	Requires a high level of investment	Requires significantly less investment compared to traditional methods
Timeframe	Usually takes a longer period	Typically, a quicker process
Risk of Failure	Higher probability of failure	Lower chance of failure
Efficacy and Safety Profiles	The drug's efficacy and safety need thorough evaluation	Efficacy and safety profiles are generally already established

Compared with standard discovery, repurposing drugs offers substantial benefits, such as rapid market entry and lower development expenses [16-18].

3. Traditional Drug Discovery versus Drug Repurposing

The classic strategy for drug development is targeted at de novo identification and new molecular entities. It involves five phases of development: discovery and preclinical studies, safety evaluation, clinical testing, FDA review, and post-market safety surveillance. The process is time-consuming and money-consuming, with a low probability of success. By contrast, the process of drug repurposing has only four stages: identifying existing compounds, acquiring the compounds, development and testing, and FDA post-market monitoring, as shown in Figure 1 [19]—general scheme illustrating the multi-step process of drug development versus drug repositioning. Increased bioinformatics and cheminformatics capabilities, plus the facilitation of access to large structural and biological databases, dramatically shorten time and cut costs in drug development while lowering the failure risks. AI integration, SBDD, and *in silico* methods have considerably paced up drug repositioning in the last few years [20].

Past accidental findings have established the use of available drugs for new therapeutic purposes as very effective. For instance, Pfizer (1985) created the phosphodiesterase-5 (PDE5) inhibitor sildenafil (Viagra) to treat coronary artery disease (angina). However, it is now used to treat erectile dysfunction. It might have resulted in lower development costs and faster development times. Clinical trials are currently underway for phases II and III to evaluate the use of metformin (Glucophage), a commonly prescribed oral medication for type 2 diabetes, as a potential cancer treatment [21].

Comparing drug repositioning to conventional drug discovery methods reveals a number of benefits. The time required for research and development is notably reduced with drug repositioning compared to traditional drug discovery methods. While the conventional process for developing a new drug typically spans 10–16 years, drug repositioning can cut this timeframe to 3–12 years. The cost of developing a new drug through repositioning is around $1.6 billion, significantly lower than traditional methods' $12 billion average. Additionally, identifying new targets for repositioned drugs usually takes 1-2 years, whereas creating a new drug from scratch averages 8 years. Repositioned drugs advance more quickly through preclinical and clinical trials, bypassing the initial 6–9 years of development required by standard approaches. Consequently, repositioned drugs often receive FDA or European Medicines Agency (EMA) approval within 3–12 years and can reduce costs by 50–60%. Since repositioned drugs have already undergone early development stages, such as structural optimization and preliminary trials, they come with existing clinical efficacy and safety data. Preclinical and clinical information availability reduces the risk of early-stage failures, lowers costs, and improves clinical safety and success rates [22].

Besides the advantages of traditional drug discovery, there are several other benefits of drug repurposing, including shorter development time, lower total cost, and lower rate of clinical trial failures. This is because repurposing projects benefit from existing data on pharmacokinetics, toxicology, clinical effects, and safety from the start.

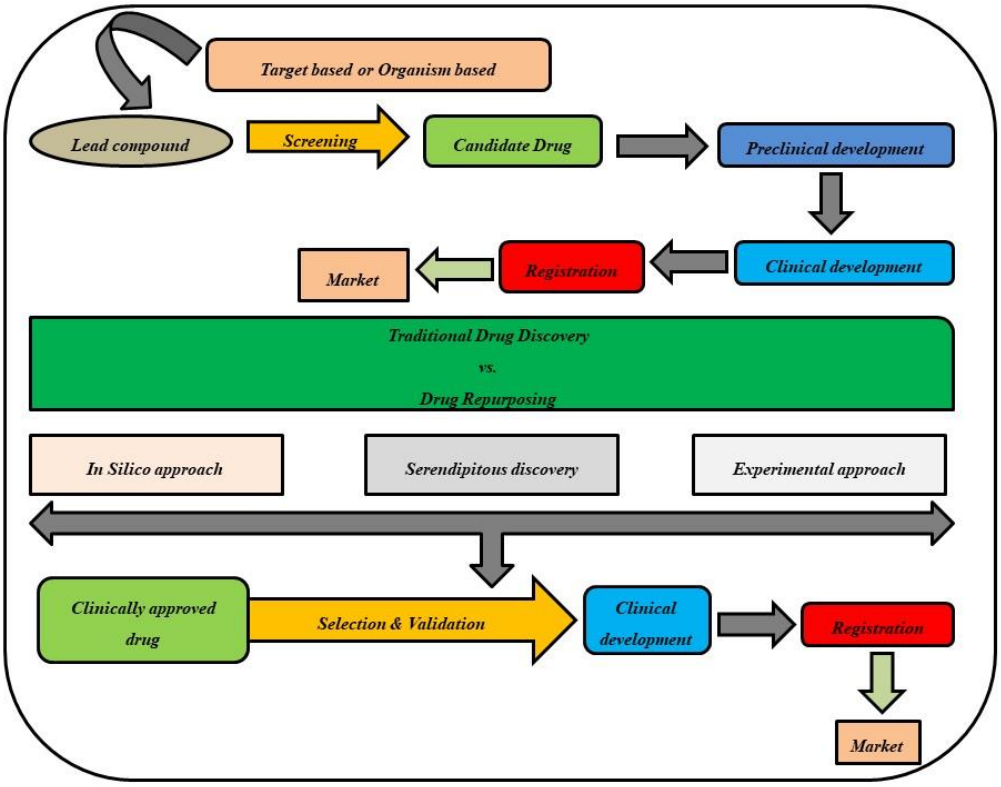

Figure 1. Comparing traditional drug discovery with drug repurposing.

A repositioned drug's development is expected to take three to twelve years, with significantly lower expenses (compared to roughly ten to seventeen years for a standard discovery program). This approach significantly reduces both time and costs for repositioning projects. Whereas the mean development cost for a new drug through conventional means is roughly USD 1.24 billion, the eventual cost of drug repurposing can be as high as 60%less. Additionally, drug repurposing is particularly effective for addressing rapidly evolving, re-emerging, or neglected diseases, whereas traditional drug discovery often focuses on chronic and complex conditions. Targeted repositioning strategies have been further facilitated by bioinformatics, cheminformatics, and in-depth omics data such as proteomics, transcriptomics, metabolomics, and genomics in studying new mechanisms of action and drug targets, identification of similar drugs, and new disease biomarkers [23].

4. Stages for Drug Repurposing

The stages of drug repurposing are outlined in Figure 2 [24].

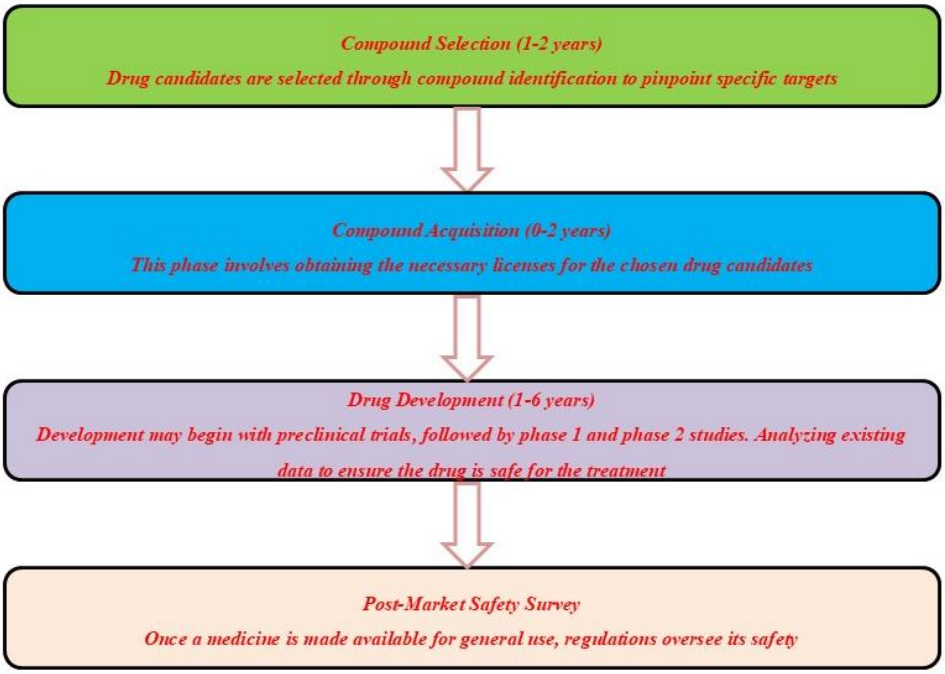

Figure 2. Stages of repurposing.

5. Strategies for Repurposing Drugs

Drug repositioning techniques mainly include two approaches: on-target and off-target, as shown in Figure 3. In on-target repositioning, the known pharmacological effect of a drug is utilized for a new therapeutic application, but the same biological mechanism is targeted for a different disease.

An example of an on-target approach is the repurposing of minoxidil (Rogaine). Originally developed as an antihypertensive vasodilator, minoxidil was later found effective for treating androgenic alopecia (male pattern baldness). It works on the same biological target, enhancing blood flow to hair follicles, which promotes hair growth. On the other hand, off-target repositioning involves discovering new uses for drugs that act on different biological targets from their original purpose. Aspirin (Colsprin) exemplifies this approach. Initially used as an NSAID for pain and inflammation, aspirin also functions as an antiplatelet agent to prevent blood clots, aiding in the prevention of strokes and heart attacks. Recent studies are

exploring its potential role in treating prostate cancer, highlighting its off-target applications [25].

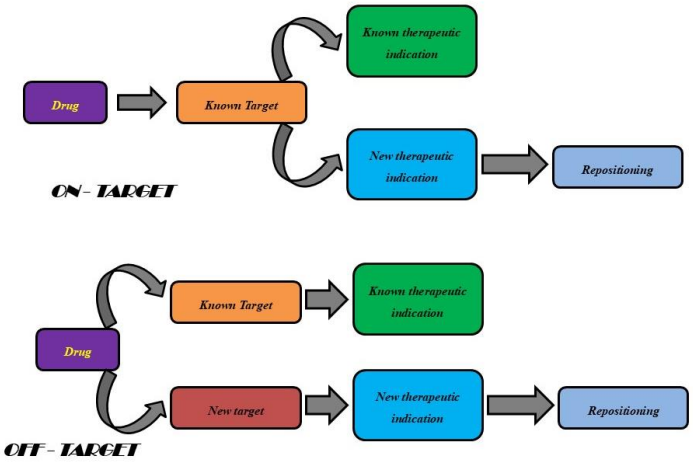

Figure 3. Strategies for drug repositioning involve on-target and off-target.

6. Approaches for Repurposing Drugs

Drug repositioning may be done in two complementary and different ways: experimental and in silico approaches. The experimental method, also known as activity-based repositioning, involves screening existing pharmaceuticals for new pharmacological uses through experimental testing. This method utilizes cell or organism screens combined with protein target screens in both *in vitro* and *in vivo* disease models without relying on any structural data of the target protein. Experimental repositioning can be implemented through various methods, including target screening, animal models, cell assays, and clinical studies [26,27].

In contrast, *in silico* repositioning employs computational biology and bioinformatics or cheminformatics techniques to screen public databases containing extensive drug or chemical libraries virtually. This approach relies on identifying potential bioactive compounds through a molecular interaction between the drug molecule and the protein target [28]. Table 2 shows overall activity-based versus *in silico* approaches [29].

Table 2. Distinctive features of activity-based and *in silico* approaches.

Aspect	Activity-based approach	*In silico*-based approach
Screening method	Experimental screening	computational screening
Focus of screening	Target-focused screening with cell and organism assays	Screening specific to protein targets
False positives	Lower incidence of false positives in screening results	Higher incidence of false positives in screening results
Labor and time	Labor-intensive and time-consuming	Labor-saving and time-efficient
Data requirements	Does not need structural details of target proteins or data on drug-induced phenotypes	Requires detailed structural data regarding target proteins

Over the past few years, this *in silico* method has garnered considerable attention and has shown remarkable potential in drug development programs. Due to easy access to large data on protein structures, bioactive compounds, and pharmacophore models, most drug discovery laboratories and pharmaceutical companies have successfully implemented *in silico* tools and techniques to explore different chemical spaces. It has a number of advantages over experimental approaches: development time and cost are reduced, with fewer failures. However, very accurate structural information on the drug targets is required; if this is not

feasible, other genotypic profiles must be utilized [30]. Figure 4 illustrates the various drug repositioning approaches. The term "mixed approach" refers to the latest strategy that merges the aforementioned in silico and experimental methods in repositioning the drug to discover new treatment purposes for already approved medications. This approach combines preclinical biological studies with clinical trials to confirm the results generated by computational methods. Such a systematic fusion of experimental and computational techniques means that this hybrid approach represents a much faster and certain path to new indication development compared with serendipity and enables repositioned drugs to potentially reach the market much faster and/or with greater success [31].

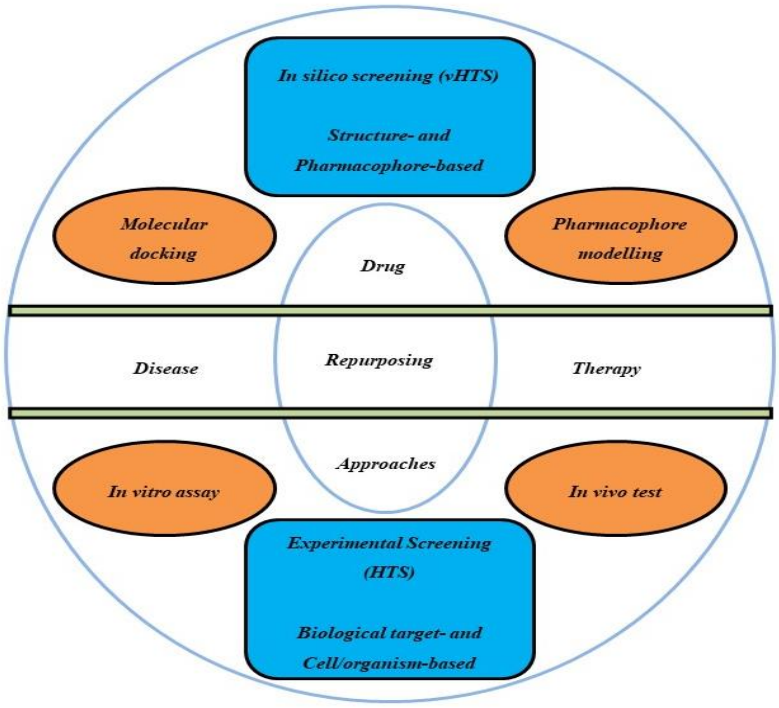

Figure 4. Approaches for drug repositioning.

7. Methodologies for Drug Repurposing

Methodologies employed in drug repurposing can be generally divided into 3 types based on the quality and amount of available data respecting toxicological, biological, and pharmacological effects.

7.1. Drug-oriented methodology.

In this, the researchers check the extracted molecules' structural properties, biological functions, potential adverse reactions, and toxic effects to detect compounds possessing biological responses via cellular or animal tests. Traditional pharmacology and drug development practices form the basis of this approach, which focuses on establishing the biological effectiveness of medicinal compounds without prior knowledge about particular biological targets.

7.2. Target oriented methodology.

This is done through *in silico* high throughput screening of drugs from the libraries or databases, utilizing methods such as ligand-based screening and/or molecular docking. It is

followed by high-content, high-throughput, and/or *in vitro* testing of these pharmaceuticals against target protein molecules or biomarkers. Given that most biological targets are related to disease processes or mechanisms, this method often yields a higher success rate compared to traditional drug-oriented techniques.

7.3. Disease/therapy oriented methodology.

When more knowledge of the disease model is available, this becomes useful as the repurposing of drugs can be directed by insights into the treatment and/or disease, which are informed by:

- Proteomics, which provides information on target proteins for specific diseases;
- Genomics imparts knowledge about the genetic aspects of the disease;
- Metabolomics, which provides information about disease-related profiles and metabolic pathways;

The phenotypic data gives knowledge about off-target mechanisms, drug targets, pathological states, disease processes, and potential adverse and side effects [32]. Figure 5 provides a summary of drug repositioning methodologies and steps.

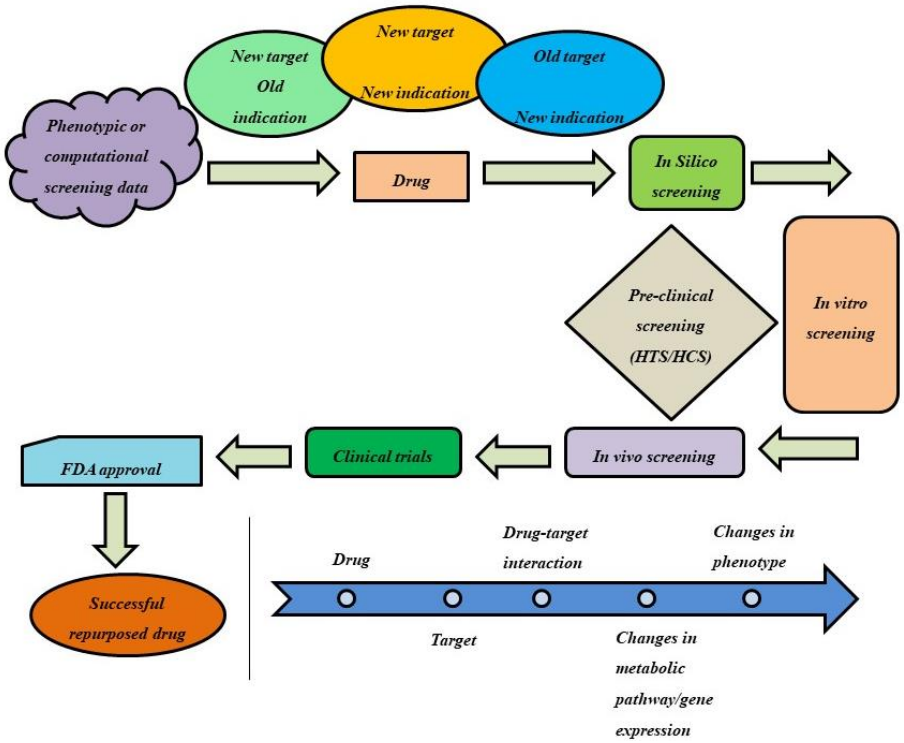

Figure 5. Steps and methodologies in drug repositioning.

Some of the methods applied in the drug repositioning, along with appropriate examples, are summarized in Table 3.

Table 3. Different methods for drug repositioning.

Methodology and Category	Specific Approach and Examples
"Drug-Oriented"	
The Phenotypic Screening Target-focused, blinded screening	Experimental screening using *in vitro* and *in vivo* methods **Example:** Sildenafil
Target Structure Analysis Structure-Based Cheminformatics	Virtual screening, fragment-based approaches **Example:** Fluorouracil
Chemical Structure & Target Data Knowledge-Based, Bioinformatics/Cheminformatics	Drug target prediction **Example:** Simvastatin
Clinical Trial Data & Adverse Effects	Drug similarity analysis based on trial data

Methodology and Category	Specific Approach and Examples
Knowledge-Based Bioinformatics	
FDA-approved product Labeling Information-based Bioinformatics	Analysis of pharmacological similarities using FDA labels
"Disease-Oriented"	
The Available Pathway Data Information-based Bioinformatics	Recognizing disease mechanisms and associated targets **Example:** Vismodegib
The Omics or Genetics Data Signature-Based Bioinformatics	Analyzing gene signatures and genomic data to pinpoint essential targets
Disease Omics, Protein & Pathway Networks Pathway/Network-Based Biology	Examining pathways and networks to pinpoint important targets **Example:** Sunitinib
"Therapy-Oriented"	
The Drug Omics Data Network-Based Bioinformatics, Network Biology	Gene signatures analysis **Example:** Sirolimus
Data on Disease Omics and Drug Omics Signature-Based Bioinformatics	Recognizing similarities between medications and diseases **Example:** Cimetidine
Data on drug omics, disease pathways, and protein interaction networks Mechanism-focused, utilizing network biology and systems biology	Uncovering specific target pathways **Example:** Daunorubicin

7.3.1. Blinded screening methods.

Describe the finding of new applications for drugs through biological testing or experimental screenings against given pharmaceuticals and disease simulations. These techniques have the benefit of flexibility, which allows more drugs and disorders to be investigated.

7.3.2. The target-based methods.

Involve high-throughput screening (HTS) and/or high-content screening (HCS) of therapeutic compounds *in vitro* and/or *in vivo* against predefined biomarkers or protein targets, along with *in silico* screening utilizing large compound libraries by employing techniques such as the ligand-based approaches or molecular docking. The potential for identifying drugs/drug leads is higher than with blinded search methodologies, and the completion of screening can be realized more quickly.

7.3.3. Knowledge-based methods.

Identify, through informatics of chemical and biological data, detailed knowledge about the profile of a drug on chemical structure, interaction with drug targets, and clinical trial information on signaling, metabolic activity, and adverse effects. Compared to blind or target-based approaches, these methods provide richer information, enabling the prediction of novel mechanisms, such as new disease biomarkers, undiscovered drug targets, and drug-drug interactions.

7.3.4. Signature-based methods.

Detect disease processes or new off-targets by comparing gene profiles of the data, either with or without treatment. Publicly available genomic databases support these methods. They are very important for studying drugs that have unknown mechanisms of action. Unlike knowledge-based methods, signature-based approaches rely on computation in studying pharmacological processes on a molecular level, such as alterations in the expression of genes.

7.3.5. Network-based methods.

Use established protein interaction networks, metabolic or signal pathways, and omics data related to diseases to reconstruct disease-specific pathways that can be targeted for drug repositioning. Methods used here can focus on specific networks with fewer proteins rather than broad signaling networks with many target molecules or proteins.

7.3.6. Methods based on Targeted mechanism.

Integrates established signaling pathways treatment omics data to decipher unfamiliar pharmacological mechanisms of action. In particular, such methods' key advantage is that mechanisms that directly relate to the drug administration against specific diseases could be highlighted, and mechanisms associated with either drugs or diseases could be uncovered more broadly [33-35].

8. Examples of Successful Drug Repurposing

The examples of successful drug repurposing are elucidated in Table 4 [36].

Table 4. Examples of successful drug repurposing.

Drug	Original use	Repurposed use and approach	Approval year and outcome
Zidovudine	Cancer	HIV/AIDS Approach: *In vitro* compound library screening	1987: First FDA-approved anti-HIV drug
Minoxidil	Hypertension	Hair loss Approach: Clinical data analysis of unintended side effects	1988: Reached US$860 million in global sales by 2016
Sildenafil	Angina	Erectile dysfunction Approach: Retrospective clinical data analysis	1998: Marketed as Viagra, generating $2.05 billion by 2012
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma Approach: Off-label use and pharmacological analysis	1998 (and 2006): Approved for multiple myeloma, clinically successful
Celecoxib	Pain and inflammation	Familial adenomatous polyps Approach: Pharmacological analysis	2000: Generated $2.69 billion in revenue by 2014
Atomoxetine	Parkinson's disease	ADHD Approach: Pharmacological analysis	2002: Strattera had $855 million in sales by 2016
Duloxetine	Depression	Stress urinary incontinence (SUI) Approach: Pharmacological analysis	2004: Approved in the EU for SUI, also used for depression
Rituximab	Various cancers	Rheumatoid arthritis Approach: Retrospective clinical analysis	2006: Achieved $7 billion in global sales by 2015
Raloxifene	Osteoporosis	Breast cancer Approach: Retrospective clinical data analysis	2007: FDA- approved for invasive breast cancer
Fingolimod	Transplant rejection	Multiple sclerosis Approach: Structural and pharmacological analysis	2010: First oral MS treatment, generating $3.1 billion by 2017
Dapoxetine	Depression	Premature ejaculation Approach: Pharmacological analysis	2012: Approved in Europe, projected sales of $750 million
Topiramate	Epilepsy	Obesity Approach: Pharmacological analysis	2012: Combined with phentermine in Qsymia for obesity
Ketoconazole	Fungal infections	Cushing syndrome Approach: Pharmacological analysis	2014: EMA approved for Cushing syndrome
Aspirin	Analgesia	Colorectal cancer prevention Approach: Retrospective clinical pharmacological analysis	2015: Recommended for colorectal cancer prevention

9. Examples of Failed Drug Repurposing

The examples of failed drug repurposing are elucidated in Table 5 [37].

Table 5. Examples of failed drug repurposing.

Drug	Original use	Repurposed use and approach	Year and outcome
Latrepirdine	Antihistamine	Huntington's disease **Approach:** Pharmacological analysis	2011: Failed Phase III trial (HORIZON)
Ceftriaxone	Antibiotic	ALS **Approach:** High-throughput Drug Screening	2014: Ineffective in Phase III trial
Topiramate	Epilepsy	IBD **Approach:** Transcriptome-based Signature Matching	2014: Positive results in rodents; however, a retrospective cohort study was unsuccessful, and no clinical trials have been carried out to date

10. Obstacles to Drug Repurposing

As mentioned above, it is clear that significant achievements have already been made in the repurposing of drugs. Repurposing, however, is not always successful; for some drug candidates, repurposing was unsuccessful, primarily during the phase III trial stage. Similar to the process of developing completely new drugs, some are expected to fail in late-stage development, but because their safety profiles are known, toxic failures should be fewer. Yet, additional factors contribute to the repurposing industry's failure, such as organizational impediments, patent concerns, and regulatory issues, as well as reasons why a promising candidate may not even be pursued beyond preliminary research.

10.1. Patent considerations.

Repurposing drugs is hampered by several legal and intellectual property issues [38]. The main obstacles to encouraging medicine repurposing are those related to securing a novel patent for a repurposed indication and upholding patent protections since these issues significantly affect the possible profit anticipated from repurposed medication. In most major pharmaceutical markets, a repurposed drug molecule can receive protection as a new medical application, provided the new use is novel and as well as inventive, meaning it is not obvious. However, many potential repurposing applications are already well-established in clinical practice or documented in scientific literature. The availability of scientific knowledge regarding the repurposed use limits the possibility of seeking patent protection, even when efficacy has yet to be confirmed through clinical testing. This is especially true if the patentee is unable to distinguish their patent claims from information already in the public domain.

An MOU patent can be acquired for off-patent drugs by identifying a novel and innovative application for an existing generic medication (provided, as previously mentioned, that the new use is supported by appropriate facts to make the new use believable). Enforceability, however, may become a significant problem in this case if the newly repurposed indication uses the generic drug's readily available dosage forms and formulations. This is because other manufacturers may make the generic medication readily accessible, and doctors may prescribe it for non-patented uses. It is legal for the generic producer to market their product exclusively for unpatented uses (often known as "skinny labeling"). It will be hard for them to claim infringement as long as they do not promote the patented indication of the new MOU patent. Under these circumstances, the newly patented repurposed indication may be

hard to halt non-label use, which could lower the product's potential profitability. Non-label use, however, may be restricted if a newly therapeutic indication calls for special preparation and/or dosing schedules, which are difficult to fulfill with the drug's readily available generic equivalents. Given these challenges, it may be important to consider at as early a stage as possible in the project how and to what extent it will be possible to protect intellectual property for a product to be repurposed.

It is evident that securing market exclusivity for repurposed drugs presents various challenges. For instance, the Patent Drugs Bill 2015-16 was introduced in June 2015 to the UK Parliament. This measure was designed to address situations where a medication, after its patent has expired, is discovered to have a new use beyond the scope of its original license. Several medical charities supported it, but it was not enacted into law. Later, in November 2017, the AMRC published a report recommending how to ensure drug repurposing benefits patients in the UK. It was drafted in partnership with various stakeholders, such as NICE, the MHRA, Royal Colleges, and industry representatives. This report summarizes how sponsors can collaborate with the MHRA to navigate various pathways to licensing. It further recommends creating a testing framework for drug repurposing and financial incentives to encourage generic manufacturers to participate in this process. "OPEN ACT (Orphan Product Extensions Now Accelerating Cures and Treatments)" proposes a drug used for some rare disease treatment in the US that will get an additional six months of market exclusivity. To enhance patentability, new formulations, dosage forms, or compounds can be prepared for similar therapeutic effects, and even exclusive marketing rights could be sought in markets that were hitherto unentered [39].

10.2. Organizational hurdles in industry.

Pharmaceutical companies are increasingly collaborating with academic institutions and smaller biotech startups as they recognize the possibility of repurposing drugs beyond their primary illness area of emphasis. The AstraZeneca Open Innovation Platform is one such initiative to encourage external partnerships and facilitate drug repurposing research. It allows access to well-characterized compounds amenable to repurposing in translational research, preclinical studies, and phase II clinical trials for researchers.

In the pharmaceutical industry, repurposing can face organizational challenges, particularly if the new use is outside the company's core therapeutic focus or if the compound has been discontinued, leaving the R&D team without an active project to allocate resources for the new indication. This would indicate a lack of resources and financing to further the idea within the organization and a shortage of employees qualified to work on a potential drug repurposing project. One strategy to overcome such obstacles in clinical trials is outsourcing the needed services, which include contract manufacturing for drug supply, regulatory, and pharmacovigilance-related services. When it would not have been feasible to move the idea forward inside the organization, alternative financing sources might be taken into consideration. Additionally, expanding the selection of compounds would open up more chances for repurposing, particularly for those focusing on innovative systems. However, because most of these compounds are still in the early stages of development, there are concerns about the risks of sharing them outside the pharmaceutical industry, including the possibility of discovering additional safety risks and issues related to intellectual property rights. It might help alleviate worries in this regard by providing positive instances of substances that are still in active development and being repurposed [40].

11. Advantages of Repurposing Drug

After careful consideration, it is clear that the drug repurposing strategy is advantageous because some rejected compounds and approved medications have already undergone human testing, providing detailed information on their pharmacology, dosage, potential toxicity, and formulation. Compared to traditional drug discovery approaches, drug repurposing offers several benefits, such as: (i) It significantly reduces spending on R&D expenses; (ii) Shortens the time frame for medication development because it eliminates the need for Phase I clinical trials because a number of substances have previously been shown to be safe in humans; (iii) Possibility of reusing pharmacological molecules despite side effects and ineffectiveness without certain indications [41].

12. Opportunities and Challenges

Drug repositioning, unlike traditional drug discovery programs that are time-consuming, costly, and often prone to failure. The effectiveness of drug repositioning has significantly improved due to the use of computational and machine-learning techniques. Experimental approaches that provide direct, evidence-based insights into the connections between medications and diseases. However, in order to find new indications for outdated medications, computational and experimental methods have been integrated more often in recent years; these approaches are known as mixed approaches. This strategy uses clinical trials and biological experiments to validate computer technologies. With an increasing number of available databases and technological advancement, it's possible to adopt a hybrid approach to drug repositioning, whereby a systematic and comprehensive consideration of all options would be taken into account. Furthermore, drug repositioning requires less research and development than traditional drug development. As a result, many pharmaceutical companies can develop new medications with lower investment due to the advantages of drug repositioning [42,43]. The hybrid approach toward drug repositioning opens prospects for acceleration and smoothing of the developmental process of repositioned drugs. From a market perspective, many diseases require the creation of new treatments, which could influence both the economy and market demand. For instance, there is a sizable untapped market for developing medications for less common or ignored disorders. Thus, there is an opportunity to repurpose medications for treating rare, underdiagnosed, or orphan diseases or conditions that are difficult to cure. More than six thousand uncommon diseases are untreated. Five percent are in the process of being examined. There is a significant potential market for rare diseases. This forms the basis of why repositioning already known drugs to address common and rare disorders is increasingly seen as a promising approach, especially given the high attrition rates, substantial costs, and slow progress associated with traditional drug discovery and development. This is because it involves using drug molecules with lower development costs and a shorter failure rate [44-46].

With the development of technologies like transcriptomics, genomics, and others, as well as the accessibility of large databases containing disease omics data and drugs, there are many possibilities to find new medications through drug repositioning through an integrated and collaborative effort involving all of the aforementioned methods and approaches. Using advanced, valid approaches and data for the first time allows the investigation of new, previously unknown mechanisms of action/pathways by target proteins/genes for a given

disease or by biomarkers related to disease progression. For pathway analysis, proteomics, metabolomics, and genomics, a number of resources and programs are openly accessible [47].

However, with drug repositioning, opportunities are frequently accompanied by a number of difficulties. One of the biggest obstacles to repositioning is finding additional clinical indications for an already authorized drug. Drug repositioning, however, is a complex procedure that considers several variables, including technology, business models, patents, investment, and consumer demand [48].

13. Trends in Repurposing: Initiatives Advancing the Field

Due to the lack of treatments for numerous uncommon diseases, drug repurposing has become increasingly popular in recent years [49]. Many international programs are in place to facilitate the repurposing of drugs, and the expected market value of repurposed drugs is shown in Figure 6. Figure 7 provides a summary of these, along with other examples. The data is given below.

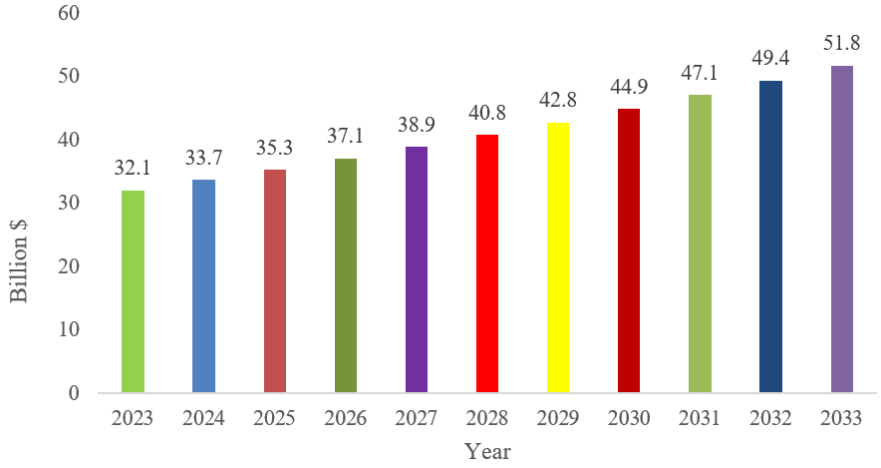

Figure 6. Global repurposing market size in $.

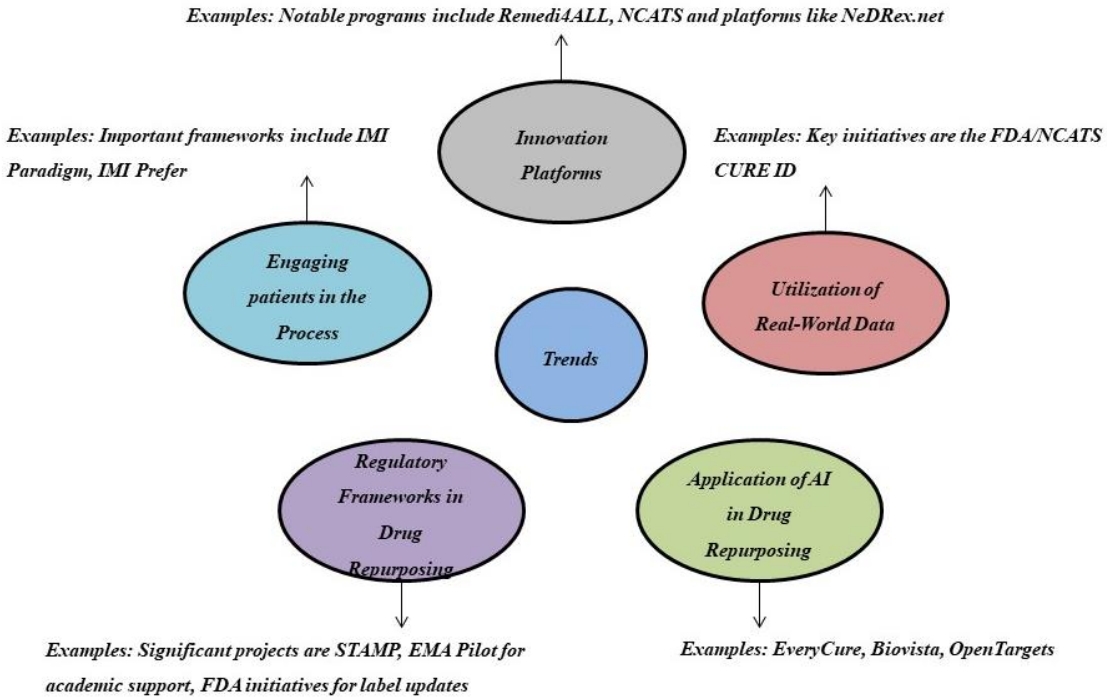

Figure 7. Summary of trends with examples of relevant initiatives.

13.1. Innovation platforms.

To help the medication repurposing community, several international innovation platforms have been established. A five-year research project sponsored by the EU, REMEDi4ALL (repurposing medicines for all), aims to advance pharmaceutical repurposing in Europe by building a globally linked and sustainable platform [50]. Having the infrastructure resources at its disposal, the REMEDi4ALL collaboration brings together unique skills to tackle the challenge of drug repurposing. To address the current systemic inefficiencies in medication repurposing and create a catalog of services, 24 organizations have teamed up under the direction of "EATRIS-the European platform for translational medicine" [51-53].

These collaborations include NHS England, MHRA, and the Department of Health and Social Care in the NHS England Medicines Repurposing program context. The purpose is to generate opportunities to use present medicines novelly [54]. Three key objectives are stimulating and advancing new research on drugs suitable for repurposing for the NHS; identifying opportunities for repurposing priority medications to enhance patient outcomes, experiences, and cost-effectiveness; and providing support for the licensing of repurposed medicines, thereby informing clinical practice and improving access equity. It was recently announced that the Medicines Repurposing Program has achieved its first success [55]. In November 2023, the MHRA approved anastrozole as prophylactic therapy in postmenopausal women having a higher-than-average risk of developing breast cancer. It was used majorly by those who have been diagnosed to have a strong family history of the disease. Despite NICE's 2017 recommendation that it be used as a preventive measure, few people took up the treatment because it was not approved. In order to get the medication on the label, the Medicines Repurposing Program played a key role in facilitating drug licensing and scientific advice. The company was competitively selected through an open process on a cost-neutral basis to perform the regulatory work. The British Generic Manufacturers Association and Medicines Repurposing Programme will collaborate to ensure that all other manufacturers of anastrozole use the newly approved label.

13.2. Utilization of real-world data.

Since real-world data (RWD) provide information on the efficacy, safety, and usage patterns of current medications across a range of patient populations, it is essential for drug repurposing. Besides its role as evidence for the safety and effectiveness of monitored licensed products in post-marketing surveillance, real-world data can also be utilized to uncover potential links between existing medications and new therapeutic uses. National Center regarding Advancing Translational Sciences (NCATS/NIH) and the FDA collaborated to build CURE ID, an online platform that makes it easier to report new applications of approved medications for difficult-to-treat communicable diseases [56]. This is currently undergoing expansion to encompass significant unmet medical needs in areas other than infectious diseases, such as uncommon genetic diseases and malignancies. It allows patients, caregivers, and healthcare practitioners to discuss actual clinical results for medications used in novel demographics, circumstances, dosages, or combinations. The crowdsourcing project analyzes the medical data gathered so that it expedites the development of medicines for rare and overlooked diseases. This has especially been important for uncommon illnesses, and holding RCT might become impracticable, if not impossible. For instance, meningoencephalitis can occasionally be caused by the amoeba *Balamuthia mandrillaris*. It

can't be easily investigated in an RCT due to its quick and dangerous nature, and its fatality rate is around 90%. Nitroxoline, a quinolone antibiotic that has received authorization for 50 years in Europe as a treatment for UTIs, has been repurposed and seems to offer a promising approach for treating Balamuthia, according to initial case studies from physicians and caregivers in CURE ID that were obtained through active collaboration with patient care teams [57]. Besides this, the increasing use of electronic health records to directly extract drug repurposing data is increasing the number of real-world data sets from which lessons can be drawn to discover possibly safe and effective solutions for uncommon conditions. With partners like Cure Drug Repurposing Collaboratory, the CURE ID has evolved into the "EDGE Tool," allowing for the automation of certain inpatient case reports from data extraction on the CURE ID platform. We are now expanding this tool to investigate medications that are being repurposed for uncommon conditions like uncommon meningitis causes [58,59].

13.3. Application of AI in drug repurposing.

AI, ML, and sophisticated computer methods are being used more frequently to find possible drug repurposing candidates. By analyzing vast knowledge graphs containing biological, clinical, and chemical property data gleaned from databases and literature, these systems can forecast novel therapeutic applications for already marketed medications. One such platform is EveryCure, which builds an open-source database of repurposing opportunities to find novel therapeutic uses for currently approved medications [60]. It uses machine learning and natural language processing methods to compile and evaluate data from various sources, such as clinicaltrials.gov, PubMed, and medical records. These evaluations should be taken forward by collaboration with research institutions to perform clinical trials for the most viable prospects, based on collaboration with pharmaceutical corporations and illness experts.

In conjunction with this endeavor, REPO4EU, a project sponsored by the European Union, aims to create a complete platform on a global and European level for mechanism-based drug repurposing. This platform will redefine diseases using advanced artificial intelligence and bioinformatics to analyze real-world big data [61].

13.4. Regulatory frameworks in drug repurposing.

In 2021, the European Medicines Agency and the Heads of Medicines Agencies initiated a pilot program to encourage the repurposing of medicines. The work is based on the outcome of the European Commission's expert group on safe and timely access to medicines for patients, which was tasked with evaluating a draft concept for the repurposing of medications [62,63]. This program aims to assist academic institutions, individuals, and not-for-profit groups in gathering or providing sufficient data to obtain official regulatory clearance for the new use of an established medication. Available to an individual keen on repurposing approved drugs for novel public health purposes and having a solid scientific basis, it seeks scientific input from regulatory authorities. The Medicines Repurposing International Network has established 12 organizations dedicated to exchanging expertise and insights. It was established to address the increasing prevalence of drug repurposing initiatives that are funded by public resources and driven by regulatory bodies.

The current draft proposal by the European Commission for the EU pharmaceutical legislation scheduled to take effect in April 2023 further reinforces the growing interest in drug repurposing [64]. Incentives and special provisions are included for repurposing to facilitate the translation of research into approved medications for researchers and non-profit organizations. According to Article 48: Draft text, A non-profit organization that does not participate in economic activities may present significant nonclinical or clinical evidence for a new therapeutic indication to fulfill an unmet medical need to the Agency or the relevant authority in the Member State. The Agency may perform a scientific assessment of the benefit-risk profile of a medicinal product that has a new therapeutic indication intended for the treatment or prophylaxis of a medical condition that, by itself or together with other medicinal products, would satisfy an unmet medical need, either on its initiative, on request of a Member State or at the request of the Commission, and based on all data available. While this draft proposal toward the pharmaceutical legislation of the EU is still under discussion and the final text is still uncertain, repurposing programs have already been recognized as important.

13.5. Engaging patients in the process.

A patient's involvement is increasingly a key aspect of a drug repurposing program, and the patients themselves can steer the process by bringing together stakeholders and funding for effective drug repurposing initiatives. To guarantee that the repurposed drug satisfies patient needs, patient involvement is crucial at every stage of the process [65]. By keeping track of their pharmaceutical side effects, patients can offer insightful information about the efficacy of various medications for treating various ailments and aid in discovering new uses for already approved medications. Furthermore, the toolkit for patient engagement and guidelines for performing studies on patient preferences and their potential to influence regulatory decision-making were the main contributions of the two prior IMI projects, Prefer and Paradigm, which targeted patient engagement tools [66-68]. The Horizon Europe-funded project SIMPATHIC aims to accelerate the repurposing of medications for neurometabolic, neuromuscular, and uncommon neurological conditions. To this end, patient representatives will get training modules that will enable them to take the lead in the repurposing process. To optimize the repurposing of medicine, REMEDi4ALL will create supplementary patient education courses and patient engagement initiatives.

14. Conclusions

Historically, drug repurposing has a well-documented track record in therapeutic molecule discovery, often arising from serendipitous observations. Recently, it has emerged as a vital strategy for developing new treatments by utilizing already approved medications. More strategic and systematic approaches have significantly enhanced innovation, leading to the identification of pharmacological compounds with previously unrecognized therapeutic uses. The demand for drug repositioning is increasing in the market owing to its substantial reduction in research and development costs, improved success rates, shortened timelines, and lowered investment risks. These advantages benefit drug researchers, consumers, pharmaceutical companies, and discovery scientists, making innovative repositioning strategies applicable across a wide spectrum of human disorders.

Moreover, integrating artificial intelligence (AI) tools, pharmacophore modeling, and in silico techniques can accelerate the drug repurposing process. These strategies have proven particularly valuable in recent years, especially in precision medicine, for investigating new diseases, metabolic pathways, off-target interactions, and specific action mechanisms. They are also instrumental in examining gene expression profiles and hereditary disorders. Advancements in genomics have equipped researchers with extensive transcriptomic and genomic data facilitated by technologies such as transcriptomics and next-generation sequencing. The application of systems biology and network biology approaches is especially beneficial in uncovering new mechanisms of action, as they provide insights into the molecular and genomic profiles of drug-target interactions. A comprehensive understanding derived from a blend of computational and experimental methods is essential for optimizing the repositioning process to enhance the success rates of repurposed drugs. Ultimately, drug repurposing holds significant promise for discovering and developing novel therapies with innovative and beneficial applications for various human diseases.

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Conflicts of Interest

The authors declare no conflict of interest.

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