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REVIEW ARTICLE

Web-based Tools for Drug Repurposing: Successful Examples of Collaborative Research

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Abstract: Computational approaches have been proven to be complementary tools of interest in identifying potential candidates for drug repurposing. However, although the methods developed so far offer interesting opportunities and could contribute to solving issues faced by the pharmaceutical sector, they also come with their constraints. Indeed, specific challenges ranging from data access, standardization and integration to the implementation of reliable and coherent validation methods must be addressed to allow systematic use at a larger scale. In this mini-review, we cover computational tools recently developed for addressing some of these challenges. This includes specific databases providing accessibility to a large set of curated data with standardized annotations, web-based tools integrating flexible user interfaces to perform fast computational repurposing experiments and standardized datasets specifically annotated and balanced for validating new computational drug repurposing methods. Interestingly, these new databases combined with the increasing number of information about the outcomes of drug repurposing studies can be used to perform a meta-analysis to identify key properties associated with successful drug repurposing cases. This information could further be used to design estimation methods to compute a priori assessment of the repurposing possibilities.

Keywords: Drug repurposing, web-based tools, database, computational methods, validation, data integration.

1. INTRODUCTION

The objective of drug repurposing (DR) (also called drug repositioning, re-profiling, re-tasking, or therapeutic switching) is to identify new indications for already approved drugs. This concept initially discussed by Ashburn and Thor in 2004 [1, 2] is attracting the interest of the drug discovery industry. Indeed, pharmaceutical companies are facing a challenging societal environment coupled to strong financial pressures principally driven by the cost of bringing a drug to market, which has increased due to a combination of factors including increased safety requirements by regulatory authorities, a demand for larger clinical trials and greater overall development costs [3, 4]. As a result, pharmaceutical companies have been developing new research paradigms, strongly relying on process automation [5], to optimize key steps of the drug discovery pipeline [6] and to compensate for the lack of technical efficiency of the traditional drug discovery approaches that results in a high failure rate and continual decline of the number of new approved small molecular entities released by the pharmaceutical industry pipelines [7, 8]. Within this context, DR is seen as a strategy of choice to develop original drugs at a reduced cost [9, 10]. The main advantages of DR are that the preclinical and toxicity profiles of the drug are already known. Consequently, repurposed drugs could probably skip the preclinical and phase-I study and directly undergo Phase II and III clinical studies resulting in an accelerated development time [11], a decreased development cost [8] and a better return on investment. DR is also interesting to manage Intellectual Property (IP) and patent protection.

Indeed, patent protection for a new use of an existing drug whose composition of matter patents are still running can be obtained, assuming that the new use is not covered and proven in the original patents [12, 13]. Furthermore, by reusing already approved drugs, a pharmaceutical company can protect its original IP against competitor adjacency moves.

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Table 1. Successful drug repurposing examples. MS, multiple sclerosis; SUI, stress urinary incontinence.

Drug Name	Original Indication	New Indication	Date of Approval
Duloxetine [21]	Depression	SUI	2004
Rituximab [22]	Various cancers	Rheumatoid arthritis	2006
Raloxifene [23]	Osteoporosis	Breast cancer	2007
Fingolimod [24]	Transplant rejection	MS	2010
Dapoxetine [25]	Analgesia	Premature ejaculation	2012
Topiramate [26]	Epilepsy	Obesity	2012
Ketoconazole [27]	Fungal infections	Cushing syndrome	2014
Aspirin [28]	Analgesia	Colorectal cancer	2015

Today, DR is commonly performed for finding alternative candidates to cure various kinds of diseases. Many successful DR cases have been reported so far (For a list of DR cases, the reader is advised to consult the website: http://drugrepurposingportal.com/repurposed-drug-database.php). For example, methotrexate, a drug initially developed for treating leukemia, was subsequently repurposed to treat various types of cancers, including breast, ovarian, bladder to head and neck cancers [14, 15]. Another example is Tamoxifen initially designed to treat breast tumors and now used bipolar disorder mania [16] again. Zonisamide was firstly developed and marketed as an anti-epileptic drug and it was later repurposed as an anti-Parkinson's disease drug [17]. Among the neuropsychiatric disorders, Alzheimer's disease is worth mentioning as alternative candidates are at various development stages or in clinical trials [18, 19]. Other cases of drug successfully repurposed to treat neuropsychiatric disorders were discussed in reference [20]. Additional recent successful repurposing cases for various indications are summarized in Table **1**.

Currently, one estimates that about 30% of the recent FDA-approved drugs and vaccines in the USA are repurposing discoveries [29], and there are high expectations regarding the use of DR for addressing important health issues. For example, efforts are carried out to identify new candidates for anti-aging therapies [30]. Furthermore, DR attracts attention from the anticancer and oncology drug discovery industry [31, 32]. Indeed, only 5% of anticancer drugs entering Phase I clinical trials end up as marketed drugs and one expects to answer the continuously increasing demand for new anticancer drugs by making use of the availability of a wide variety of cell- and target-based screening assays through DR. Several alternative candidates at advanced development stage or already ongoing clinical trials were discussed in [33] and other already well-known drugs such as metformin [34] and vitamin D [35] are being analyzed to discover potential anticancer properties. Finally, DR is considered for finding cures to treat orphan diseases [36] which affects around 400 million people worldwide. Indeed, between 5000 and 8000 of such diseases have been identified but considering the research and development costs, it is impossible to develop de novo therapies for each of them [37, 38].

Initially, DR was mostly through serendipity and demonstrated a very low efficacy. Today, it is common to perform DR studies supported by specific computational methods [33]. From a technical perspective, the development and use of these algorithms result from two technological trends [33, 39]. First of all, the advances of genomics, sequencing, and high throughput technologies which have generated a huge amount of data providing characterizations of disease phenotypes and drug profiles which are used to better understand diseases and drugs mechanism of action [40]. Secondly, the progress made in computational sciences [41] which, combined with increasingly powerful computational resources, allows the development of computational tools and web-based databases which are required for the gathering and classification of the large volumes of diverse datasets used for drug discovery [38, 39, 42-44], some of these tools and databases are listed in Supplementary Table **1**. Examples of publicly available and searchable tools providing valuable data resources and used by DR algorithms (For lists of DR algorithms, the reader is invited to consult the websites: https://omictools.com/drug-repositioning-cate gory and http://www.vls3d.com/links/ chemoinformatics/off-targets-repurposing) include DrugMap Central [45], DRAR-CPI [46], e-Drug3D [47], PharmDB [48] and PROMISCUOUS [49]. Despite the fact that the biological significance of the candidates identified using DR

algorithms must be validated through experimental testing [2, 50], *in silico* methods allow us to quickly perform key steps of DR processes at a reduced cost.

Computational DR being an active field of research; several reviews already presented a comprehensive synthesis of the field status from different perspectives and often suggested further directions of research to solve commonly encountered issues. For example, Hodos *et al*. [38] considered a point of view that encompasses three main aspects. More precisely, prediction of drug-target interactions, application to DR and prediction of side effects or adverse drug reactions were considered. In addition to the description of algorithms applied to handle these aspects, this work also discussed the methods used to measure the pharmacological space and provided a list of databases and tools used for data processing. A broader approach was taken by Shameer *et al*. [51] who emphasized the role of DR as a component of therapeutic stratification in the precision medicine paradigm. This work described pharmaceutical compound re-use strategies, the corresponding experimental approaches and detailed required validation steps. It also provided tables with diverse computational methods available as well as extensive lists of open-access databases, software libraries and databases to aid in DR. On the other hand, the work of Alaimo *et al*. [52] was essentially focused on the algorithmic aspects. The different categories of computational methods are shortly described following [53]. Then, the work described the mathematical foundations of the network-based inference methods and used the DT-Hybrid algorithm as an example to discuss several algorithmic issues of DR. Finally, the work presented in [54] described key algorithmic properties of the main classes of DR methods [42] while emphasizing that DR method can be systematically designed as work-flows of three interconnected components with their specific assigned tasks. These three components were identified as data processing, in silico generation of putative candidates for DR and validation of the predictions. By including these three aspects together it was possible to emphasize common technical issues shared by these algorithms together with their respective mathematical limitations.

Thus, from a conceptual and practical point of view, the advantages of developing such computational approaches are well-recognized and many public and private entities support the efforts to improve and extend their use. Research and results includes the identification of Tricyclic Antidepressants as inhibitors of small cell lung cancer by NuMedii [55], the development of monoclonal antibodies to innovative and therapeutic targets in oncology and autoimmune disease by Capella biosciences, the development and use of a cloud-based drug discovery platform by TwoXar that aims at finding unanticipated associations between drug and disease with a focus on therapeutic areas including autoimmunology, oncology, and neurology and the development and use of parametric and artificially-intelligent drug discovery and repurposing systems by Insilico Medicine [56, 57]. Many other foundations and bio ventures are involved in the development or support of DR including Cure Within Reach [58] and H.M. Pharma Consultancy [59]. Nevertheless, in the past, these initiatives remained difficult to reproduce on a very large scale. This absence of larger repurposing programs can be explained by the lack of a definitive physical drug collection, the low quality of drug annotations, and insufficient readouts of drug activity from which new indications can be predicted. These limitations, summarized on the (Fig. **4a**) had a strong impact of the systematic use of computational methods which typically requires high-resolution structural information of targets as well as either disease and phenotype information or gene expression profiles of drugs depending on the nature of the targets, making any of them strongly dependent on the availability and quality of experimental data.

The purpose of this work is to review a set of tools proposing methods to overcome or solve some of these limitations. The tools considered here take advantage of recent improvements for the design of web-based computational services and these web-based solutions are usually available with a friendly user interface. These features make their use easier for all scientists working in the DR area independently of their initial background and technical expertise. In the following section, databases containing information specifically required for performing DR studies are described. The key features of these databases are summarized in Fig. (**1**). Then, a set of web-based algorithms for DR is presented (Fig. **2**) and in the last section, we focus on the problem of method validation and comparison. Indeed, as computational DR methods are heavily dependent not only on the availability but also on the quality of these data, it is important to have access to correctly curated databases for training, testing and validation of these methods. Several solutions recently proposed are summarized.

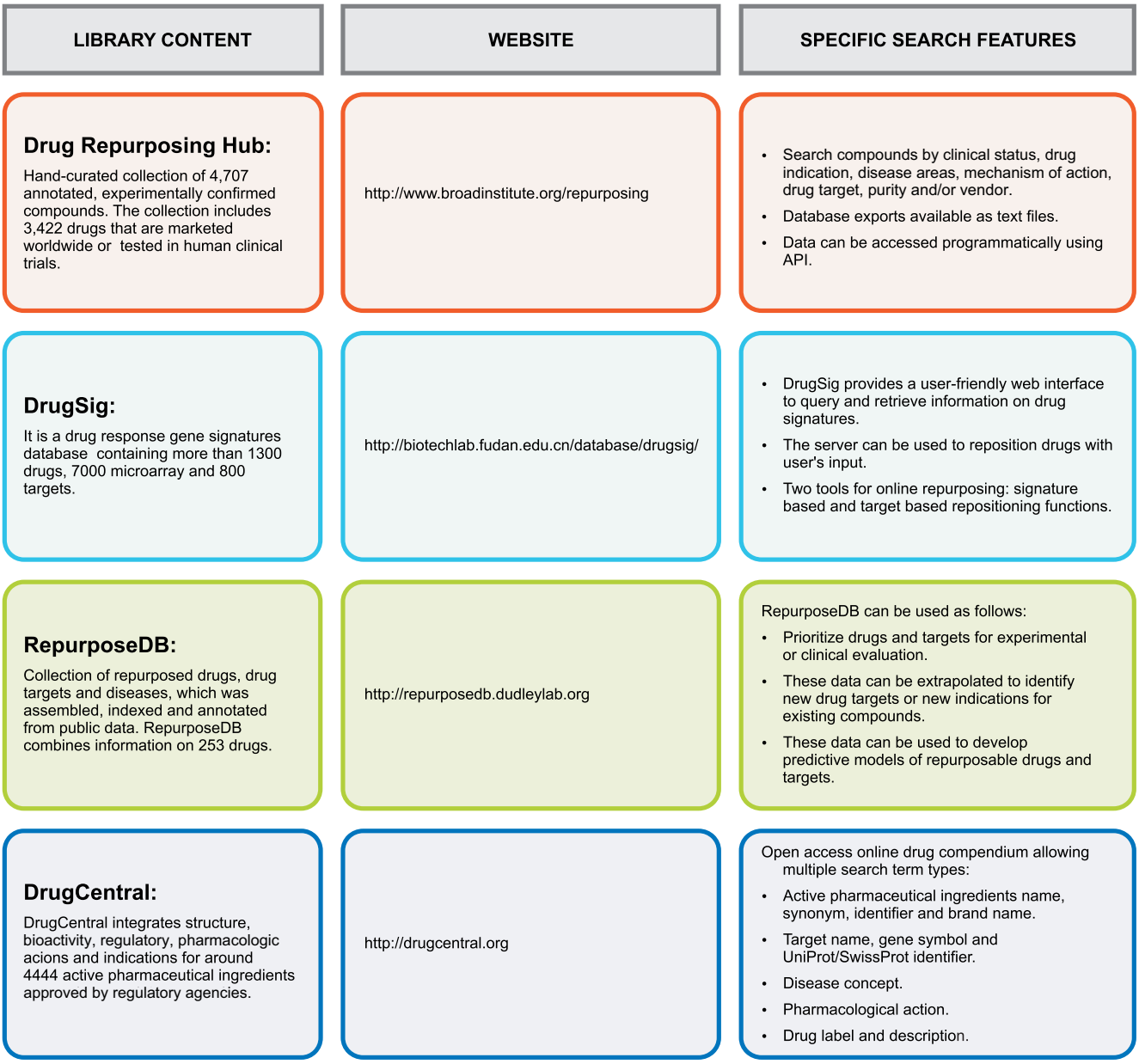

Fig. (1). Description of the content, web-access and implementation features of some recently released web-based database specifically designed to gather and extract data for performing or validating DR studies. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. DEVELOPING WEB-BASED TOOLS FOR DRUG REPURPOSING

2.1. Interactive Drug Libraries for Drug Repurposing

In reference [63], a library of clinical compounds suitable for testing is presented. The novelty of this library is that it connects the outcomes of disease-genetics studies to drugs available for preclinical and clinical testing. As a result, this library can provide a manually curated list of compounds whose identities were experimentally confirmed and whose properties were annotated with literature-reported targets. The tool was designed as follows. The clinical-drug structures were selected by gathering marketed or approved ingredient lists from regulatory agencies worldwide and by searching within separate databases such as DrugBank, the NCATS NCGC Pharmaceutical Collection (NPC), Thomson Reuters Integrity, Thomson Reuters Cortellis, and Citeline Pharma projects. In total, one assembled a set of 10000 unique small-molecule drugs and all of them have reached clinical

development. A chemical-structure analysis was performed on all clinical-drug structures to estimate the structural diversity within the library. The most important step towards the assembly of the database was to annotate drug functions and clinical-development status through manual curation based on primary sources. According to the authors, annotation of drugs in clinical development appeared to be difficult to obtain and the same situation prevailed for accessing the approved clinical indications for existing drugs. This is because the availability of the information is not systematic and standardization of the terminology used to store this information is sometimes missing. This experience demonstrated that the standardization of drug-mechanism and protein-target information would benefit the experimental interpretation of DR efforts. Nevertheless, the assembled library is able to provide information on compounds representative of the majority of chemotypes that have reached clinical development. It is worth mentioning that in order to assess the quality and purity of the compounds incorporated within the database, 8,584 samples (representing 5,691 unique compounds) were purchased from 75 chemical vendors. Quality and purity assessment was done by ultra-performance liquid chromatography-mass spectrometry (UPLCMS). A main concern of the authors was that a significant percentage of compounds failed the quality control. These failures concerned compounds stored in DMSO.

It is well known that the quantity and quality of drug response gene signatures available are essential for computational DR methods. However, many of these data are scattered in different databases or individual resources. This makes them difficult to use for the building, testing or using such methods. To address this issue, an online resource called DrugSig was designed for archiving large amounts of drug response gene signatures for computational DR [76]. To assemble the database, around 7000 microarray raw data were gathered by performing a literature search through scientific papers covering a total of 1300 drugs. Downloaded raw data were processed using standard approaches (RMA method from affy package). Then, drug-induced signatures were constructed following two approaches in the function of the number of replicates available. Signatures were constructed using simple fold changes when less than 3 replicates were available and using the linear models to calculate the different expressed genes based on the Limma package otherwise. Using public databases, around 800 available targets were constructed according to descriptions from the literature. Finally, all the information was organized in different tables and incorporated within the database. DrugSig includes a web interface to query and retrieve information on drug signatures. This can be done using either the signature-based or the target-based drug repositioning function. The signature-based drug repositioning function provides an interface to input the user's gene list to compute against DrugSig whereas the target-based drug repositioning function provides an interface to explore the specified target and its targeting drugs, as well as target gene expression level in cells after treated by drugs.

In the article of Shameer *et al*. [60], a centralized database of repurposed drugs, drug targets and diseases was presented. As explained by the authors, the tool aims at allowing systematic analyses of drugs, drug targets and associated disease indications to understand better key factors driving DR and more precisely what makes such studies successful or not. The database itself was assembled by gathering repurposed drugs using a combination of text mining of the PubMed database and manual curation of manuscripts reporting DR. Then, manual curation was performed by examining scientific articles that reported DR investigations. Data processing was done using data from DrugBank, KEGG Drug and Compound databases, PubChem, Chemical Entities of Biological Interest, SIDER and US FDA Rare Disease Repurposing Database. For disease and phenotype data, terms were manually curated and mapped to three different disease ontologies. Phenotype data and drug Data were integrated and all resources were indexed using drugs and diseases. The obtained data set was compiled in a format of "drug primary indication-secondary indications". The database was finally mapped to the repertoire of biomedical ontologies. Interestingly, the authors used enrichment analysis to explore these data. Their analysis provides new insights about biological pathways, functional mechanisms, physicochemical features and side effects commonly associated with successfully repositioned drugs but also identify new general criteria which should be included to select potential candidates in future studies.

Another online database recently released is Drug-Central [61]. This tool is defined by the authors as an open-access drug compendium gathering multiple types of data through cross-referencing to external resources. Drug-Central is assembled around three kinds of contents. Firstly, there is a list of pharmaceutical active ingredients. They are directly linked to medchem properties, description of pharmacological actions, first approval status, indications and access to external ref-

erences and list of synonyms. Mechanism of action and information about bioactivity are also provided. These two features give access to the second type of content, that is, a set of drug target pharmaceutical formulations with target annotations and target classification. The third kind of content, linked to the list of pharmaceutical active ingredients, is the pharmaceutical formulation with access to the marketing status, dose formulation administration and drug label. DrugCentral includes a user interface and all different types of data come with adapted classification and extraction features.

The platform called "Open Targets" is another good example of a flexible user-friendly tool [62]. The motivation behind the implementation of this platform was that the analysis of progress through development pipelines showed that failures, occurring particularly in the later clinical stages, are often explained by an initial lack of correctly established connections between the target and its influence on physiology and disease. To address this issue, different organizations, initially Biogen, the EMBL European Bioinformatics Institute, GlaxoSmithKline and the Wellcome Trust Sanger Institute, launched a common initiative called the "Target Validation Platform" to provide comprehensive and up-to-date data including but not limited to relevant genetics and high throughput genomics data for drug target selection and validation. The goal is to better value genetic information from genome-wide association studies (GWAS) and Mendelian inheritance in the identification and prioritization of potential target. It is worth emphasizing that this kind of information is also of great interest when performing a DR study. The platform presents a hybrid format and multiple search, classification, upload and extraction features including API capabilities. As a database, it contains public domain data sources containing core data types of primary importance to target validation. This includes rare and common disease genetics, somatic mutations in cancer, transcriptomics (comparisons from microarray or RNA-seq experiments), approved drugs (that engage a target and treat a disease) and clinical candidates, animal models with gene knockouts and phenotypes concordant with human disease, biochemical pathways that are affected by disease and associations of targets with disease in the biomedical literature identified through text mining. All these data are also linked to the initial source to allow a continuous update of the information. In order to navigate through these data, a scoring scheme was developed to describe the overall confidence and strength of a target-disease association. The scoring scheme takes into consideration all the evidence available from many data types and is based on the concept of a target-disease association object, which is used to capture and summarize the available information linking a target to a disease for a given experiment or database resource. Using this concept, score computation combines the frequency representing the relative occurrence of particular target-disease evidence together with the severity expressing the magnitude or strength of the effect described by the evidence. Finally, overall confidence is assigned for the observation that generates the target-disease evidence. The application supports two main work-flows. The user can either start from a particular target and ask what diseases are associated with a given target or start from a particular disease and look for which targets are associated with this disease. It should be emphasized that the design of the platform is initially based on advice from scientists and managers working in pharmaceutical research and development, as well as academic researchers interested in drug discovery. This methodology was followed in order to take into account how they identify and prioritize targets, and the paths they take toward validation. This makes this kind of tool adapted for all scientists working in the area independently of their domain of expertise.

It is worth emphasizing that the existence of repurposing specific databases and the increasing number of DR investigations make it possible to understand the specificities behind the use of data for DR and can also be used to identify general properties that contribute to successful repositioning studies. Such analysis of DR information was performed in the reference [60] where authors established that including pathway cross talks, shared genetic architectures and prevalence of disease comorbidities as additional data types and analytical strategies into DR pipelines could contribute to obtaining more accurate results. Furthermore, by compiling various physicochemical properties of small molecules in RepurposeDB, these authors also concluded that a molecular code equivalent to the drug-likeness estimation method Lipinski's Rule of 5 could be constructed and used to predict drug repositioning potential.

To conclude, the implementation of these databases also gives us an opportunity to learn about the major drawbacks faced by scientists when they want to use large sets of data for DR studies. The most common of them being that drug targets listed in public resources are often inconsistent and unreliable [63]. Implementing DR databases with unified annotations is thus necessary. Furthermore, these databases are also required in addition to the already existing databases because

the DR process requires access to diverse information not necessarily belonging to the standard scope of omics databases. The tools presented in this section are an answer to this lack of centralized databases and poor reporting standards for DR investigations. The availability of such platforms will help to design better DR investigations in the future and could also contribute to a more systematic, easier and larger collection of data. For example, it was estimated that around one-fifth of all available drugs are prescribed off-label. Most of such off-label uses being initiated by clinicians and then shared after establishing efficacy. Unfortunately, quite often, the observations of these off-label uses, the first proofs of DR, are not systematically published as research papers or case reports and they are finally lost for the scientific community [60]. Trying to handle this last issue, Cho has recently released a tool called COnstruct cheMical and BIological NEtwork (COMBINE) [64]. This tool is not specifically devoted to DR studies. Nevertheless, this platform and the concepts behind its assembly elicit features worth mentioning. Indeed, rather than being purely data-centric, COMBINE is designed as a user-centric drug discovery platform which, while taking into account the multidisciplinary nature of drug discovery research by combining various data types and sources, allows scientists to keep track of research history corresponding to any stored datasets or experiments of interest. This includes negative findings and exploratory activities usually not published properly. This should prevent the useless repetition of previous works, and allow researchers to plan their research more efficiently as they will gain a better understanding of what has already been done.

2.2. Web-Tools as Computational Methods for Drug Repurposing

The algorithm presented in the reference [65] called ksRepo has attractive characteristics to enable users to use any data inputs for computational drug repositioning. Thus, although, this is not a web-based tool, ksRepo constitutes an interesting answer to the compatibility problems faced by researchers when using computational DR methods. In practice, ksRepo utilizes two inputs. Firstly, an arbitrary database containing transcriptomic compound exposure data used as a reference for comparison and the case-control disease gene expression dataset. Both of them can come from any type of platforms, the only requirement is the availability of a common identifier that can be used for conversion to entry IDs. The method works by comparing a single complete gene expression profile to a number of signatures (*i.e*. short compound-gene interaction lists). All genes belonging to the expression profile are considered independently of their significance in order to guarantee an overlap between the gene expression profile and the signatures. Those sets of genes are used to compute a Kolmogorov-Smirnov (KS) enrichment score. The computation will assign highly positive KS scores to signatures with highly enriched genes and small or negative KS scores to signature with unenriched or inversely enriched signatures. To circumvent the fact that the KS test statistic does not have empirical distribution, the significance is calculated using a bootstrapping method. The complete method is implemented in four R functions. The first one is devoted to the calculation of the KS enrichment scores, two others perform the bootstrapped p-value calculation and the fourth one which is a wrapper which calls the other function and format the outputs.

The method developed by Lee *et al*. [66] is called DeSigN and is available as a web-based platform. It is designed for associating gene signatures with the drug response phenotype based on IC50 data. As the first method described above, DeSigN also uses a reference database that contains a set of pre-defined gene expression profiles representing a set drug response data corresponding to 140 drugs. The input which must be provided by the user is a set of differentially expressed gene signatures. The core of the method is a pattern-matching algorithm based on a KS test which evaluates the degree of similarity between the user input and the gene expression profiles of the reference database. The reference database contains a set of baseline microarray and drug sensitivity data extracted from the Genomics of Drug Sensitivity in Cancer (GDSC) project. Depending on the IC50 value, the cancer cell lines drug response phenotype was classified either as resistant or sensitive. A list of DEGs was obtained for both resistant and sensitive phenotypes using the limma algorithm and further sorted and converted into ranked lists according to the gene moderated t-statistic. The rank-based pattern matching algorithm is based on the KS test similar to the one used in the Connectivity Map [67]. It returns a ranked list of inhibitors with the highest Connectivity Score between the DEG and the ranked-order gene expression profiles of the database. The statistical significance of the ranked list is performed using a permutation approach.

The web-based platform presented in the reference [68] is a hybrid tool that integrates both GWAS and Phenome-Wide Association Study (PheWAS) reposition datasets with pre-computed drug-gene-disease relationships and include search and export options.

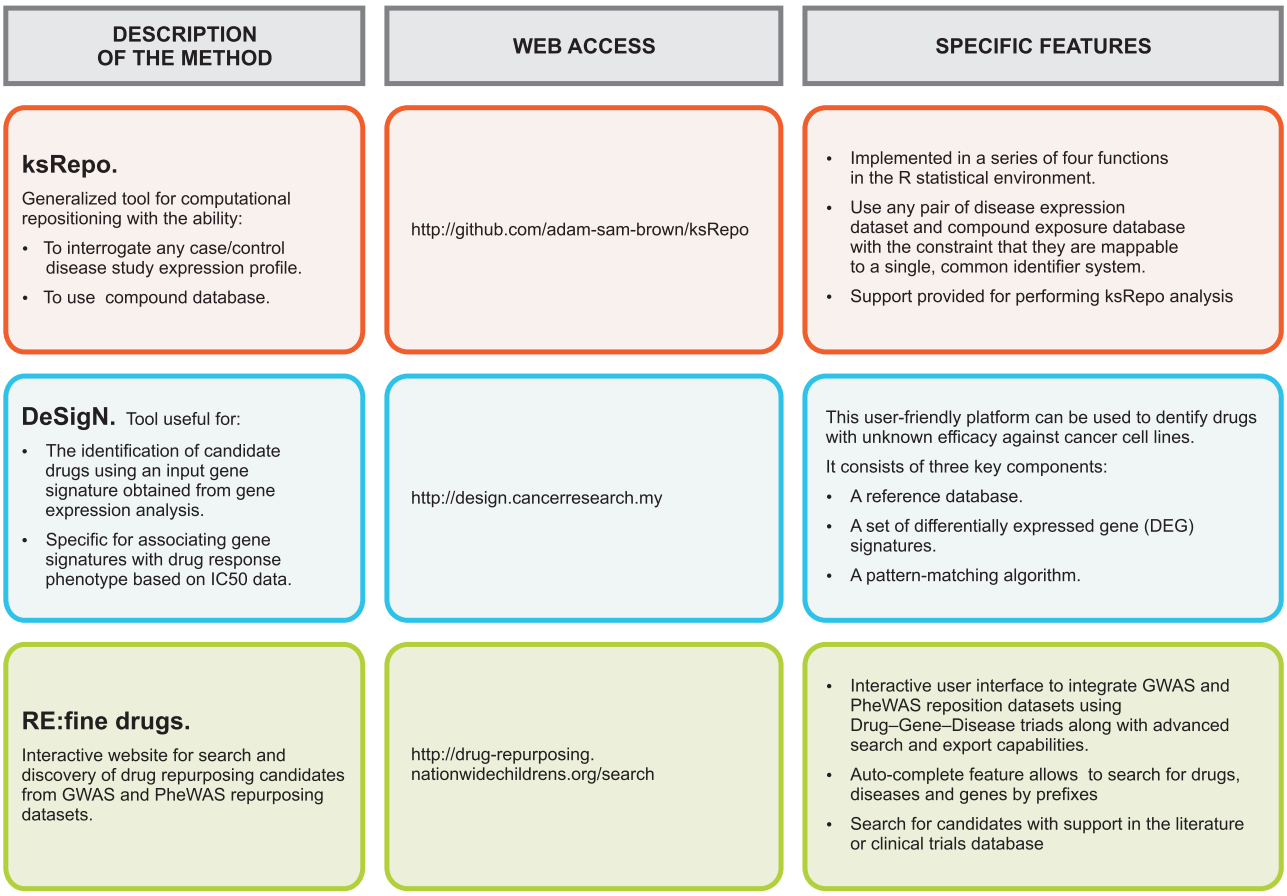

Fig. (2). Description of the main features of some web-based methods and hybrid tools designed for an easily and straight forward use for investigating DR opportunities. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

GWAS and PheWAS can be used as target-based methods to discover additional disease indications of the same drug target by leveraging the associations between a gene and multiple diseases. The primary resource of this tool is based on a previously published PheWAS dataset of around 52,900 drug-disease pairs of interest for investigating DR opportunities. Extraction and prioritizing of the set of drug-disease were done using a method developed in the reference [69]. The associations between drug and genes and between genes and diseases were assembled by firstly extracting drug-gene relationships (including direct and indirect gene targets for drugs) from DrugBank. Secondly, gene-disease relationships were generated under a hypothesis-generation framework with a p-value < 0, 05 using data from GWAS and PheWAS resources. Then the triad was completed with the potential drug-disease relationships computed by combining gene-disease pairs and drug-gene target pairs. The biological relevance of the suggested DR opportunities as well as the eventual novel findings was estimated by checking the co-occurrence of a drug and disease in literature and clinical trials database.

It should be emphasized that even if these methods have been validated (*i.e.* as being able to generate biological relevant hypothesis in various kinds of conditions), ranked list of predictions obtained using computational DR methods should be considered as a set of a priori suitable candidates under some hypothesis without automatic statistical validation. Consequently, all candidates should undergo a meticulous validation procedure including among others, *in vitro* validations. However, a relatively straightforward approach to gain some insight into the suitability of the candidates is to perform a preliminary and partial validation through a literature search. A literature search can be performed in a systematic way using methods called literature-based discovery (LBD) [70-72]. These text mining methods are useful to find new disease-drug relationships hidden within full-text articles as well as to assess the biological relevance of already identified candidates. For instance, in the reference [73], a method combining table classification and relationship extraction to extract drug-side effect pairs to investigate relationships between drug side-effects and toxicity is developed. The method uses extractable tables from on-

cological full-text articles as an input. Then a clean drug and side effect lexicon is created and the tables are classified into drug toxicity-related tables and non-related ones. The lexicon and other manually curated clean drugs are used to extract drug-side effect pairs from the tables. In the reference [74], a text mining-based ranking learning method that aims at extracting disease-gene relationships and gene-drug relationships relevant for DR is presented.

Finally, it is also important to notice that besides the set of biological criteria used by computational methods to extract a list of candidates other factors such as cost of drug, availability, method of administering, side effects and other factors can also have an important impact in the clinical setting. Thus, it may be of interest to consider a large portion of any ranked list of candidates for validation instead of considering just a few top-ranked candidates [66].

2.3. A standard Database for Analytic Validation of Computational Repurposing Methods

With all the computational methods implemented for DR, two questions need to be answered. Firstly, how useful, such methods are in producing clinically efficacious repurposing hypotheses and secondly how can we compare the accuracy of the various methods available. As pointed out in the reference [75], databases used as gold standards strongly vary from one study to another. This makes difficult to correctly assess a given method or to compare the performances of different methods. Furthermore, there is no agreement about the proper method to perform validation of computational predictions and a different strategy can be used depending on the kinds of data available. As summarized in the reference [75], there are mainly three methods of validation commonly used: validation with a single example or case study of a single disease area (CSV), sensitivity-based validation only (SV) and both sensitivity and specificity-based validation (SSV). Each of these methods comes with its specific required sets of data. As summarized in Fig. (**3**), these three methods do not elicit the same reliability or the same level of analytic rigor. One of the main reason which prevents the most rigorous validation method to be applied is that most data used as an input usually contain many reliable positive examples, *i.e*. a drug is effective against a disease, but much less high confidence negative examples [75]. This issue has been recognized for

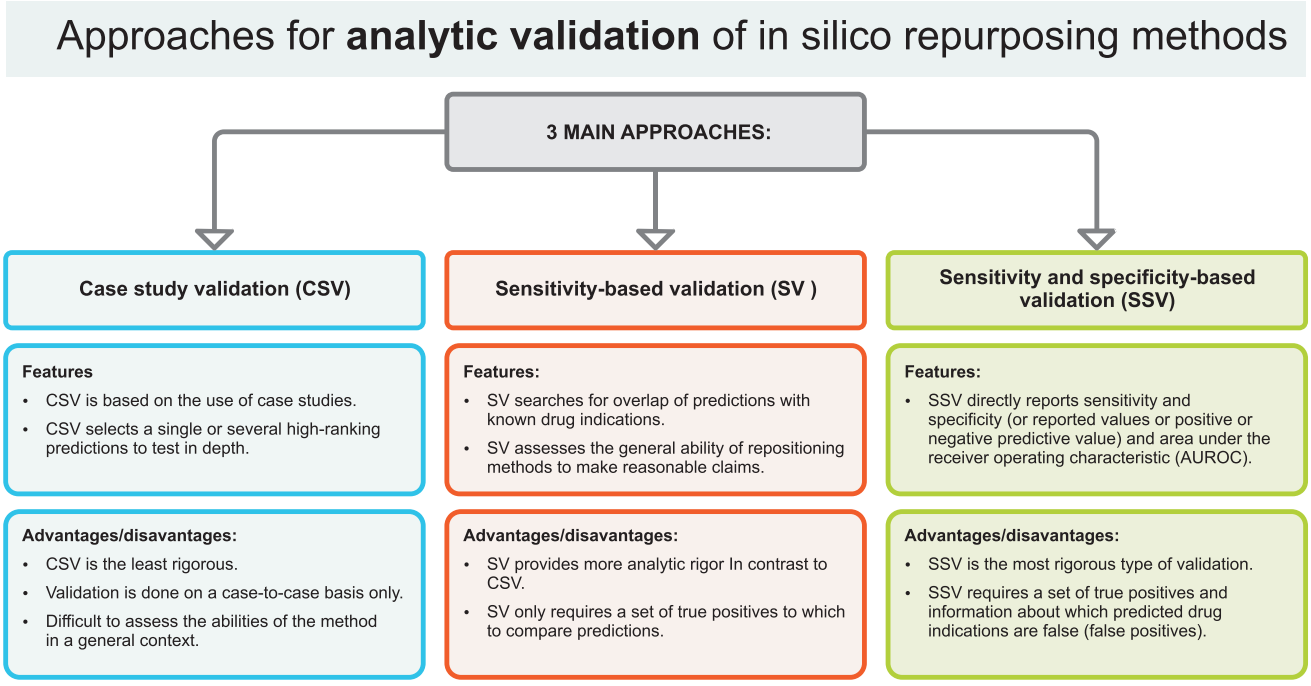

Fig. (3). Three kinds of approaches are commonly used to perform the analytic validation of new computational DR methods. Although the method assessing both sensitivity and sensibility abilities are the most accurate and reliable when it comes to confirm the capabilities of the DR algorithm to generate meaningful new prediction, it is also the most constrained in terms of input data required. Methods have been developed for overcome the lack of false positive cases and a specific database has been recently created to provide scientists with the required datasets for method validation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

a long time and adapted computational methods have been designed to handle this specific issue [77].

However, the problem is not that true negatives do not exist. Indeed, the American Association of Clinical Trials (AACT) database from the Clinical Trials Transformation Initiative website actually contains such information. The key issue is that this information is not always accessible or is widespread through different sites. As a result, gathering all the required data when building a new computational method or performing a computational DR procedure can be a long and tedious process. To address these issues, a web-based database consisting of both true positives (approved drugs), and true negatives (failed drugs) has been recently implemented [78]. This database called repoDB contains 1571 drugs and 2051 United Medical Language System (UMLS) disease concepts, for a total number of 6677 approved and 4123 failed drug-indication pairs. Unsuccessful drug-indication pairs were obtained from the AACT database whereas currently approved drugs, and

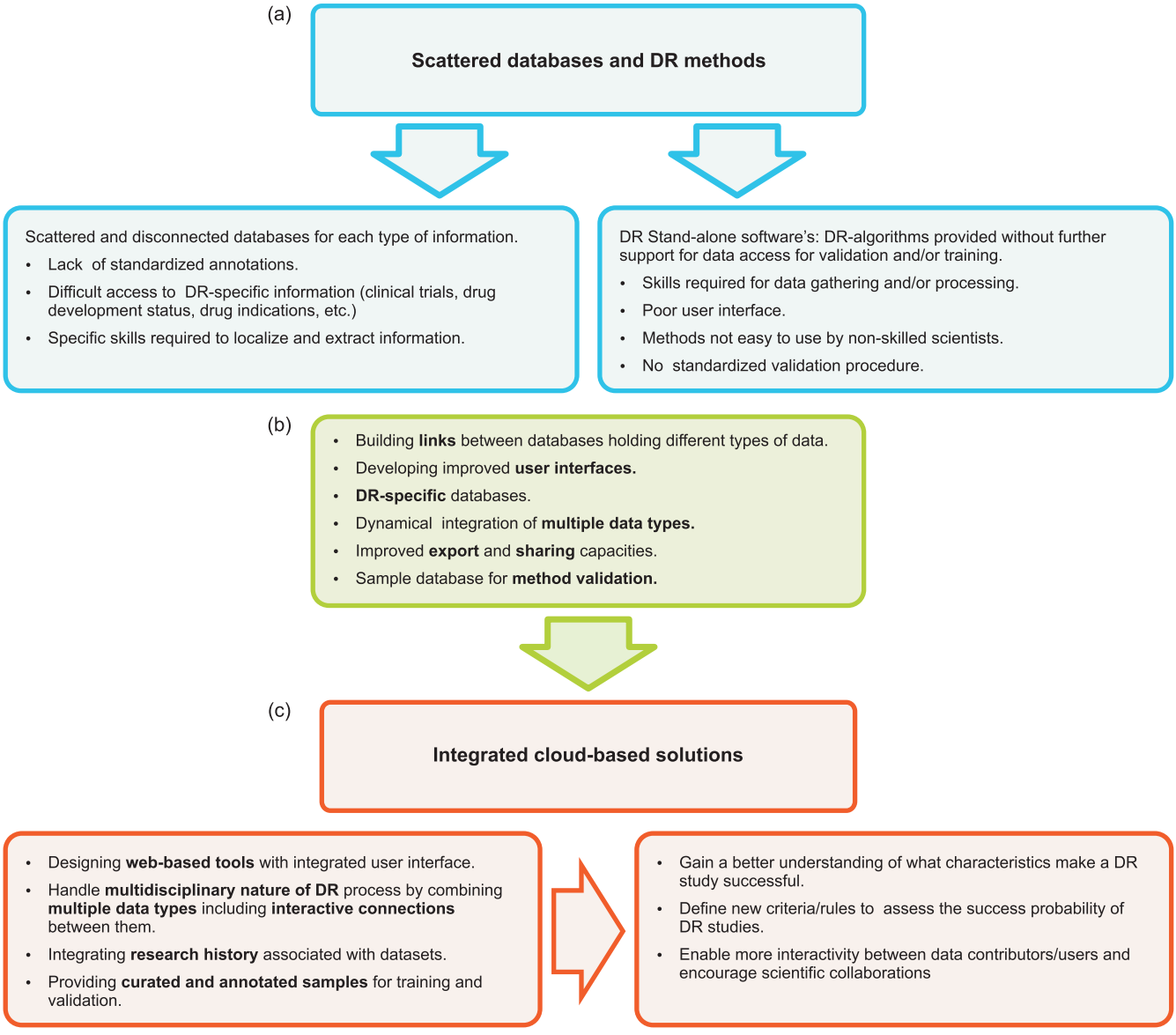

Fig. (4). (**a**) Initially, databases and algorithmic methods for DR were scattered and disconnected from each other making their use by non-trained scientists difficult. Identifying the most appropriate method and sets of data for training or validation could also be complex. (**b**) Major improvements had to be done at various levels to develop more accessible tools with integrated and connected contents and better sharing and export capabilities. (**c**) Current tools are now being designed to integrate not only adapted data and methods specific to DR studies but also practical experience of users and scientists allowing a faster and more efficient share of information about success or failure of DR studies. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

their indications were downloaded from the DrugCentral PostgreSQL database. A web application allowing browsing subsets of the data is another attractive feature of this new tool that scientists can use to benchmark more easily their computational DR methods.

2.4. A Case Study

There are numerous works using computational DR which have been published. A comprehensive description of computational DR workflows, including case studies, is presented in the reference [79]. The recently published results on computational DR of mifepristone for human vestibular schwannoma (VS) [80] is a good example of how the resources described above can be successfully applied. To identify FDA-approved drugs with potential for repositioning in VS, the platform ksRepo was used to perform a computational screen. The required input was obtained from a meta-analysis of primary human VS tissue based on the expression data from two datasets which identified 405 genes as significantly dysregulated in VS. ksRepo used the meta-analytic expression profile as input to screen a picture of tumor-related gene expression against the known interactions of 1,155 FDA-approved drugs. The steps included the identification, using a comparative toxicogenomics database, of chemical compounds known to reverse abnormal expression of listed genes and the matching of promising compound interactions against FDA-approved drugs, through DrugBank. ksRepo returned 36 drugs with potential for repositioning from the VS meta-analysis including classes of drugs that have shown limited efficacy against this tumor, such as glucocorticoids, tyrosine kinase inhibitors, and histone deacetylase inhibitors. The list of drugs with high potential for repositioning was further reviewed by neuro-otologists specializing in VS management to select mifepristone, a progesterone receptor antagonist, as a candidate worthy of further validation. This example demonstrates how computational DR of FDA-approved drugs, in which data-driven analyses of gene-compound interactions are used to identify new indications for approved drugs, provides a new promising approach for therapeutic solutions.

CONCLUSION

The identification of new indications eliciting a high success rate in clinical studies is a major obstacle faced by all DR studies and the possibilities offered by computational DR methods present many advantages [81]. Nevertheless, performing a successful computational study remains a complex multi-step process where various technical components intervene. Gathering, integrating and simply being aware of the existence of data of interest within the context of a given DR study is the very first step and probably the most critical for computational DR. The fact that biomedical data are available in many different formats and were initially spread within various databases using different conventions have made early research in this field tedious. This difficulty and other technical issues, summarized in Fig. (**4b**), are progressively solved by the continuous development of online tools and databases. Indeed, these tools are more easily accessible and specifically designed for supporting computational DR studies. These initiatives contribute to make computational DR methods more attractive among the scientific community and offer a new perspective of research and cooperation between researchers Fig. (**4c**). One can expect that computational DR will continue to gain more attention in the future especially with the encouraging results showing the success of drug candidates which were initially predicted using computational methods [82].

LIST OF ABBREVIATIONS

DR	=	Drug Repurposing
NPC	=	Pharmaceutical Collection
UPLCMS	=	Ultraperformance Liquid Chromatography-mass Spectrometry
GWAS	=	Genome-wide Association Studies
COMBINE	=	Construct Chemical and Biological Network
KS	=	Kolmogorov-smirnov
IP	=	Intellectual Property
GDSC	=	Genomics of Drug Sensitivity in Cancer
DEG	=	Differentially Expressed Gene
PheWAS	=	Phenome-wide Association Study
LBD	=	Literature Based Discovery
CSV	=	Case Study Validation
SV	=	Sensitivity-based Validation
SSV	=	Sensitivity and Specificity-based Validation
AACT	=	American Association of Clinical Trials
UMLS	=	United Medical Language System
VS	=	Vestibular Schwannoma

FDA	=	Food and Drug Administration
DMSO	=	Dimethyl Sulfoxide
RMA	=	Robust Multi-array Average

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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