Original Article

A REVIEW OF ARTIFICIAL INTELLIGENCE IN TREATMENT OF COVID-19

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DOI: 10.47750/pnr.2022.13.S01.31

Abstract

Drug repurposing, also known as repositioning, is a technique in which existing drugs are repurposed to treat emerging and complex diseases like COVID-19. Because of the potential for shorter development timelines and lower overall costs, drug repurposing has emerged as a promising strategy. In the significant data era, artificial intelligence (AI) and network medicine provide cutting-edge information science applications to define disease, medicine, therapeutics, and identify targets with the smallest error. We present guidelines for using AI to accelerate drug repurposing or repositioning, for which AI approaches are formidable and required in this Review. We discuss how to use AI models in precision medicine, such as how AI models can accelerate COVID-19 drug repurposing. Rapidly developing, powerful, and innovative AI and network medicine technologies can help to accelerate therapeutic development. This Review makes a strong case for using artificial intelligence-powered assistive tools to repurpose medications for human disease, including during the COVID-19 pandemic.

Keywords: Artificial imtelligence, COVID-19, Precision.

INTRODUCTION

AI pioneers imagined creating machines that could sense, reason, and think like humans in the 1950s—a proof-of-concept known as general intelligence AI. (1) Significant advances in AI have been made possible by rapid advances in computing power and memory storage, as well as a previously unseen wealth of data and the development of advanced algorithms. Computer vision, voice recognition, and other fields of digital pathology and natural language understanding data examination are examples of AI applications. Similarly, by extracting hidden patterns and evidence-based biomedical data, artificial intelligence (AI) has transformed the pharmaceutical industry and discovery. AI has been used in drug discovery and development by pharmaceutical companies and start-ups. (2) The Watson Health platform from IBM searches for drugs in massive amounts of textual data, such as laboratory results, clinical reports, and scientific findings publications. (3)

In this Review, we will focus on AI technologies for drug repurposing, a subfield of drug discovery that provides quick and cost-effective solutions for therapeutic advancement. These benefits are especially noteworthy. COVID-19 is a global pandemic caused by severe Coronavirus 2 (acute respiratory syndrome) (SARS-CoV-2) in which drug discovery from scratch is nearly impossible (See Figure 1). As a result, the pandemic presents an excellent opportunity to introduce advanced AI algorithms in tandem with drug repurposing via network medicine.

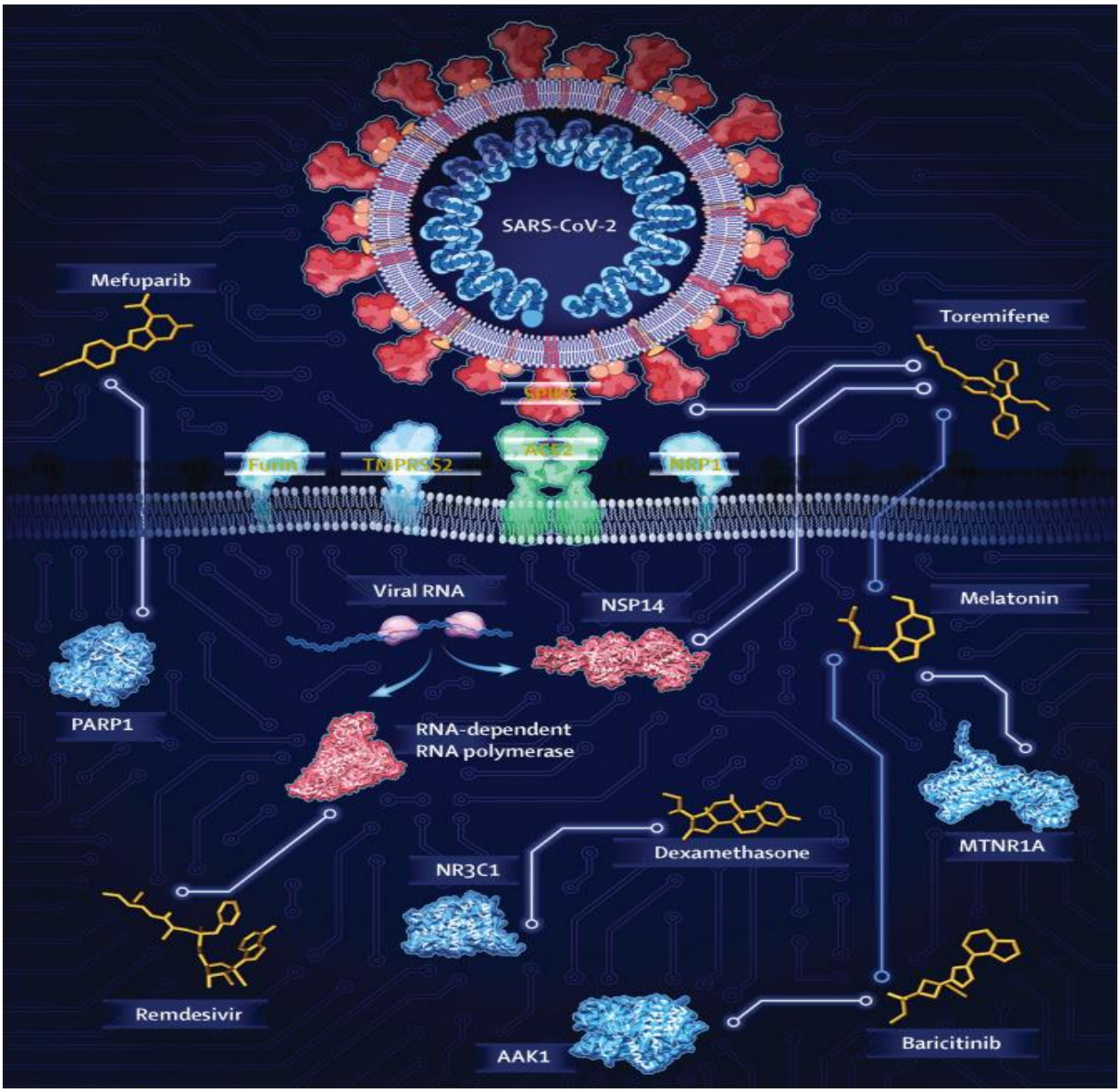

Figure 1. Overview of AI assisted drug repurposing for Covid 19.

EMERGING CHALLENGES AND OPPURTUNITIES IN DRUG DISCOVERY

According to one study, pharmaceutical companies spent $26 billion in 2015 to develop a new chemical entity, up from $802 million in 2003 approved by the Food and Drug Administration of the United States (FDA).(4) The rising cost of drug development is due to the large number of compounds to be tested in preclinical stages and a high proportion of randomized trials controlled trials (RCTs) that show no clinical benefit or when it comes to toxicity. Given the high attrition rates, high costs, and a slow rate of de-novo drug discovery, using well-known drugs to improve efficacy can help. At the same time, it is keeping side effects to a minimum in clinical trials. According to Nobel, Sir James Black, a Nobel laureate in pharmacology, stated, "To begin with, an old drug is the most fruitful basis for discovering a new drug." (5). Reusing or repositioning a drug is what drug repurposing, also known as drug repositioning, is all about. Reprofiling, also known as re-tasking, is a method of discovering new applications for approved or experimental drugs (including medications that have failed in clinical trials but have not been approved panel). Repurposing known drugs that have been tested in clinical trials for other applications can bring medications to patients because their safety has already been established. Academic institutions and government agencies have collaborated for decades to develop new pharmaceuticals much faster and at a lower cost than developing new pharmaceuticals.

Science funders have championed screening. Existing drug libraries with a variety of tests could be created. Discover new applications and observations that have resulted in medicines designed for a single disease locating applications in another

Some well-known examples are: erectile dysfunction treatment with sildenafil citrate,(6) thalidomide is used to treat myeloma multiforme,(7) as well as remdesivir for the treatment of COVID-19.(8) Indeed, the growing number of repositioned medications gave rise to the notion that a systematic A (hypothesis-free) screening of all known drugs could be conducted. Discover additional targets that are compatible. For example, the drug repurposing strategy is an effective solution for newly emerging diseases (9) COVID-19. Nonetheless, without knowledge of the entire drug-target network, developing promising and cost-effective approaches will be challenging to treat complex diseases effectively.(10)

Because drug targets do not operate in a vacuum, The molecular system is a complex system of proteins. Each cell's machinery, each cell's machinery, each cell's machinery, each cell's machinery, each cell'. A drug-target interaction (panel) should be investigated the context for integration (figure 2). (11) Interventions in Therapy are necessary to consider the disruption of the disease system properties (referred to as a network medicine [panel]), and Functionally, there is little to do with genetic and Only genomic events can be considered. 12 Observations and developments in Moreover, network medicine suggests that disruptions of the human interactome and cellular systems (panel) underpin the disease, which is the essence of the medication discovery and advancement (12).

Interplay between medication targets and human disorders may provide insights for future drug repurposing since a common functional protein-protein interaction network can explain how a treatment for one disease can target another via its interactions with various proteins. For instance, after an infection, SARS-CoV-2, a cousin of SARS, requires cellular components for reproduction (such as angiotensin I converting enzyme 2 [ACE2], transmembrane serine protease 2 [TMPRSS2], and furin; figure 1). (13,14) A new strategy to improve the success of COVID-19 drug repurposing involves systematically targeting viral protein-host protein interactions (the SARS-CoV-2 interactome). Using affinity purification mass spectrometry, an interactome with 332 high-confidence protein-protein interactions between 26 viral proteins and human proteins was built, the human proteins being targeted for interaction by the SARS-CoV-2 virus. The interactomeprioritised 1569 therapeutic candidates targeting host proteins in SARS-CoV-2. (15) Studies conducted demonstrated the antiviral properties of two agents: sigma-1 and sigma-2 receptor regulators, and mRNA translation inhibitors, such as zotatifin (i.e., haloperidol).

Another experiment investigated the interactions between the virus-host interactome and drug targets in the human interactome network by reanalyzing previously synthesised data16. A network-based methodology discovered 16 repurposed drug candidates to treat COVID-19. (16). It's essential to perform extensive investigation, which will include the use of AI and network medicine. Which protocols to take into account, what factors to focus on, and how to integrate different disciplines are all things this consideration raises (figure 2).

ALGORITHMS FOR ARTIFICIAL INTELLIGENCE AND RECENT ADVANCEMENTS

Convolutional Neural Network

Deep learning refers to a sub-field of machine learning that focuses on using hierarchies of transformations such as non-linear and linear transformations to explore data. (17) The most commonly utilised deep learning model is artificial neural networks. Non-linearly transforming the weighted sum of input feature variables, artificial neurons form the foundation of the model. The architecture of an artificial neural network is connected from input to output, layer by layer, through artificial neurons. The connection weights are used to balance the output via backpropagation of the trained sample's predictive loss. Data samples are often represented as vectors with FNNs. Aliper and his team, for example, applied FNN to classify drugs by their transcriptomic profile vectors into pharmaceutical therapeutic classes. (19)

Lenselink and colleagues used the ChEMBL database to compare the performance of various algorithms in predicting molecule and target activity.(20)The authors demonstrated how including target data can lead to improved models. Traditional machine learning methods, such as logistic regression, are outperformed by FNN. When images are used as input and each pixel is a feature variable, FNNs become infeasible due to the large number of weights. Convolutional neural networks (CNN; panel) are, on the other hand, particularly well suited to image processing. Instead of fully connecting neurons in adjacent layers, CNN uses filters (small matrices of weights) that perform a convolution operation on local patches of the images, significantly reducing the number of weights. CNN has been used to analyse chemical images in order to gain insight into drug therapeutic functions. (21) Based on structural information extracted by CNN, AtomNet, for example, predicts the binding affinity of small molecules to proteins. (22)

Some commonly researched types of data for medication repurposing include biological sequences. Despite both FNN and CNN making an effort to understand the sequential nature of the material, neither media accurately reflects the order of events. Neuron cells are recurrent cells that remain the same at each timestamp or sequence location while also learning new information in a sequence. In drug development, RNN models have generated targeted molecule libraries utilizing reduced molecular input line entry system codes, with the compounds represented as sequences.(23) Using a hybrid technique of graph neural network and RNN, Gao and colleagues established a method for predicting drug-target interactions.(24) To forecast whether any of the currently available antiviral medications had a chance of working against SARS-CoV-2, researchers built a

hybrid CNN and RNN model dubbed "Molecule Transformer-Drug Target Interaction."(25). The authors could computationally identify many antiviral medications known to combat SARS-CoV-2, including atazanavir, remdesivir, efavirenz, ritonavir, and dolutegravir.

VISUALIZATION-BASED REPRESENTATION LEARNING

Doctors use a network-based approach called medical knowledge graphs to refit approved pharmaceuticals with new disorders, which collect various medical entities (such as diseases, medications, and proteins) and then anticipate new connections between those approved drugs and diseases (e.g., COVID-19). (26)As nodes and edges are represented as low-dimensional feature vectors in a graph, techniques that rely on graph embedding are becoming increasingly relevant for link prediction. (27–30) We can quickly find successful medications for a given ailment by measuring the similarities between feature vectors of pharmaceuticals and disorders. Scalability may be an issue for the graph embedding method. Graphs in the real world are almost always massive. One to several million entities could be found in a medical knowledge graph. Systems like TensorFlow and PyTorch were initiallybuilt for data with predictable structures, but they may struggle when confronted with large-scale graphs. Therefore, various techniques have been made expressly for learning graphs from their representations. A good example is a system created by Zhu and colleagues called GraphVite, which can efficiently analyze tens or even hundreds of millions of nodes.(31)

Developing graph representation learning algorithms for drug repurposing is becoming a higher priority. Sosa and colleagues used the bio-medical literature to create a medication, disease, gene, and protein knowledge graph and then applied graph embedding techniques to determine the relationships between the different types of knowledge. (32)TheGysi et al. method was founded on a graph neural network and employed SARS-CoV-2, with 81 repurposing candidates identified.(33)BenevolentAI, Inc. built the knowledge graph by extracting medical information from scholarly papers, where they used machine learning to generate links with the information. (34) The pharmaceutical baricitinib, commonly used to treat rheumatoid arthritis, may also help fight COVID-19 with the BenevolentAI team's prediction that an AP2-associated protein kinase 1 suppressant can assist in this battle (encoded by AAK1; figure 1). CoV-KGE is a COVID-19 knowledge graph that has about 15 million connections between drugs, diseases, proteins, genes, pathways, and gene and protein expressions and spans 39 kinds of connections. (35)

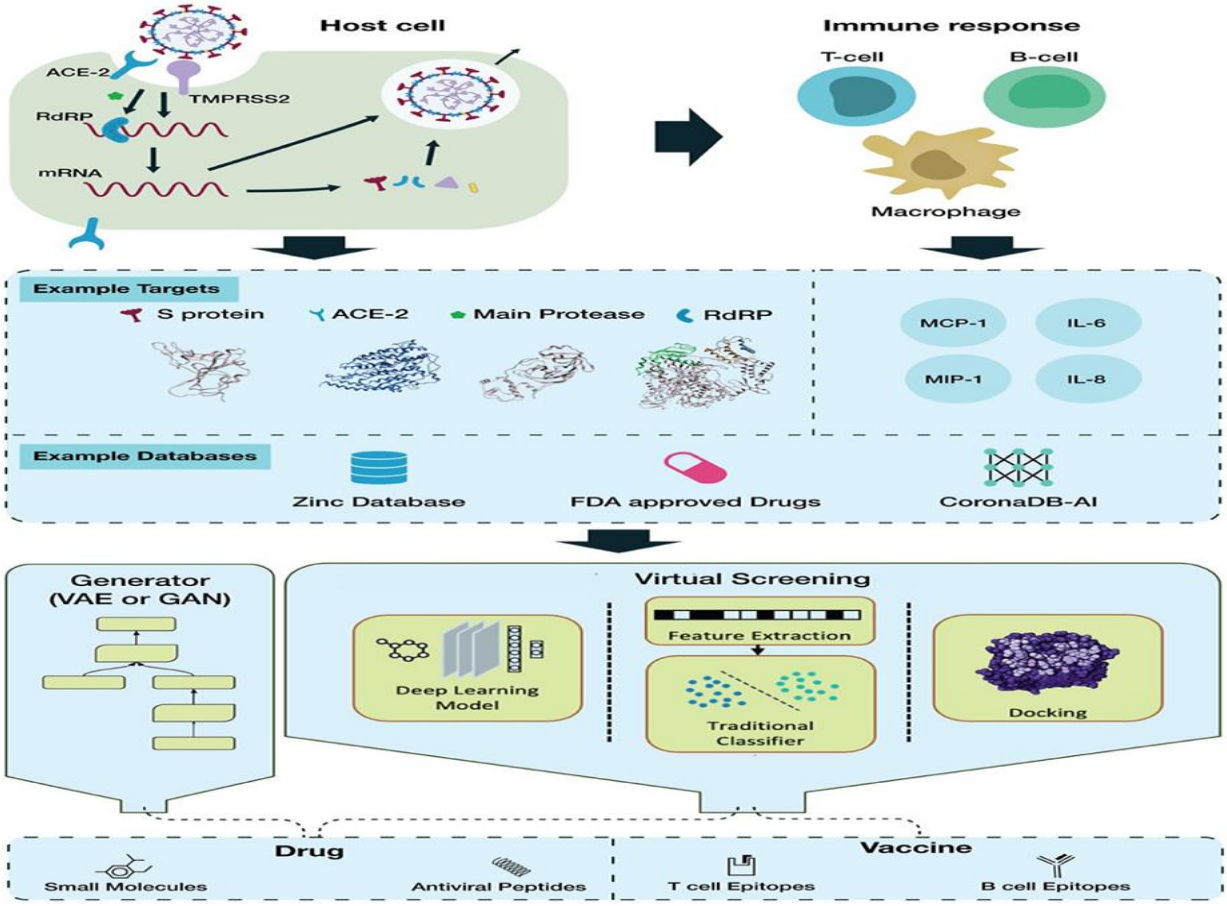

Figure 2: AI for drug repurposing in an integrative context

Using Amazon Web Services' computer capabilities and graph representation learning techniques, the researchers discovered 41 repurposed medication candidates, including dexamethasone and melatonin, among the COVID-19 treatment's targets. Building a high-quality medical knowledge graph is required for high prediction performance, and this line of research holds promise for the future.

REPURPOSED DRUGS FOR COVID-19 ARE UNDER INVESTIGATION

Antiviral medicines and host-targeting therapies have been or are being explored in clinical trials for COVID-19, including clinical trials with COVID-19 itself (figure 1). COVID-19 repurposing may be found in a peer-reviewed literature review by Sanders and colleagues. (36)

ANTIVIRAL DRUGS

Ebola virus disease was initially found to be a therapy option for Remdesivir, a monophosphate prodrug of an active C-adenosine nucleoside triphosphate analog. (36)There has been a success in treating COVID-19, prompting the FDA to implement an emergencyuse clearance. The use of the drug is limited to patients with the severe disease only. Based on preliminary data that suggests the medicine could assist hasten the recovery of hospitalized patients suffering from COVID-19, the FDA decided to approve it. Mechanistically, the viral RNA-dependent RNA polymerase was inhibited by remdesivir (figure 1). (37) In an intravenous remdesivir double-blind, randomized, placebo-controlled experiment, participants who had been admitted to the hospital for COVID-19 had a median recovery period of 11 days if they received remdesivir, versus 15 days for those who received a placebo. (8)

These preliminary data suggest that individuals hospitalized with COVID-19 and require supplementary oxygen therapy can benefit from a medicine called remdesivir. One randomized, open-label, phase 3 research did not indicate a meaningful difference between a 5-day course and a 10-day course of remdesivir in hospitalized patients not requiring mechanical breathing. (38) Additional work is needed to identify the shortest effective length of treatment for patients with COVID-19 and other patient subgroups, including or without mechanical ventilation. Not only has whether remdesivir can shorten the recovery course of persons with early COVID-19 not been proven, but the long-term effects of the drug have not been analyzed. A poly-ADP-ribose polymerase 1 inhibitor inhibited SARS-CoV-2 replication in a study integrating machine learning and statistical analytic approaches without observable side effects. (39) Mefuparib, which acts as an antiviral agent against SARS-CoV-2, acts faster during viral entrance and viral post-entry stages, showing its potential as a novel medication for SARS-CoV-2.

Toremifene, a non-steroidal selective estrogenic receptor modulator that was the first of its kind to be approved for use in treating breast cancer, received FDA approval in 1997.(40) Candidate to cure COVID-19 identified(16): toremifene In vitro experiments found that toremifene blocks many viral infections, including MERS coronavirus(41), SARS coronavirus(42), and the SARS-CoV-2 virus. (43) This second computational biophysics study(44) suggested that toremifene could block ACE2-SARS-CoV-2 spike protein interaction and inhibit nonstructural protein 14 of SARS-CoV-2 (also see figure 1). The results showed that the results and, thus, the mechanism of the antiviral activity of toremifene were validated. Toremifene, the medication used to treat postmenopausal women with breast cancer(40), has a mean plasma concentration of 0.88 mg/L (2.17 μM) and has a peak plasma concentration (more than 10 μM) that is three-times greater than the antiviral effect of SARS-CoV-2 (half-maximal inhibitory concentration of 3.58 μM). (43) The significant benefits of the CoV-KGE35(35) and network medicine(16) approaches can be summarised as follows: Toremifene, a discovered CoV-KGE35 candidate, has the potential to be tested in covid-19 clinical trials.

HOST-TARGETING TREATMENT

Patients infected with SARS-CoV-2 have heightened systemic inflammation, which can lead to a cytokine storm and the elevated inflammatory response points to the high likelihood of success when using immunosuppressants, like baricitinib, dexamethasone, and melatonin (figure 1). A COVID-19 patient registry from the Cleveland Clinic in Cleveland, Ohio, provided patient data for an investigation of an association between melatonin intake and a reduced risk of developing a positive laboratory test result for SARS-CoV-2. (46) Dexamethasone, a GR agonist that has been approved by the Food and Drug Administration (FDA) for a range of inflammatory and autoimmune disorders including juvenile rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, is one of many examples of drugs that are currently available for treatment of disorders. (47) Dexamethasone was shown to be an excellent candidate for CoV-KGE repurposing. Patients receiving dexamethasone died by one-third (95 [29 percent] of 324 individuals vs 283 [41 percent] of 683 patients; RR 0.64 [95 percent CI 0.51–0.81]) as well as a fifth (298 [23.3 percent] of 1279 individuals vs 682 [26.2 percent] of 2604 patients; 0.82 [0.72–0.94]). (48) Nonetheless, in the COVID-19 clinical trial, the use of dexamethasone did not reduce mortality in patients who did not receive respiratory support. Immunomodulators or anti-inflammatory medications administered to the host appear to be a viable therapeutic strategy for severe COVID-19, and clinical trials should be conducted to test this hypothesis.

DRUG COMBINATIONS FOR COVID-19 (COVID-19 DRUG COMBINATIONS)

No benefits have been found for patients with COVID-19 treated with monotherapies, including the antiviral remdesivir(8,38)and the antimalarial Hydroxychloroquine.(49) Combining inflammatory or immunological modulators (i.e., strengthening host immunity) with antiviral medications could be a useful treatment for patients with COVID-19 because the immune system plays a critical role in the worsening health and mortality of these patients. When treating infectious disorders like COVID-19(50) (e.g., remdesivir with baricitinib [NCT04401579]), the use of combinations that provide enhanced therapeutic effects and reduced toxicity is crucial. Even though an overwhelming growth hinders our capacity to identify and validate beneficial drug combinations in the number of possible drug pair combinations, we are on the cusp of significant advancements in this area. Three prospective therapeutic combinations for COVID-19(16) were discovered by scientists, all of whom used a network-based methodology.(51) They discovered sirolimus plus dactinomycin, mercaptopurine plus melatonin, and toremifene with emodin. This information was based on the interactome, which was theoretical and has not been tested in clinical trials or preclinical experiments. Observing that combining melatonin and toremifene showed promise for the treatment of COVID-19, the same team conducted further research. (52) Melatonin and toremifene are being tested in the Cleveland Clinic's selective estrogen modulation and melatonin in early COVID-19 (SENTINEL; NCT04531748) clinical trial to see if they are more effective than melatonin treatment alone in early COVID-19 patients. two ongoing, double-blind phase 2 trials are testing baricitinib alone or in conjunction with antiviral medications such Remdesivir for individuals with mild and severe COVID-19 (NCT04373044 and NCT04401579).(34)

EVIDENCE FROM THE REAL WORLD TO TEST DRUG RESPONSIBILITY

Good use of AI in repurposing drugs has to consider what researchers call "real-world data," such as electronic health records and various medical conditions. Electronic health records (EHRs) are the clinical data, like demographics, diagnoses, prescriptions, procedures, and lab results, collected regularly and digitally preserved. This data may be traded and accessed securely. (53) A wealth of research has been dedicated to real-world research data being put to use in medication discovery and development. (54) In clinical trials, participants are enrolled according to precise inclusion and exclusion criteria.

In addition, it is typical to run control and treatment groups, who then calculate the impact of treatment. Some drugs, such as remdesivir, don't have a control group and therefore do not permit calculation of treatment impact. (55) An RCT may use the vast data found in the real world to create an accurate control group, which can then be used to determine the effectiveness of a treatment. Real-world data are in many ways far different from RCT data. Firstly, it has more variance, since it also includes confounding factors. It also has a much larger population, and its data quality is poor. To locate a match between patients who receive therapy and the factors that may be influencing their treatment, the propensity score, which applies logistic regression to estimate the probability of a patient receiving treatment, is frequently utilised. (56) The real world presents several complications that, unfortunately, include high dimensionality, longitudinality, inconsistency, and incompleteness. This technique would be more suited for getting a decent propensity score. (57,58). There is a great deal of potential for new matching methodologies, including patient similarity analytics, given the complex circumstances at hand. (59)

Efforts have been made to build COVID-19 electronic health record repositories on a national or global scale. The International Consortium of E-Health Record project, which incorporates data from 96 institutions across five nations and patients' electronic health records—using Integrating Biology and the Bedside(60) or Observational Medical Outcomes Partnership to facilitate a single data model to connect participants' electronic health records—is a good example of a globally interconnected health repository (OMOP). (61) A retrospective study of COVID-19-positive hospital admissions in metropolitan New York, USA, discovered that treatment with Hydroxychloroquine (or, when combined with azithromycin, Hydroxychloroquine plus azithromycin) was not significantly associated with lower in-hospital mortality for COVID-19 patients when compared to no treatment. (49) Using a user-active comparator design and propensity score adjustment for confounding, melatonin use was linked to a lower risk of a positive SARS-CoV-2 test result. (46) Mancia and colleagues discovered that ACEIs and ARBs did not increase the risk of COVID-19 in a study. (62) Using national health records, it was discovered that ACEIs or ARBs had no relationship with an increase in the likelihood of a positive COVID-19 test, as well as an increase in COVID-19 severity. Thirty-three randomised controlled trials are currently being conducted to assess the therapeutic benefits of melatonin in COVID-19 patients (NCT04409522 and NCT04353128).

DISCUSSION, PERSPECTIVE, AND FUTURE DIRECTIONS

Since the mid-twentieth century, translational science has had to contend with the question of how to transform research discoveries into novel medical treatments and technology capable of providing these treatments promptly. This goal has both translational and basic sciences working together to reach it. Innovative drug discovery has been the target of numerous generations of scientists. It is theoretically possible to circumvent the constraints of de novo drug discovery by using an approach including drug repurposing, in which the US FDA has already approved a medicine. However, this underlines the

difficulties of which drug to select to be highly effective for the illness.

CHALLENGES IN DRUG REPURPOSING

Despite the great interest in applying drug repurposing for treating COVID-19, there are numerous obstacles to overcome. Tissue culture or animal models may not adequately represent the human host milieu where a viral infection occurs. In addition, repurposed medications may have been specifically targeted, dosed, or applied to a particular tissue during the initial indications. Antiviral, antimalarial, and immunomodulatory medicines already in use or under development have been tested rapidly against COVID-19. Most of the trials did not achieve their optimal therapeutic benefits and biological objectives due to their rushed study design, the limited number of patients, the absence of clinical goals, and inadequate statistical power. (64) An excellent example is Hydroxychloroquine, which possesses in vitro SARS-CoV-2 anti- actions. (65) Although Hydroxychloroquine has shown little or no efficacy in preclinical and clinical trial trials, this may not mean that Hydroxychloroquine does not have utility in the clinic. (49) COVID-19 tests could fail to find clinical benefits because of reproducibility problems in animal models and a lack of gold-standard clinical outcome metrics. Increased sensitivity is also required to identify differences between medications and placebos, notably for the slightly affected people with COVID-19; WHO now make up most of the patient population in clinical trials. The prevalence of diverse genetic backgrounds among various populations may impact the findings of clinical tests. Several factors may have contributed to these clinical trial findings, including incorrectly targeting the pathobiological or pathophysiological mechanisms in COVID-19; using drugs that do not successfully engage the intended target (virus proteins and virus-host and protein-protein interactome); and intervening at the incorrect stage of the disease, which includes early, mild, moderate, and severe diarrhoea.

Several examples of AI-based medication repurposing have shown promising results, including baricitinib discovered by BenevolentAI (34) and dexamethasone discovered by CoV-KGE (35) and melatonin discovered through network medicine research (figure 1). (46) COVID-19 drug repurposing can be improved by developing effective and robust in vitro and in vivo models. (67,68) Personalized medication repurposing may improve clinical trial success rates overall. (69)

CHALLENGES IN BIOLOGICAL INTERPRETATION

To design successful and efficient AI applications for drug repurposing, a long-term vision is required to help developers navigate the various research components inside the drug development ecosystem and allow them to identify new treatment alternatives.The applications of AI, such as visible neural networks(70), combine AI models and the internal workings of the AI model itself into actual biomedical systems, such as humans and animals. An example of machine learning-based visible methods may be applied to various models that need to deal with data heterogeneity in the life sciences, such as models in the medical field. (71) The body comprises multiple levels, including cells, tissues, organs, and organisms, forming complex and hierarchical systems (Figure 2). A multi-layered interaction takes place between many chemical substances and biological systems during drug discovery. As a result, the biological-inspired visual neural network model(72) can be made more effective and interpretable by enriching it with entities linked to drug discovery, such as chemical compounds and disorders. Computing modules that correspond to various entities in the biological sciences could be designed in light of insights derived from the vast amount of biomedical knowledge about how various entities interact at different levels. (35)This divide-and-conquer model represents various components within a complex system and how they interact with one another. Other deep learning models can be optimised from start to finish.

CHALLENGES IN DATA AND MODEL HARMONIZATION

Standardizing and integrating data from various sources to build a uniform database is known as data harmonization. Ensuring the applicability of machine learning models across multiple settings is crucially dependent on machine learning data harmonization. A good data model helps with the harmonisation process by making it possible to organise and standardise the data. The National and International activities include the creation of data models that will help research groups at home and abroad. Examples include the creation of the National Patient-Centered Clinical Research Network and the creation of the observational health data science and informatics project. (73) Fast and reliable healthcare services are interoperable. A new standard has been established; it is to be used in order to send information.

Harmonization of models and models themselves is another critical factor for increasing the generalizability and effectiveness of computational drug repurposing tools. Another example of developing standards for transferring models is the open neural network exchange (ONNX). An extended acyclic graph model (or "EGG") is a set of implemented models. Each node in the graph represents a call to an integrated operator with an input and an output defined with a standard data type.

DIFFICULTIES IN DATA SHARING AND SECURITY

The fears of data security and privacy have increased with the increased availability of health-related data (especially patient data).(75) For example, personal and genetic data have a higher likelihood of identifying patients. A lot of attention should be focused on investigating the entire data life cycle. For example, you need to think about whether the data you are collecting is

required, who will manage it, where it will be stored, and who will access it. Other measures include laws and openness. People should also be informed of this. Training algorithms on decentralized edge devices (e.g., individual mobile phones) or servers hosting diverse local samples can be a potential route toward this ultimate aim (e.g., data owned by different samples). In data security and privacy(76), only trained models are shared, and the sharing of the samples that went into training such models may increase data security and privacy.

PERSONALIZED DRUG REPURPOSING

With the recent advances in pharmacogenetics and pharmacogenomics, there is reason to believe that the effectiveness of illness treatment will be improved if treatments are targeted based on an individual's genomic profile. Some disorders, including cancer, have seen preliminary progress with this idea. (77) genetic, epigenetic, and environmental factors all impact how responsive someone is to medicine. Studies have found substantial interindividual variability in SARS-CoV-2 infection, ranging from asymptomatic to deadly disease. Clinical characteristics, pharmacological reactions, and human genetics might be interconnected and explored as one possible explanation. (69,78) For example, in a study that analyzed the genomes and exomes of about 81,000 people, researchers found that Hydroxychloroquine or chloroquine would only be effective in treating SARS-CoV-2 infection patients who lack the gene for TMPRSS2. In African green monkeys, Hydroxychloroquine possesses antiviral action but not reconstituted human airway epithelium formed from human primary nasal or bronchial cells (in vitro). (67) In addition, a second group discovered that chloroquine does not inhibit the infection of TMPRSS2-positive lung cells by SARS-CoV-2/SARS-CoV-2-like virus (SARS-CoV-2/SARS-CoV-2-like virus) Calu-3.(68) It appears that pharmacogenomics research is essential in enhancing the effectiveness of medication and the odds of successfully repurposing a treatment. To help accelerate efforts to develop, distribute, and analyze data, a COVID-19 host genetics program is underway to discover, collect, and organize genetic data in a search for the components of COVID-19 susceptibility, the impact of the disease, and treatment preferences. Laying the groundwork for the personalization of medical treatment, it is now possible to tailor medication and treatment to a patient's unique genetic makeup by leveraging large genetic and genomic data. (figure 3).

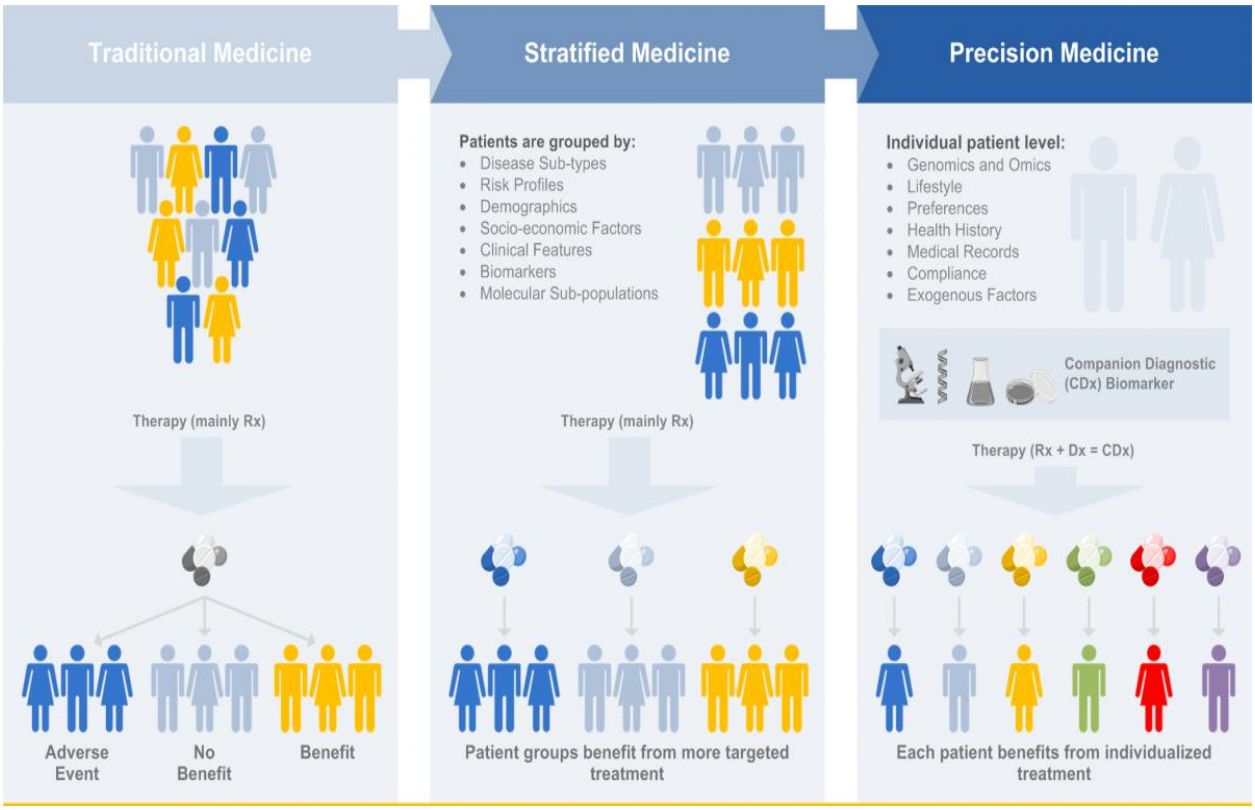

Figure 3: AI for patient stratification and personalized treatment

THE FUTURE OF AI-INFORMED DRUG REPURPOSING

A prescription drug search may be extended and time-consuming, but using just approved prescription drugs. AI's capabilities in discovering new candidates for clinical trials and bringing these into the clinical realm have not yet been matched; making AI a cornerstone of advanced technologies. AI promises to speed up the medication repurposing process for human diseases, namely disorders such as COVID-19. Big data, which includes biological, clinical, and open data (science papers and data

repositories), creates a wealth of new opportunities for AI, as seen by the unique AI techniques developed to take advantage of these resources. The involvement of pharmacologists, computer scientists, statisticians, and physicians in the process of AI-based tech creation and adoption is expanding. With big data and AI techniques, medication repurposing and medical decision-making for complicated human disorders like COVID-19 (figure 1) and Alzheimer's disease will see significant improvements. (79) Nonetheless, hurdles to developing these AI tools still exist, such as the heterogeneity of data and the low quality of the data, and the security and the capacity to comprehend the models. Drug repurposing is likely to be more successful in the future thanks to artificially intelligent (AI) models, which we believe will have a high degree of accuracy in predicting the outcomes generated, integrated with a variety of data types and sources, interoperable in various deployment settings, and sufficiently explanatory of their internal working mechanisms to combat external noise and adversaries.

REFERENCES

1.Turing AM. Computing machinery and intelligence. Mind 1950; 49: 433–60.
2 Fleming N. How artificial intelligence is changing drug discovery. Nature 2018; 557: S55–57.
3 Smalley E. AI-powered drug discovery captures pharma interest. Nat Biotechnol 2017; 35: 604–05.
4 Avorn J. The $2·6 billion pill·methodologic and policy considerations. N Engl J Med 2015; 372: 1877–79.
5 Chong CR, Sullivan DJ Jr. New uses for old drugs. Nature 2007; 448: 645–46.
6 Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. Nat Rev Drug Discov 2006; 5: 689–702.
7 Laubach JP, Richardson PG, Anderson KC. Hematology: thalidomide maintenance in multiple myeloma. Nat Rev ClinOncol 2009; 6: 565–66.
8 Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—Preliminary Report. N Engl J Med 2020; 2020: 22.
9 Cheng F, Murray JL, Zhao J, Sheng J, Zhao Z, Rubin DH. Systems biology-based investigation of cellular antiviral drug targets identified by gene-trap insertional mutagenesis. PLOS ComputBiol 2016; 12: e1005074.
10 Zeng X, Zhu S, Lu W, et al. Target identification among known drugs by deep learning from heterogeneous networks. ChemSci (Camb) 2020; 11: 1775–97.
11 Cheng F, Desai RJ, Handy DE, et al. Network-based approach to prediction and population-based validation of in silico drug repurposing. Nat Commun 2018; 9: 2691.
12 Greene JA, Loscalzo J. Putting the patient back together—social medicine, network medicine, and the limits of reductionism. N Engl J Med 2017; 377: 2493–99.
13 Hoffmann M, Kleine-Weber H, Pohlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell 2020; 78: 779–84.e5.
14 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020; 181: 271–80.e8.
15 Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. Nature 2020; 583: 459–68.
16 Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov 2020; 6: 14.
17 LeCun Y, Bengio Y, Hinton G. Deep learning. Nature 2015; 521: 436–44.
18 Rumelhart DE, Hinton GE, Williams RJ. Learning representations by back-propagating errors. Nature 1986; 323: 533–36.
19 Aliper A, Plis S, Artemov A, Ulloa A, Mamoshina P, Zhavoronkov A. Deep learning applications for predicting pharmacological properties of drugs and drug repurposing using transcriptomic data. Mol Pharm 2016; 13: 2524–30.
20 Lenselink EB, Ten Dijke N, Bongers B, et al. Beyond the hype: deep neural networks outperform established methods using a ChEMBL bioactivity benchmark set. J Cheminform 2017; 9: 45.
21 Meyer JG, Liu S, Miller IJ, Coon JJ, Gitter A. Learning drug functions from chemical structures with convolutional neural networks and random forests. J ChemInf Model 2019; 59: 4438–49.
22 Wallach I, Dzamba M, Heifets A. AtomNet: a deep convolutional neural network for bioactivity prediction in structure-based drug discovery. arXiv 2015; published online October 10. https://arxiv.org/ abs/1510.02855 (preprint).
23 Segler MHS, KogejTyrchan C, Waller MP. Generating focused molecule libraries for drug discovery with recurrent neural networks. ACS Cent Sci 2018; 4: 120–31.
24 Gao KY, Fokoue A, Luo H, Iyengar A, Dey S, Zhang P. Interpretable drug target prediction using deep neural representation. IJCAI 2018; 3371–77.
25 Beck BR, Shin B, Choi Y, Park S, Kang K. Predicting commercially available antiviral drugs that may act on the novel coronavirus (SARS-CoV-2) through a drug-target interaction deep learning model. ComputStructBiotechnol J 2020; 18: 784–90.
26 Tang J, Qu M, Wang M, Zhang M, Yan J, Mei Q. LINE: large-scale information network embedding. Proceedings of the 24th International Conference on World Wide Web; Florence, Italy: May 2015 (pp 1067–77).
27 Bordes A, Usunier N, Garcia-Durán A, Weston J, Yakhnenko O. Translating embeddings for modeling multi-relational data. 26th International Conference on Neural Information Processing Systems; Lake Tahoe, NV: Dec 2013 (pp 1–9).
28 Trouillon T, Welbl J, Riedel S, Gaussier E, Bouchard G. Complex embeddings for simple link prediction. In: Maria Florina B, Kilian QW, eds. Proceedings of the 33rd International Conference on Machine Learning. New York, NY, USA: Proceedings of Machine Learning Research, 2016: 2071–80.
29 Dettmers T, Minervini P, Stenetorp P, Riedel S. Convolutional 2D knowledge graph embeddings. arXiv 2017; published online July 5. https://arxiv.org/abs/1707.01476 (preprint).
30 Sun Z, Deng Z-H, Nie J-Y, Tang J. RotatE: knowledge graph embedding by relational rotation in complex space. arXiv 2019; published online February 26. https://arxiv.org/abs/1902.10197 (preprint).
31 Zhu Z, Xu S, Qu M, Tang J. GraphVite: a high-performance CPU-GPU hybrid system for node embedding. arXiv 2019; published online March 2. https://arxiv.org/abs/1903.00757 (preprint).
32 Sosa DN, Derry A, Guo M, Wei E, Brinton C, Altman RB. A literature-based knowledge graph embedding method for identifying drug repurposing opportunities in rare diseases. Pac SympBiocomput 2020; 25: 463–74.
33 Gysi DM, Do Valle I, Zitnik M, et al. Network medicine framework for identifying drug repurposing opportunities for COVID-19. arXiv 2020; published

online April 15. https://arxiv.org/abs/2004.07229 (preprint).
34 Richardson P, Griffin I, Tucker C, et al. Baricitinib as a potential treatment for 2019-nCoV acute respiratory disease. Lancet 2020; 395: e30–31.
35 Zeng X, Song X, Ma T, et al. Repurpose open data to discover therapeutics for COVID-19 using deep learning. J Proteome Res 2020; published online July 12. https://doi.org/10.1021/acs. jproteome.0c00316.
36 Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A Review. JAMA 2020; 323: 1824–36.
37 Yin W, Mao C, Luan X, et al. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. Science 2020; 368: 1499–504.
38 Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 2020; published online May 27. https://doi.org/10.1056/NEJMoa2015301. e676 www.thelancet.com/digital-health Vol December 2, 2020, Review
39 Ge Y, Tian T, Huang S, et al. A data-driven drug repositioning framework discovered a potential therapeutic agent targeting COVID-19. bioRxiv 2020; published online March 12. https://doi. Org/10.1101/2020.03.11.986836 (preprint).
40 Wiseman LR, Goa KL. Toremifene. A review of its pharmacological properties and clinical efficacy in the management of advanced breast cancer. Drugs 1997; 54: 141–60.
41 Cong Y, Hart BJ, Gross R, et al. MERS-CoV pathogenesis and antiviral efficacy of licensed drugs in human monocyte-derived antigen-presenting cells. PLoS One 2018; 13: e0194868.
42 Dyall J, Coleman CM, Hart BJ, et al. Repurposing of clinically developed drugs for the treatment of Middle East respiratory syndrome coronavirus infection. Antimicrob Agents Chemother 2014; 58: 4885–93.
43 Jeon S, Ko M, Lee J, et al. Identification of antiviral drug candidates against SARS-CoV-2 from FDA-approved drugs. Antimicrob Agents Chemother 2020; 64: e00819–20.
44 Martin W, Cheng F. Repurposing of FDA-approved toremifene to treat COVID-19 by blocking the spike glycoprotein and NSP14 of SARS-CoV-2. J Proteome Res 2020; published online September 9. https://doi.org/10.1021/acs.jproteome.0c00397.
45 Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26: 1017–32.
46 Zhou Y, Hou Y, Shen J, et al. A network medicine approach to prediction and patient-based validation of disease manifestations and drug repurposing for COVID-19. ChemRxiv 2020; published online July 2. https://dx.doi.org/10.26434/chemrxiv.12579137 (preprint).
47 Ramamoorthy S, Cidlowski JA. Corticosteroids: mechanisms of action in health and disease. Rheum Dis Clin North Am 2016; 42: 15–31, vii.
48 Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. N Engl J Med 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.
49 Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with Hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in new york state. JAMA 2020; 323: 2493–502.
50 Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation, and intervention. Nat Rev Immunol 2020; 20: 363–74.
51 Cheng F, Kovács IA, Barabási AL. Network-based prediction of drug combinations. Nat Commun 2019; 10: 1197.
52 Cheng F, Rao S, Mehra R. COVID-19 treatment: combining anti-inflammatory and antiviral therapeutics using a network-based approach. Cleve Clin J Med 2020; published online June 30. https://doi.org/10.3949/ccjm.87a.ccc037.
53 Häyrinen K, Saranto K, Nykänen P. Definition, structure, content, use, and impacts of electronic health records: a research literature review. Int J Med Inform 2008; 77: 291–304.
54 Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? N Engl J Med 2016; 375: 2293–97.
55 Bauchner H, Fontanarosa PB. Randomized clinical trials and COVID-19: managing expectations. JAMA 2020; 2020: 4.
56 Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70: 41–55.
57 Lee BK, Lessler J, Stuart EA. Improving propensity score weighting using machine learning. Stat Med 2010; 29: 337–46.
58 Linden A, Yarnold PR. Combining machine learning and propensity score weighting to estimate causal effects in multivalued treatments. J EvalClinPract 2016; 22: 871–81.
59 Sun J, Wang F, Hu J, Edabollahi S. Supervised patient similarity measure of heterogeneous patient records. SIGKDD Explor 2012; 14: 16–24.
60 Murphy SN, Weber G, Mendis M, et al. Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). J Am Med Inform Assoc 2010; 17: 124–30.
61 Stang PE, Ryan PB, Racoosin JA, et al. Advancing the science for active surveillance: rationale and design for the Observational Medical Outcomes Partnership. Ann Intern Med 2010; 153: 600–06.
62 Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020; 382: 2431–40.
63 Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensinaldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020; 382: 2441–48.
64 Mehta HB, Ehrhardt S, Moore TJ, Segal JB, Alexander GC. Characteristics of registered clinical trials assessing treatments for COVID-19: a cross-sectional analysis. BMJ Open 2020; 10: e039978.
65 Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020; 6: 16.
66 Park SJ, Yu KM, Kim YI, et al. Antiviral efficacies of FDA-approved drugs against SARS-CoV-2 infection in ferrets. MBio 2020; 11: e01114–20.
67 Maisonnasse P, Guedj J, Contreras V, et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. Nature 2020; 2020: 22.
68 Hoffmann M, Mösbauer K, Hofmann-Winkler H, et al. Chloroquine does not inhibit infection of human lung cells with SARS-CoV-2. Nature 2020; published online July 22. https://doi. org/10.1038/s41586-020-2575-3.
69 Hou Y, Zhao J, Martin W, et al. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. BMC Med 2020; 18: 216.
70 Ma J, Yu MK, Fong S, et al. Using deep learning to model the hierarchical structure and function of a cell. Nat Methods 2018; 15: 290–98.
71 Yu MK, Ma J, Fisher J, Kreisberg JF, Raphael BJ, Ideker T. Visible machine learning for biomedicine. Cell 2018; 173: 1562–65.
72 Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV, Brown JS. Launching PCORnet, a national patient-centered clinical research network. J Am Med Inform Assoc 2014; 21: 578–82.
73 Hripcsak G, Duke JD, Shah NH, et al. Observational health data sciences and informatics (OHDSI): Opportunities for observational researchers. Stud Health Technol Inform 2015; 216: 574–78.
74 Braunstein ML. Healthcare in the age of interoperability: the promise of fast healthcare interoperability resources. IEEE Pulse 2018; 9: 24–27.
75 Mello MM, Wang CJ. Ethics and governance for digital disease surveillance. Science 2020; 368: 951–54.
76 Xu J, Glicksberg SB, Su C, Walker P, Bian J, Wang W. Federated learning for healthcare informatics. arXiv 2019; published online Nov 13 2019.

https://arxiv.org/abs/1911.06270 (preprint).
77 Nussinov R, Jang H, Tsai CJ, Cheng F. Review: Precision medicine and driver mutations: Computational methods, functional assays and conformational principles for interpreting cancer drivers. PLOS ComputBiol 2019; 15: e1006658.
78 Ellinghaus D, Degenhardt F, Bujanda L. Genomewide association study of severe Covid-19 with respiratory failure. N Engl J Med 2020; published online June 17. ht--tps://doi.org/10.1056/ NEJMoa2020283.
79 Fang J, Pieper AA, Nussinov R, et al. Harnessing endophenotypes and network medicine for Alzheimer's drug repurposing. Med Res Rev 2020; published online July 13. https://doi.org/10.1002/