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REVIEW

Informatics on Drug Repurposing for Breast Cancer

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Abstract: Moving a new drug from bench to bedside is a long and arduous process. The tactic of drug repurposing, which solves "new" diseases with "old" existing drugs, is more efficient and economical than conventional ab-initio way for drug development. Information technology has dramatically changed the paradigm of biomedical research in the new century, and drug repurposing studies have been significantly accelerated by implementing informatics techniques related to genomics, systems biology and biophysics during the past few years. A series of remarkable achievements in this field comes with the practical applications of in silico approaches including transcriptomic signature matching, gene-connection-based scanning, and simulated structure docking in repositioning drug therapies against breast cancer. In this review, we systematically curated these impressive accomplishments with summarization of the main findings on potentially repurposable drugs, and provide our insights into the current issues as well as future directions of the field. With the prospective improvement in reliability, the computer-assisted repurposing strategy will play a more critical role in drug research and development.

Keywords: drug repurposing, breast cancer, CMap, network, molecular docking

Introduction

One of the ultimate missions of biomedical research is to connect human diseases with causal genes and effective drugs. The successful deciphering of the human genome sequence at the beginning of this century accelerated the elucidation of the associations between genes and diseases. However, drug development remains daunting due to the lengthy bench-to-bedside process and the extremely high cost and low success rate. Drug repurposing refers to developing approved and investigational chemicals or biologics for novel utilization beyond their initial medical indications. With compounds having existing research basis and risk elimination, this "drug-recycling" approach could significantly reduce the time and cost of introducing novel drugs. Previous advancements, including successful drug repurposing examples and late-stage clinical candidates arising from deliberate repurposing studies, proved the feasibility and reliability of this tactic.[1]

Breast cancer (BC) is a heterogeneous disease that occurs in the epithelial tissue of the breast and is the leading cause of cancer death among female cohorts, with approximately 627,000 died cases worldwide in 2018.[2] Although management for certain BC subtypes has been greatly improved over the past decades, and up to 30 BC drugs received the Food and Drug Administration (FDA) approval between 2010 and 2020, there is a continued need for the development of therapies for patients with treatment-resistant or refractory disease.[3] Besides, some subtypes, such as triple-negative breast cancer (TNBC), still lack targeted therapies.[4] Therefore, as a shortcut to drug discovery, drug repurposing has already become an essential supplementary means for BC drug developers,[5] and more than a dozen medicines have been approved for BC treatment through this method.[6]

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Repositioning an old drug for a specific disease was estimated to save 3–5 years compared to de novo drug development due to the well-defined pharmacodynamics and pharmacokinetics, as well as known side effects and metabolic profiles.[5] In the past, some redirected drugs were discovered by accidental findings in the retrospective clinical analyses.[1] For example, Minoxidil, once for hypertension on the market, was identified with an adverse effect of hair growth and is now a popular treatment for pattern hair loss and baldness. Several other reprofiled drugs were spotted via experimental approaches, including pharmacological assay and in vitro screening of compound libraries.[1] Fingolimod was the first oral disease-modifying therapy approved for multiple sclerosis. The initial indication of this drug was transplant rejection, and the new use was revealed by pharmacological and structural analysis.

Either occasional observations or labor-intensive experimental screenings are often not hypothesis-driven.[7] In contrast, pinpointing a drug with (1) a specific transcriptomic perturbative effect (Figure 1A), (2) a certain target connected to the undruggable gene/gene to be drugged in a pathway/network (Figure 1B), or (3) designated docking ability and binding stability (Figure 1C), through in silico way is more directional. In addition to this strong purposiveness, the high-throughput-and-low-cost feature makes the computational approaches promising in substantively facilitating drug discovery and availability. In this review, we focused on and summarized the advances in the innovative methodology driven by advanced informatics for BC drug repurposing with the curation of main findings on potentially repurposable drugs, and discussed the associated limitations and future directions in the field. We sincerely hope our review could bring clues and inspiration to the practitioners devoted to BC drug discovery.

Transcriptomic Signature Matching

Theoretically, when two drugs lead to a similar gene expression profile alteration, they might have a therapeutic effect on the same disease. Here, a study guided by this forward transcriptomic signature matching theory (Figure 1A) was described first.

The transcription factor estrogen receptor α (ERα), a driver of cancer progression was expressed in about 70% of BC cases.[8] ERα-positive BCs were treated with endocrine therapy (ET) agents that interfere with ERα signal. Busonero et al constructed a particular "estrogenic signature" downregulated by conventional ERα antagonists in the human breast cancer cell MCF-7.[9] With the 57-gene signature, they screened more than 60,000 compounds in the Connectivity Map (CMap)[10] to find drugs with a similar downward signature. A list of candidate drugs was generated by comparing the concordance of gene signatures. Three drugs including mitoxantrone, thioridazine and menadione were selected for the subsequent experimental validation and eventually, thioridazine was identified as the preferential one with the ability to induce ERα degradation and inhibit the proliferation of ERα-positive BC cells.

As with reverse transcriptomic signature matching, a drug inducing transcriptomic changes opposite to those in a disease is considered to hold the potential to therapeutically reverse the illness (Figure 1A). Reverse matching utilizes prioritized genes from the result of differential gene expression analysis of disease transcriptomic data. Generally, top and bottom-ranked genes are selected as the signature of the disease. This transcriptomic signal is then compared with that generated from the expression profiles of drug interferences. Finally, the degree of negative correlation determines the drug usability and priority.

Vasquez-Bochm et al compared a reported signature containing 25 upregulated and 14 downregulated genes of breast cancer stem cell (BCSC), to the cell-line transcriptomic changes induced by over 1300 compounds in CMap.[11] They identified five candidate drugs with reversed signals. Subsequent in vitro experiments confirmed that lovastatin was an effective BCSC-targeting drug by inhibiting SOX2 promoter transactivation and reducing mammosphere formation efficiency.

CMap[10] for signature matching query is a famous cloud-based computing infrastructure with a database containing over one million gene expression profiles from thousands of compounds and reagents tested in multiple cell types. Thanh et al proposed DeCoST (Drug Repurposing from Control System Theory) based on the system control paradigm to tackle the drug repurposing tasks, and compared its performance with CMap.[12] Before matchmaking, genes overexpressed and under-expressed in disease were marked by 1 and −1 respectively, while genes that were known to be activated and

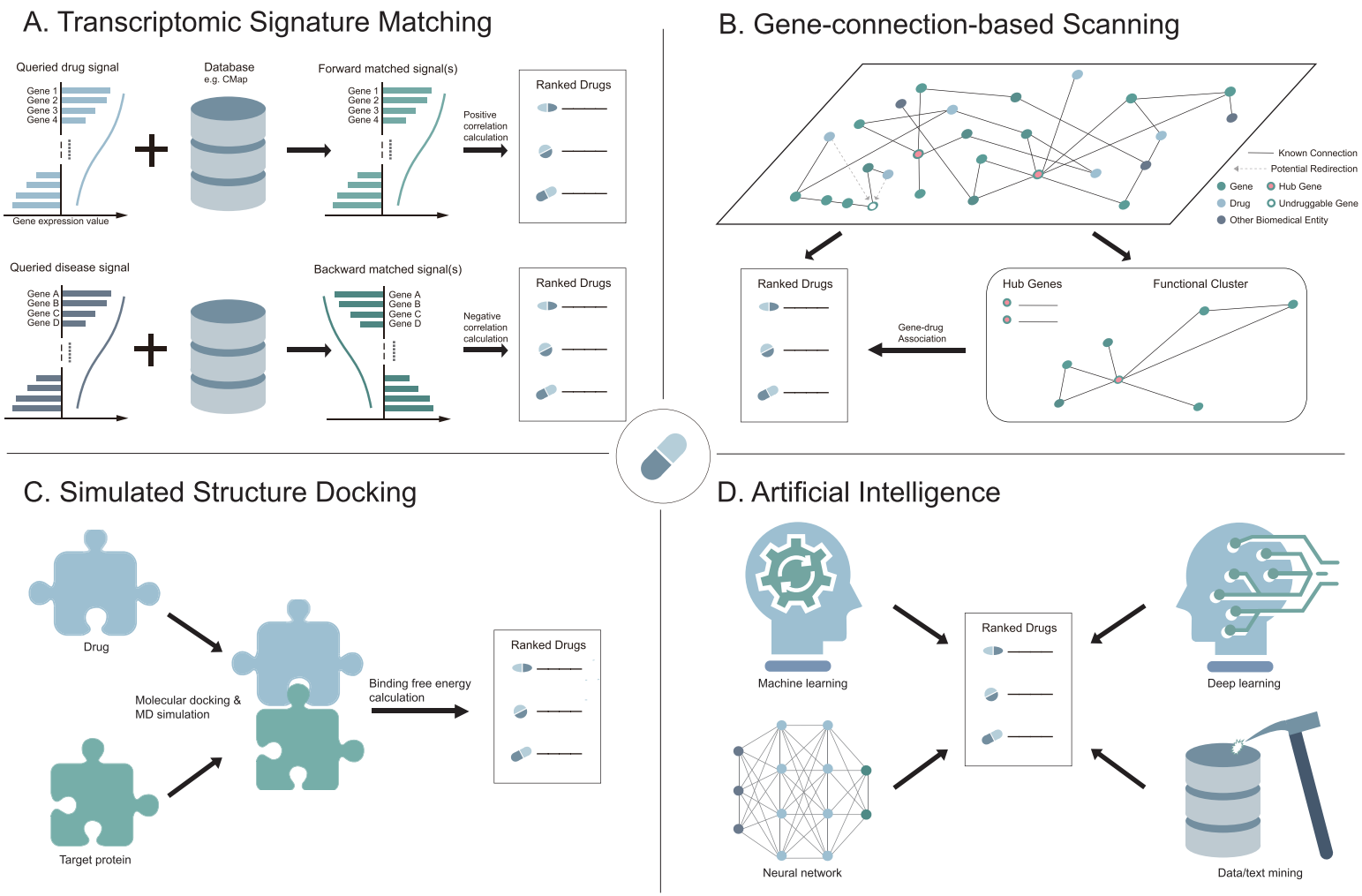

Figure 1 Illustration of four informatics-driven approaches for breast cancer drug repositioning described in this review. (**A**) Transcriptomic signature matching. (**B**) Gene-connection-based scanning. (**C**) Simulated structure docking. (**D**) Artificial intelligence.

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inhibited by a drug were quantified as +1 and −1 separately. Via reverse matching, DeCoST reprofiled eight drugs for ERα-positive BC and two for ERα-negative. The authors held that their work could provide complimentary capability to CMap for that DeCoST utilized tissue-level expression profiles while CMap used cell-line-level.

Appropriate query transcriptomic signal selection is crucial for the signature matching strategy. However, determining the optimal query signal is tricky in a real scenario, and the selection criteria vary drastically among studies.[13] In order to solve this issue, Chan et al developed Dr Insight (Drug Repurposing: Integration and Systematic Investigation of Genomic High-Throughput data), which employed order statistics to directly measure the reverse association between disease and drug-perturbed expression data genome-wide.[14] This automated tool eliminated the need for subjective selection of fixed-sized query signatures and identified five new drug candidates for BC using The Cancer Genome Atlas (TCGA) dataset.

BC is a highly heterogeneous disease, and genomic and transcriptomic characterization differ significantly among patients. This inter-tumor heterogeneity subdivides BC at the molecular level, and each subtype has unique treatment schedules. Mejía-Pedroza et al developed a pathway-based drug repositioning method for BC subtypes.[15] Based on two public large-scale gene expression datasets, the authors found the most deregulated pathways for each subtype via a robust probabilistic manner. Each deregulated pathway was associated with its known pharmacological targets according to information from the Drug–Gene Interaction Database (DGIdb).[16] These associations were finally classified to generate a contextual prioritization of pathways and drugs in BC subtypes. With this method, 79 drugs over eight significantly deregulated pathways displayed potentialities for transcriptomic recovery, and individualized drug regimens were provided for two patients with basal subtype.

Single-cell transcriptome sequencing technology has enabled the detailed characterization of intratumoral heterogeneity in BC.[17,18] He et al invented a drug repurposing recommendation tool inspired by single-cell RNA data.[19] This tool identified differentially expressed genes (DEG) between tumor and normal cells within each cell cluster (type), and then queried against its drug reference library to seek and rank compounds which significantly reversed the expression pattern in a single cluster or multiple clusters. The tool's performance was validated with public TNBC data and several top-ranked drugs were found to have been approved by FDA or used in clinical trials.

Gene-connection-based Scanning

The development and progression of BC is a systematic process involving multiple interactions among different genes. Theoretically, a genotype-phenotype association could make the gene a prospective drug target for that altering the effect of the gene would contribute to achieve a desired clinical outcome.[20] However, if the gene product, ie, a protein or an RNA molecule could not be perturbed via compounds, directly or indirectly connected genes upstream or downstream of the same pathway, or among the interactive network, could be chosen as alternative drug targets (Figure 1B). Through this compromise, existing drugs aimed at those connected genes could be explored for repurposing.

Protein–protein interaction (PPI) networks characterize physical interactions between proteins. Ma et al systematically investigated the cluster of PPI network of BC cell line MCF-7 by using four cluster detection algorithms and compared the performance of these algorithms for drug target prediction.[21] The authors revealed that the Walktrap (CW) cluster detection algorithm performed best in extracting functional clusters from the network. By integrating the extracted clusters produced by CW with drug-induced differential gene expression data, potential drugs redirected to BC were provided. In this research, the authors pointed out that the connections in the PPI network should be modified by the transcriptomic landscape of specific cell lines, as the dynamic gene expression profiles among cell types caused differential functional interaction patterns between the molecular components. In another research, Turanli et al noted that different subtypes of BC had different PPI networks.[22] They presented an integrated omics approach with transcriptome and interactome data to identify active PPI networks in TNBC patients. EED, DHX9, and AURKA were found to be aberrantly activated in TNBC tumors compared to both normal tissues and other BC subtypes, and thus proposed as potential drivers of proliferation as well as candidate drug targets. The authors queried each gene signature separately against the L1000CDS2 database[23] and identified ten drugs with potentiality to reverse the aberrant activity in basal-like tumors.

Azam et al built a drug-disease network by considering all interactions between drug targets and disease-related genes in the context of all KEGG human-signaling pathways.[24] A repurposing score was computed for each drug-disease pair by integrating expression data into the network. Finally, a ranked list of drugs with potential therapeutic effects for the given disease was generated based on the repurposing score. This method proposed six candidate drugs with preliminary evidence from preclinical or clinical studies against BC. Also with KEGG data, Firoozbakht et al developed a network-based integration approach to find drugs for each BC subtype.[25] Copy number variation and aberration data were employed in their work for disease subtyping.

In optimization theory, the maximum flow problem is defined as finding a feasible flow through a flow network that obtains the maximum possible flow rate. In drug repurposing, the idea is that proteins with the maximum flow to disease-related risk proteins in a network could be regarded as an alternative drug target for the disease. Based on this theory, Islam et al constructed a maximum flow-based PPI network through which new drug targets were identified from the targets of the FDA drugs and their associated drugs for chronic disease treatment.[26] Existing drugs were repurposed based on the maximum flow values of each newly identified target protein. The top four repurposed drugs for BC had been reported by other independent studies, demonstrating the feasibility of this framework.

A hub in a network refers to a core point which connects multiple elements and is therefore regarded as a vital network component. Neoadjuvant chemotherapy (NAC) was the frontline treatment for patients with locally advanced BC before tumor excision. However, drug resistance remained a major issue in NAC. Hence, identifying the key genes involved in driving NAC resistance and targeting them with approved drugs was a cost-effective solution. Detroja et al identified 1446 DEGs from public RNA-seq datasets of NAC-resistant BC patients.[27] Subsequently, key hub genes were obtained via gene co-expression network analysis and Multiple Correlation Clustering. With four publicly available databases, they finally identified 19 prospective drugs, including eight FDA-approved ones for redirecting to the hub genes.

According to the drug-gene-disease relationship, a protein–protein network could evolve into a direct drug–drug network. Di et al[28] developed an R-based package PriorCD for cancer drug repurposing by first considering the drug functional similarities at the pathway level. The research team constructed a functional similarity network between drugs by enriching mRNA and microRNA expression data into pathway activity profiles and correlating them with drug activity profiles derived from the drug–disease relationship. Drug prioritizing scores were calculated based on a global network propagation algorithm. The authors evaluated and validated the performance of this in silico approach by using several kinds of public resource. At last, 14 prioritized candidate drugs for BC were provided and four were FDA-approved.

Gene network could be coupled with other networks consisting of heterogeneous biomedical entities. Al-Taie et al dissected TNBC patients into five subgroups based on genotypic data and clinical information including age, race and neoplasm subdivision, and discovered appropriate therapeutic candidates separately through drug repurposing.[29] In particular, this research team built a drug repositioning knowledge network which employed a gene-centric schema including relations between genes, pathways, GO domains, disease and drugs. With the curated knowledge base, the researchers repurposed drugs for each subgroup based on the gene expression patterns and the relationship between genes and other biomedical entities. They concluded that different targeted mechanisms should be suggested for different BC subgroups.

Simulated Structure Docking

Computationally predicting the complementarity of the binding area between a drug and a therapeutic target (Figure 1C) is another strategy for drug repositioning. This kind of method simulates the dynamic behavior of compound-target binding and predicts the stability of the binding compound by calculating the binding free energy. The recent progress using this structure-based virtual screening for BC drugs is briefly described here.

EGFR and HER2 were frequently overexpressed in BC and were targets of many approved anti-BC drugs.[30] Balbuena-Rebolledo et al obtained dozens of FDA-approved drugs structurally similar to lapatinib and gefitinib, two well-known inhibitors of EGFR and HER2.[31] These drugs were then investigated through a series of in silico prediction programs including virtual molecular docking, molecular dynamics (MD) simulation and the molecular mechanics

generalized Born surface area (MM-GBSA) binding free energy prediction. Specifically, the best binding structures in the docking studies were chosen using the criteria of the lowest energetic ligand conformations at the receptor's binding site. Then, the prevalence of the interactions was evaluated during MD simulation and unstable protein-ligand complexes were discarded. Binding free energy was calculated to measure the binding affinity, and compounds with higher affinities for EGFR/HER2 than those of known inhibitors were identified. In the in vitro assay, five drugs showed growth inhibitory activity on BC cell lines at micromolar concentrations. With the same series of in silico methods, Kandasamy et al predicted four compounds as potential repurposed drugs for target blocking in BC.[32] Their in vitro studies demonstrated the anti-proliferative property of a known anti-psychotic drug Pimozide.

The Notch signaling pathway was a pivotal regulatory component in BC etiology and progression, and most associated genes were overexpressed in BC.[33] One method of effectively blocking NOTCH activity was preventing its cleavage at the cell surface with γ-secretase inhibitors. Pathak et al used molecular docking analysis to virtually screen 1615 FDA-approved drugs and found that Venetoclax was superior in simulated docking capability to one of the standard γ-secretase inhibitors: RO4929097.[34] The Venetoclax-γ-secretase complex was computationally confirmed in stability and thus was inferred with a probable inhibitory effect on NOTCH activity. Rui et al found that many γ-secretase inhibitors had various side effects, and impeding the Recombination Signal Binding Protein for Immunoglobulin Kappa J Region (RBPJ), an essential transcription factor in Notch signaling, could be a more specific way.[35] The authors collected 10,527 pharmacologically active compounds by integrating four public database and used the docking module of Molecular Operating Environment, the GROMACS software package and the molecular mechanism/Poisson–Boltzmann surface area (MM-PBSA) binding free energy prediction for virtual screening of RBPJ inhibitors. Fidaxomicin, schaftoside and acarbose were identified as the most robust RBPJ binders for the strict occupation of the binding site and the formation of hydrogen bonds with multiple key RBPJ amino acid residues within the binding area. After cellular assay and in vivo anticancer investigation, FDA-approved fidaxomicin was identified as a potential RBPJ inhibitor against BC.

Drug repurposing strategies could also be employed in finding new indications for natural active compounds in clinical trials or still under investigation. Maruca et al explored the probable anticancer activities of native compounds from mushroom species.[36] In their study, an in-house chemical database was utilized for the virtual screening against the isoform 7 of the Histone deacetylase (HDAC), a gene that regulated cellular proliferation, differentiation and development in BC. Via in silico docking simulation, MD simulation and cell viability assay, the authors proposed ibotenic acid as a lead compound for developing novel HDAC7 inhibitors.

Artificial Intelligence

Artificial intelligence (AI) has enabled leaps in discovering novel drug targets and drug-disease associations in multiple cancer types.[37] Recently, AI technologies including machine learning, deep learning, neural network and data/text mining (Figure 1D) have been implemented in the investigations of BC drug repositioning.

Song et al developed a feature-based method to predict unknown drug–target interaction (DTI) called PsePDC-DTIs.[38] The authors investigated seven common classification algorithms of machine learning and observed that random forest outperformed others in the quality of a prediction model. In exploring new targets for BC treatment using identified risk genes, the PsePDC-DTIs model provided ten potential drugs, six of which were found with direct or inferred evidence. Some traditional machine learning approaches showed limits in efficiently analyzing high-dimensional datasets extracted from drugs and targets. Given this, You et al proposed LASSO (least absolute shrinkage and selection operator)-based deep learning method to predict DTIs.[39] The method successfully identified five BC drugs with literature evidence. As one form of deep learning, the neural network was also applied in drug reprofiling against BC. Chen et al proposed a graph neural network model called GraphRepur.[40] The research team constructed a graph containing drug–drug links information and drug gene expression signatures. They established a drug repurposing prediction model by extracting the drug signatures and topological structure information in the graph. Among the predicted BC drugs by the model, ten had supported literature. Data/text mining is a process of finding and extracting patterns from massive datasets using computer programming, and it greatly facilitates knowledge discovery in many fields. Wang et al developed a recommender system named ANTENNA for the prediction of novel drug-gene-disease associations by mining large-

Table 1 Brief Introduction and Candidate Drugs of Each Research Collected in This Review

Strategy	Ref.	Brief Introduction	Candidate Drugs for Repurposing*
Transcriptomic signature matching	[9]	A 57-gene "estrogenic signature" downregulated by conventional ERα antagonists was constructed and CMap was utilized for forward matching.	Mitoxantrone, thioridazine, menadione.
	[11]	A reported signature containing 25 upregulated and 14 downregulated genes of breast cancer stem cell was used and CMap was utilized for reverse matching.	Fasudil, pivmecillinam, ursolic acid, 16,16-dimethylprostaglandin E2, lovastatin.
	[12]	DeCoST, a framework based on the Control System Theory was proposed and tissue-level expression profiles were utilized in the framework.	Erbitux, flutamide, medrysone et al for ERα+ BC; Daunorubicin and donepezil for ERα- BC.
	[14]	Dr Insight, an automated tool eliminating the need for subjective selection of query transcriptomic signatures was proposed.	15-delta prostaglandin J2, trichostatin A (TSA), LY-294002, wortmannin, trifluoperazine
	[15]	A pathway-based method for BC subtyping was proposed and contextual prioritization of pathways and drugs was generated.	Individualized drug regimens for two patients with basal subtype
	[19]	ASGARD, a drug repurposing recommendation tool inspired by single-cell RNA data was proposed and compounds which significantly reversed the expression pattern in a single cell cluster or multiple clusters were ranked.	Fostamatinib and colchicine for advanced metastatic BC; Mebendazole and crizotinib for TNBC.
Gene-connection -based scanning	[21]	Four cluster detection algorithms were utilized to systematically investigated the cluster of PPI network of BC cell line MCF-7 and compared in the performance for drug target prediction.	Fulvestrant, tanespimycin, geldanamycin et al
	[22]	An integrated omics approach with transcriptome and interactome data was presented to identify active PPI networks in TNBC patients.	Selumetinib, trametinib, wortmannin et al
	[24]	A drug-disease network was built by considering all interactions between drug targets and disease-related genes in the context of all KEGG human signaling pathways.	Captopril, glibenclamide, fluorometholone et al
	[25]	Copy number variation and aberration data were employed in the development of a network-based integration approach.	Ruxolitinib, bromocriptine, deferiprone et al
	[26]	A maximum flow-based PPI network was constructed and new drug targets were identified from the targets of the FDA drugs and their associated drugs through the network.	Guanidine, phenethyl isothiocyanate, caffeine et al
	[27]	Key hub genes involved in driving neoadjuvant chemotherapy resistance were obtained via gene co-expression network analysis and Multiple Correlation Clustering.	Carfilzomib, bortezomib, Ixazomib citrate et al
	[28]	An R-based package named PriorCD for cancer drug repurposing was developed by first considering the drug functional similarities at the pathway level.	Amythiamicin A, zorubicin, daunorubicin et al
	[29]	A knowledge network based on a gene-centric schema including relations between genes and other biomedical entities was built.	Different targeted drugs were suggested for different BC subgroups

(*Continued*)

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Table 1 (Continued).

Strategy	Ref.	Brief Introduction	Candidate Drugs for Repurposing*
Simulated structure docking	[31]	FDA-approved drugs which were structurally similar to two well-known inhibitors of EGFR and HER2 were investigated through molecular docking, molecular dynamics simulation and MM-GBSA binding free energy prediction.	Terazosin, alfuzosin, prazosin, irinotecan, quinacrine.
	[32]	Drugs from the library of 1293 FDA-approved drugs to block all three target proteins including IR, ITGB1 and CD36 were investigated through the same series of in silico methods in.[31]	Capmatinib, ponatinib, naldemedine, pimozide.
	[34]	Virtual screening for γ-secretase inhibitors was performed via molecular docking and molecular dynamics simulation.	Venetoclax.
	[35]	Virtual screening for RBPJ inhibitors was performed via molecular docking, molecular dynamics simulation and the MM-PBSA binding free energy prediction.	Fidaxomicin, schaftoside, acarbose.
	[36]	Virtual screening for HDAC7 inhibitors was performed via molecular docking, molecular dynamics simulation and cell viability assay.	Ibotenic acid.
Artificial intelligence	[38]	A feature-based method to predict unknown drug-target interaction called PsePDC-DTIs was developed.	Erlotinib, caffeine, afatinib et al
	[39]	A LASSO (least absolute shrinkage and selection operator)-based deep learning method to predict drug-target interaction was developed.	Hypericin, ingenol mebutate, D-Myo-Inositol-Hexasulphate, hyperforin, carboxyatractyl oside
	[40]	A graph neural network model called GraphRepur was proposed.	Selinexor, mycophenolic acid, pitavastatin et al
	[41]	A recommender system named ANTENNA for prediction of new drug-gene-disease associations by mining a large scale of chemogenomics and disease association data was developed.	Diazoxide.
	[42]	Word2Vec, which conducted Literature-Wide Association Studies (LWAS) based on the text mining results from millions of cancer-related PubMed abstracts was developed.	Cytarabine, dacarbazine, hydroxyurea et al

Note: *Drugs with in vitro evidence are underlined.

scale chemogenomics and disease association data.[41] With this system, the authors predicted Diazoxide for TNBC targeted therapy. Ji et al conducted text mining in about 3.8 million cancer-related PubMed abstracts and identified 18 diseases similar to inflammatory breast cancer (IBC). As a result, 24 drugs were proposed for redirection.[42]

Discussion

The journey of obtaining a safe and effective medicine to market is long and arduous, and only a few dozen drugs are licensed officially each year. Behind are tens of thousands of failed candidate drugs. In the researches collected in our review (Table 1), a limited part of candidate drugs redirected against BC succeeded in in-vitro validations (Table 1 Column 4 underlined), not to mention further in vivo experiments and rigorous preclinical/clinical trials with high rejection rates.[43] One of the possible reasons is the uncertain predictive reliability by which general in silico strategies are always challenged. To be specific, first, the current reverse Transcriptomic Signature Matching manner (Figure 1A) commonly exploits disease signals generated from bulk RNA-seq data which reflects the expression profile of a cell mixture. However, not all these cells play equal roles in the disease or have a relationship to the ailment. Hence, the biased disease signal might lead to inaccurate drug matching. Second, the Gene-connection-based Scanning method (Figure 1B) is highly dependent on the existing knowledge base storing the information about the physical interactions between proteins (genes). Nevertheless, PPI databases contain a few false-positive interactions.[44] This defect could bring uncertainty to the final predictive results. Third, for the Simulated Structure Docking approach (Figure 1C), neither of the current binding free energy calculation methods is reliable enough in drug-target binding affinity prediction.[45]

Here, for each of the three main tactics mentioned in our review, we suggest a possible solution or direction for the future improvement of predictive performance:

1. Employing single-cell expression profile alteration data to pinpoint efficient drugs for particular cell cluster(s) allows for avoiding non-target cell clones.[46]
2. Integration of a PPI network in a multi-omics context is conducive to highlighting key proteins or central clusters in drug action and response mechanisms, and removing the false interactions.[47]
3. Cross-verification using multiple binding free energy calculation methods as all such methods currently have limitations and advantages that partially overlap and complement one another.[45]

This article summarized the recent progress of computational drug repurposing approaches in BC. Even though at the early stage of development, informatics-driven repurposing approaches are rational to serve as a preceding routine for preliminary drug screening prior to in vitro/in vivo assays. With the joint efforts of the whole community, this kind of repurposing strategy is promising in revolutionizing the present paradigm of drug research and development toward precision oncology.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Disclosure

H.L., Y.Y. and X.Y. are all employees of Changsha Kingmed Center for Clinical Laboratory. X.Y. is also an employee of Guangzhou Kingmed Center for Clinical Laboratory. All other authors declare no financial or non-financial competing interests in this work.

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