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Artificial intelligence unifies knowledge and actions in drug repositioning

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Abstract

Drug repositioning aims to reuse existing drugs, shelved drugs, or drug candidates that failed clinical trials for other medical indications. Its attraction is sprung from the reduction in risk associated with safety testing of new medications and the time to get a known drug into the clinics. Artificial Intelligence (AI) has been recently pursued to speed up drug repositioning and discovery. The essence of AI in drug repositioning is to unify the knowledge and actions, i.e. incorporating real-world and experimental data to map out the best way forward to identify effective therapeutics against a disease. In this review, we share positive expectations for the evolution of AI and drug repositioning and summarize the role of AI in several methods of drug repositioning.

Introduction

We reckon that Artificial Intelligence (AI) contributes to the ultimate unity of knowledge with actions, i.e. machine intelligence that perceives its environment and digests real-world data to take actions that maximize its chance of achieving goals. Long before AI became an active branch of computer science, it has been entertained by our ancestors and recorded by philosophers and litterateurs. Nevertheless, despite decades of developments, along with other aspects of scientific and technological advances, two of the three types of AI systems, artificial general intelligence or strong AI (e.g. the character Andrew Martin in the movie Bicentennial Man, who was able to deal with everything thrown at him by human life with human-like cognition and reasoning, and ultimately accepted as a member of human society) and artificial superintelligence (e.g. masterminds for robots uprising in dystopian science fictions that surpass the capacity of human intelligence and ability in everything we do) remain an illustration [1]. Meanwhile, there are great successes in realizing artificial narrow intelligence or weak AI, where goal-oriented systems were established to perform relatively singular tasks ranging from searching the internet, driving a car, or guarding a secured entry, to managing every connected part in a house, an assembly line, or a factory, to regulating certain aspects of daily life like traffic flow in the city and power grids in a country.

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Author Contributions

Z.Y. and S.T.C.W. planned and wrote the paper together, Z.Y. created the figures based on discussions with S.T. C.W.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Operating under established sets of constraints and limitations, ‘knowing’ through the ever-expanding technologies of data generation and storage, and reasoning through advanced machine learning and deep learning algorithms, weak AI systems are doing various jobs with accuracy and even assuming the role of trainer after beating the world’s best human players in games such as chess and Go [2,3].

Although full of promise and excitement since its first establishment as a scientific discipline in 1956, there have been several ‘AI winters’ featuring disappointments and loss of funding; yet through each ‘winter’, the AI community was able to establish new theories and approaches to overcome previous obstacles and attract renewed funding [4,5]. In the latest wave of AI, statistical deep learning methods took advantage of the advancement of computational power and availability of big real-world data to dominate AI research landscape. Given the widespread interests of applying AI to all aspects of lives and the chance of opening many new markets to grow business, industrial firms are joining academic institutes and government agencies as a major driving force for the development and deployment of AI. The combination of deep learning algorithms, high performance computing, and industrial powers has not produced successful transformation from weak to strong AI, yet the deep and wide incorporation of AI into the socioeconomic landscape created great opportunities for AI to evolve and become a driving force to unite ‘knowing’ and ‘doing’ in medicine.

Shortly after the end of the previous AI winter between late 1980s and early 1990s, the transformation from weak to strong AI was vividly depicted by the character of ‘The Doctor’ in the TV series of Star Trek: Voyager (1995–2001). As a holographic projected AI doctor who was designed as a short-term, task-oriented supplement to the medical staff during emergency situations, The Doctor was forced to step in as the medical chief for years and grew to be an integrated member of the USS ***Voyager.*** Given the unique characteristics of medical science, it is conceivable such a story about the growth and evolution of an AI system to be a trusted AI doctor. On one hand, dealing with the matters of life and death requires deep knowledge and proficient execution with accuracy, precision, and repeatability, which play into the strength of task-oriented AI and robotic systems. On the other hand, the efforts of respecting basic human rights are often hindered by so many disparities and socioeconomic challenges that a physician often requires exploring the most pragmatic therapeutic options acceptable by the patients and feasible to administer under the resource constraints. The exploration of pragmatic medical options starts as a compromise to limitations imposed by certain socioeconomic confinements, but when executed under rigorous scientific principles, such explorations may lead to new branches for medical science and optimized clinical practice. The development of bloodless surgery [6] provided a fine example for such pragmatic explorations. It was started as an effort to compromise with a group of patients who were candidates of heart transplantation but rejected blood transfusion due to religion belief. This ultimately prompted the surgeons to reconsider their over-reliance on blood transfusion during the transplantation and established novel technological standards and principles that eventually benefit many more heart transplant patients.

AI systems are being deployed in both healthcare and public health sectors as well as biomedical research. For example, smart wearable devices such as the Apple Watch are gaining momentum with FDA approval and double as readers for electrocardiography [7] and peripheral capillary oxygen saturation. Augmented intelligence decision supports and analytics are embedded with data sources big and small, ranging from personal wearable devices and electronic health record (EHR) to contact tracing systems covering the entire city, state, or country in order to provide timely reminders, flag adverse events, and request clinical assistance. A primary care physician longing for more time spent with the patients could equip the office with AI assisted scheduling and prescription management, natural language and voice processing enhanced access to EHR, and image diagnosis with deep learning tools. Yet when it comes to making treatment plans, the doctors tend to rely on their own judgment and medical knowledge. Although medical AI systems are sufficiently powered to find or recite optimal solutions to defined clinical diagnosis, those answers generated by the machine are often considered ‘optimal in vacuum’ [8,9]. Involving AI to generate hypotheses regarding patient care and training them to incorporate socioeconomic factors in due process during hypothesis generation would not only benefit the care providers, but also promote the evolution of AI to optimize patient care.

Drug repositioning is an attractive pursuit for AI to contribute and evolve. It aims to reuse existing drugs, shelved drugs, or drug candidates that failed clinical trials for different medical indications [10]. It could provide answers to diseases and conditions that attract limited attention or investments from pharmaceutical companies and thus would fill the gap of unmet medical needs. The repositioning of sildenafil citrate (brand name: Viagra) from a less-heralded hypertension drug to a world renowned therapy for erectile dysfunction [11] is one of the most well-known success stories of drug repositioning. Recent achievements do not even necessarily target a defined disease, but rather control side effects of therapies like chemotherapy induced diarrhea [12] and alleviating cancer drug toxicity [13] ***en route*** to improve patients’ quality of life and expand the patient population that can tolerate an effective treatment for devastating diseases. As showcased by the global frenzy of finding quick fixes in the beginning of the Covid-19 pandemic [14,15], drug repositioning can quickly become a hot topic when the standard drug discovery pipelines need much longer turn-around time to generate therapeutic options.

Unifying the knowledge and action thus forms the essence of AI in drug repositioning. Either taking advantage of the enriched data for existing drugs or shelved candidates and salvage them towards benefiting patient groups for less invested diseases and conditions [12,13,16,17], or providing the rationale for the best way forward when the world seems ready to rush into clinical trials based on high risk but far-from-perfect ideas [18–23], the application of AI in drug repositioning could promote constructive changes in both areas.

Advancements of drug repositioning studies require effective handling of multi-modality data

Drug repositioning studies converge multidisciplinary expertise from bioinformatics, cheminformatics, structural biology, medical informatics, systems biology, and drug

screening and leverage multi-scale, multi-modality datasets from transcriptomic and proteomics profiles, electronical medical records and medical imaging, to social media and epidemiology surveillance to gain comprehensive understanding of disease mechanisms and drug effects.

Figure 1 illustrates the workflow of several types of drug repositioning methods [10] as organized into three modules, i.e. data and knowledge, modeling, and testing. Computational modeling methods (light green boxes) are shown to be the key to unite knowledge and actions in drug repositioning methods, that is, taking advantage of ever-expanding knowledge bases and data resources regarding targeted disease (light yellow boxes) and drugs (light blue boxes) to prioritize candidates for multi-layer testing and validations. Each drug repositioning method described in the workflow presents unique requests and challenges for computational modeling that can be addressed by AI.

Phenotype-based methods

Phenotype-based methods of drug repositioning are based on solid models of disease phenotyping and use high-throughput and/or high-content screening to obtain drug candidates that achieve desirable phenotypes in the model, e.g. compounds that can clear phosphorylated tau tangles in a multi-plate cell-based assay for Alzheimer's disease drug screening [24,25]. Such methods do not require large amounts of pharmaceutical or biological information to start, but sophisticated biochemistry validations and meticulous follow-up studies are required to reveal mechanisms of action underlying the ability of the screening hits to achieve favorable phenotypes. Although often scolded as 'blind' or 'brute-force,' if applied to reliable disease models, phenotype-based methods can effectively cover large numbers of drug candidates and are regularly employed by large pharma companies and nascent biotech firms. The method is responsible for discovering a considerable portion of small molecules and biologics approved by FDA [26–28]. Off-label use of FDA approved drugs can be considered as a variant for phenotype-based methods as the underlying logic is to control the same biological process found in a different disease. For instance, Covid-19 pandemic has prompted a wide range of phenotype-based drug repositioning studies for candidates targeting different stages of virus infection [29–32].

It is worth noting that effective image quantification [33–36] is critical to the operation of phenotype-based methods, and the advancement of deep learning has drastically improved the performance of image quantification in high throughput and high content screening studies [37–40]. In addition, deep learning-based systems facilitate the incorporation of pharmaceutical, mechanical, and biological information, allow summarization of drug profile and toxicity [41], help identify novel mechanisms to achieve favorable phenotypes [42] ***en route*** to hit prediction, and enable smart ***in silico*** screening, which saves costs and time spent on ***in vitro*** screening.

Target-based methods

Target-based methods search for drugs that can impact known disease related target. It can be achieved through ***in vitro*** and ***in vivo*** (in animal models like zebra fish or drosophila)

high-throughput/high-content screening of drugs targeting a protein or a biomarker of interest [43–45]. It is also feasible to carry out ***in silico*** screening through ligand-based screening or docking [46,47] to efficiently cover large searching space of compounds. Integration of target information into the drug repositioning process ensures a higher possibility of finding useful drugs. Drug chemical structure data was integrated with molecular activity and drug side effect data to check for drug similarity and predict drug-disease interactions [48]. An 'expression profile' was proposed by integrating 3-D drug chemical structure information, gene semantic similarity information, and drug-target interaction networks [49]. Free tools for compound-protein docking were being developed [50,51], and the results from multiple tools can be crosschecked and filtered [52], further facilitating the application of target-based drug repositioning.

Lack of reliable structure information for target proteins have long been the bottleneck for expanding the usage of ***in silico*** compound-protein docking. Accurate prediction of protein structures has been actively investigated by the deep learning community [53,54]. The recently reported high predictive accuracy achieved by AlphaFold [55] presents a great opportunity for pursuing compound-protein docking to a wider range of disease targets.

Knowledge-based methods

Knowledge-based methods apply bioinformatics or cheminformatics approaches to include the available information of drugs, drug-target networks [56–60], chemical structures [60], clinical trial information (adverse effects) [61,62], FDA approval labels [63], signaling or metabolic pathways [64] and drug effect profiles stored in EHR [65,66] into drug-repositioning studies. Knowledge-based methods incorporate known information into discovery of new disease mechanisms, including new targets for drugs, novel drug-drug similarities, and new diagnostic or prognostic biomarkers for diseases. While the discovery of artemisinin fifty years ago was inspired by a handful of records extracted from large amounts of traditional Chinese medicine literatures [67], today there are large amounts of drug effect profiles for patients stored electronically in EHR databases, providing opportunities for data mining or hypothesis generations on the beneficial [68,69] or adverse side effects [70] of drugs towards comorbidities. Natural language processing (NLP) is a branch of AI that has been used to extract, mine, and incorporate published information in medical science literature [71–73]. Its recent integration of deep learning further improves the efficacy and reliability of NLP programs–the quantity and quality of information used in the knowledge-based drug repositioning methods remains a critical condition for their success.

Signature-based methods

Signature-based methods analyze multiple types of -omics profiles, e.g. transcriptomics, proteomics, and meta-bolomics, of certain diseases and drug effects, use computational methods to extract target signatures, and search for candidate drugs with maximized impact on the target signatures. Whole-genome data allows for the discovery of off-target effects for drugs or unknown disease mechanisms, thus bringing a new dimension on the disease-drug relationships than the aforementioned methods of drug repositioning. Pioneered by the

cMAP platform [74], where a database of drug effects on cancer cell lines allows the users to provide a customized target signature, there have been various public platforms with similar hypothesis generation functions, culminated by the Touchstone module in Clue.io [75,76], the direct heir of cMAP, where specific signatures were eliminated, and the similarity calculated across the whole transcriptomic profile was used to rank candidate compounds.

A major barrier for expanding signature-based methods using public data sources is the compatibility of drug effect profile to the biological questions at hand, as the drug effect profiles for Clue.io were generated by applying certain dosages of compounds for certain time periods on a small number of cancer cell lines. As non-cancer research communities speed up the efforts to build their own -omic databases for drug effects, it may be beneficial to carry out the signature-based drug repositioning in an iterative loop of prediction→validation→modeling, as shown in Figure 2. The key would be obtaining a list of successful vs. failed predictions after each round of validation, carrying out classifications between those transcriptomic profiles, and refining the target signature for a new round of prediction. While classification has been one of the most basic functions of AI, the ability of incorporating the validated and classified results to generate new target signatures with improved success rates for predicting hits would demand more sophisticated machine learning and decision-making algorithms.

Pathway- or network-based methods

Pathway- or network-based methods use disease omics data, available signaling or metabolic pathways and protein interaction networks to reconstruct disease-specific pathways that provide the key targets for repositioned drugs [77,78]. Compared with the signature-based methods, this scheme requires in-depth modeling on the disease-specific omics data, incorporation of existing knowledge on pathways and functionally related gene sets, and the ability to prioritize significantly expressed targets. Due to the level of information redundancy within the pathway databases, a dataset on obesity-induced adipose inflammation reported that 12 of top 20 significant pathways center around the same group of genes [79,80]. Training AI programs to understand the hierarchical structure of the signaling networks is critical to improve the efficacy of this category of drug repositioning methods.

Targeted mechanism-based methods

Targeted mechanism-based methods are becoming highly popular in the era of precision medicine. Such methods integrate treatment omics data, available signaling pathway information, and protein interaction networks to delineate the unknown mechanisms of action of drugs [81–84]. The advancement of technologies like single cell RNA sequencing (scRNAseq) and spatial transcriptomics facilitates the in-depth modeling of disease phenotypes and allows novel types of drug targets, e.g. cross-talk between different cell types in a microenvironment or a signaling sub-network needing to be targeted by combinations of multiple drugs, to be defined. In a recent work, epithelial–stromal cross-talk signaling networks were found as potential drug target for chemo-resistant ovarian cancer [85]. Meanwhile, the systems biology community is busy creating novel methods to predict

the synergy effects between drugs and create optimal combinations for network-level targets [16,86,87].

Requests on data sources and the strategies regarding imperfect datasets

Large amount of high-quality data is required in various steps within an Al-based drug repositioning pipeline. The most computational intensive, and thus data-hungry, steps are (1) generation of target signatures and (2) ranking of candidates based on the comparisons between the target signatures and drug effect profiles from the candidates. The quality of drug effect profiles has been a bottleneck in Al-based drug repositioning. On one hand, the popular choice of EHR data was originally designed for billing and financing purposes and often fail to document detailed drug effects on critical disease phenotypes, let alone molecular level disease biomarkers [88,89]. On the other hand, the most widely used transcriptomic dataset for drug effects, i.e. cMAP/Clue.io L1000 dataset, was generated mostly on cell lines related to solid tumors, covered very limited range of dosage and treatment time, and was a mixture of measurements of mRNA transcript for 987 landmark genes and mathematically inferenced expression profile for another 11 350 genes in the transcriptome [75]. Worse still, the reproducibility between data generated in different iterations of cMAP project is limited with respect to matching top-ranked drug candidates [90].

While the drug repositioning community eagerly awaiting the generation of public drug effect profiles applicable to various target diseases, AI combined with rigorous functional validations already showcased the ability of overcoming vague and noisy data resources and answering carefully defined drug repositioning questions. Scalable and accurate deep learning workflows are being developed [91,92], while cMAP/Clue.io L1000 dataset helped produce candidates for diseases far beyond solid tumor in adults, e.g. childhood cancer [16], leukemia [93] and SARS-Cov-2 infection [94], and also contributed in designing of drug combinations [87,95].

Several points can be made from those success stories regarding the preparation of data sources and dealing with imperfect datasets encountered in AI based drug repositioning.

In-house omics profiles for extracting disease-related target signatures

In-house omics profiles for extracting disease related target signatures are valuable resources. When planning the data generation, evaluate the ‘effect size’ achievable by the experimental design and technology in use, e.g. for comparing the difference of average through student’s t-test, the effect size can be evaluated by Cohen’s ***d*** [96]:

$$d = \frac{M_2 - M_1}{SD_{pool}},$$

where

$$SD_{pool} = \sqrt{\frac{SD_1^2 + SD_2^2}{2}}$$

***SD**pool* was obtained through investigation of the variance amongst samples. Different experimental designs require different strategies for evaluating desired effect sizes [97], and such evaluations are critical for obtaining enough samples and achieve sufficient statistical power. In addition, target-mechanism-based drug repositioning often requires multiple sets of data from each subject, e.g. transcriptome profiles from multiple cell types to model cell–cell communication [85,98], or matched multi-omics profiles to model the systems-level coordination [99]. The data generation procedures should be carefully planned to avoid batch effects.

Extracting target signatures from public resources

Extracting target signatures from public resources requires sufficient statistical power, yet the dataset also needs to be evaluated to select the samples that best fit the hypothesis of the specific drug repositioning applications. A highly re-used [100,101] single-cell RNAseq dataset from Alzheimer's patients [102] contains patients with different levels of diseases, defined by both codex categories and image phenotypes. For larger data resources like TCGA, specialized tools were developed to summarize the metadata [103]. Researchers will benefit from an effective selection of outside dataset with matching disease subtypes and phenotypes that matches their specific applications.

Crosschecking the compound ranking results based on public drug effect data

Crosschecking the compound ranking results based on public drug effect data will also help improve the success rate of the AI-based drug repositioning. The touchstone tool of Clue.io provides the option of ranking the candidates based on all available or certain individual cell lines. We try to understand the genetic characteristics of the cell lines used in generating cMAP/Clue.io L1000 dataset and compare the candidate ranking results from all cell lines vs. certain subgroups. When possible, we will take positive control assays and generate in-house drug effect profiles to obtain reliable and concise target signature for the query with L1000 dataset. After the initial query, we will download the transcriptomic profiles for the top candidates and perform pathway overrepresentation analysis. This strategy evaluates whether the candidates are impacting the target signature in pathway level and compensates the bias of cMAP algorithm towards outliers.

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Abbreviations

AI	artificial intelligence

EHR	electronic health record
NLP	natural language processing

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Summary

- The field of drug repositioning has dealt with the coldest of cold cases over the years while also enjoying the status of the hottest of hot shots during the Covid-19 pandemic. Meanwhile, AI has been full of promise since its infancy, but experiencing several hype cycles, followed by disappointments, criticism, funding cuts, and then followed by renewed interest years later.
- Recent enthusiasm and optimism on AI, especially the sub-field of machine learning, coupled with the widespread availability of big real-world data in healthcare and experimental data in disease biology and drug profiles led to a dramatic increase in funding and investment of drug repositioning and could bring cost-effective therapeutic solutions for various unmet medical needs quickly to the clinics.
- While there are many types of AI methods, seemingly only a few of them, notably deep-learning and natural language processing, have been successfully incorporated into drug repositioning.
- It is necessary to deploy the full repertoire of AI methods and establish effective feedback through testing and validation to train the AI models to trim existing information and generate meaningful hypotheses.
- Search and optimization algorithms need to be updated to answer questions involved in drug combination design.
- Logic programing and automatic reasoning are necessary to summarize validated results and create new target signatures.
- Novel probabilistic methods are needed for reasoning involving incomplete or noise EHR datasets.
- New graph convolutional neural network and machine learning constructs have to be built to provide more explainable processes and models that allow human users to comprehend and trust the results and output created for subsequent experimental validation and clinical studies.

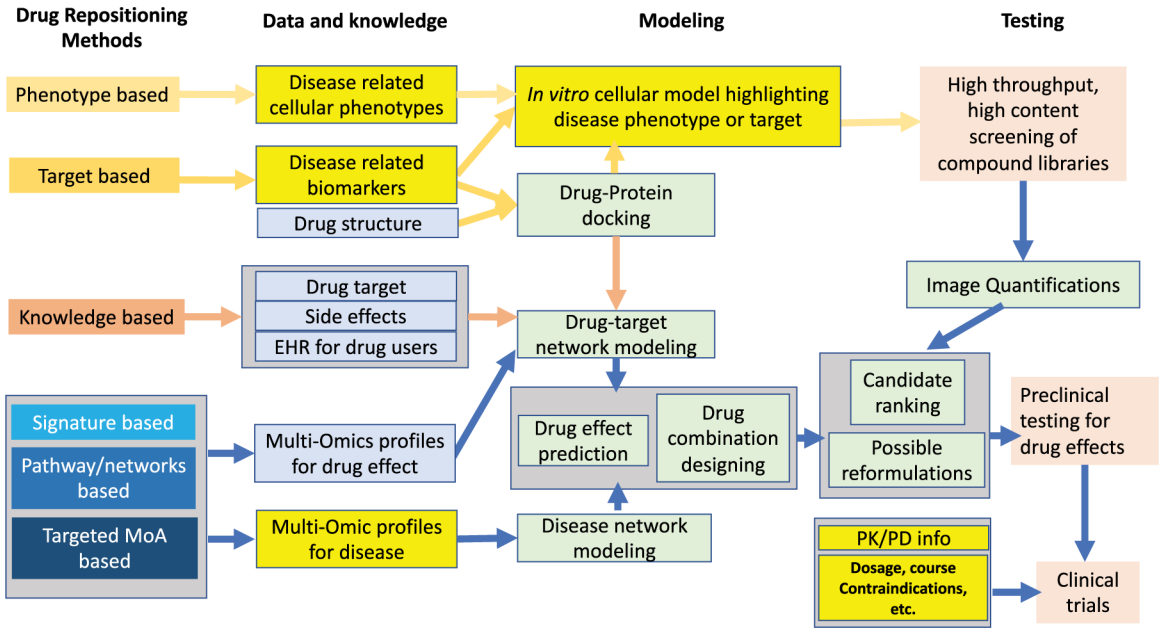

Figure 1. The conceptual workflows for major types of drug repositioning methods.

Each type of methods features unique combinations of disease (light yellow boxes) and drug (light blue) related data and knowledge, computational modeling methods (light green), and rigorous testing and validation.

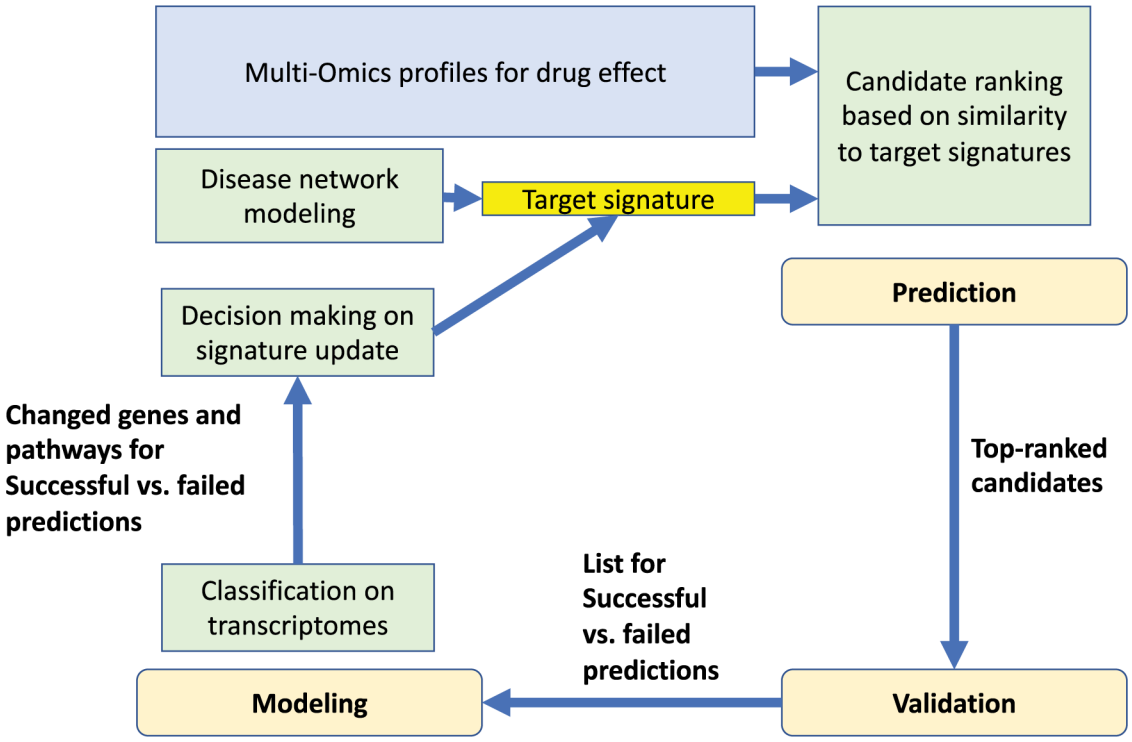

Figure 2. An iterative loop of prediction→validation→modeling for improving the success rate of candidate predictions.

This iterative workflow converges disease (yellow box) and drug (blue box) related data and knowledge and uses computational modeling (light green) guided validation to compensate for the concerns of low predictive accuracy caused by factors such as imperfect drug effect profiles.