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COMMENTARY

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Repurposing current therapeutics for treating COVID-19: A vital role of prescription records data mining

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Abstract

Since its outbreak in late 2019, the SARS-Cov-2 pandemic already infected over 3.7 million people and claimed more than 250,000 lives globally. At least 1 year may take for an approved vaccine to be in place, and meanwhile millions more could be infected, some with fatal outcome. Over thousand clinical trials with COVID-19 patients are already listed in ClinicalTrials.com, some of them for assessing the utility of therapeutics approved for other conditions. However, clinical trials take many months, and are typically done with small cohorts. A much faster and by far more efficient method for rapidly identifying approved therapeutics that can be repurposed for treating COVID-19 patients is data mining their past and current electronic health and prescription records for identifying drugs that may protect infected individuals from severe COVID-19 symptoms. Examples are discussed for applying health and prescription records for assessing the potential repurposing (repositioning) of angiotensin receptor blockers, estradiol, or antiandrogens for reducing COVID-19 morbidity and fatalities. Data mining of prescription records of COVID-19 patients will not cancel the need for conducting controlled clinical trials, but could substantially assist in trial design, drug choice, inclusion and exclusion criteria, and prioritization. This approach requires a strong commitment of health provides for open collaboration with the biomedical research community, as health provides are typically the sole owners of retrospective drug prescription records.

KEYWORDS

COVID-19, drug repositioning, drug repurposing, electronic health records (EHR), TMPRSS2

1 | ELECTRONIC HEALTH RECORDS FOR COVID-19 DRUG REPURPOSING

At time of writing this commentary (late April 2020), humanity is struggling with the SARS-Cov-2 pandemic which has already infected more than 3.7 million people and caused over 250,000 fatalities globally, mostly among older individuals. Even the most optimistic scenarios estimate that it may take until mid-2021 to develop, receive approval, and start population-wide distribution of an effective SARS-Cov-2 vaccine (Callaway, 2020; Gewin, 2020). Meanwhile, many million further individuals will likely be infected, some with fatal outcome. Drug repurposing, also termed drug repositioning, attempts to apply drugs already approved for certain indications for a new indication; this approach is by far less costly and more efficient compared with developing a new drug (Koromina, Pandi, & Patrinos, 2019; Xu et al., 2015; Xu, Li, Jiang, & Chen, 2020). A notable example is the demonstration, based on prescription records data mining, that the diabetes drug metformin is protective against many solid cancers: decreased mortality following a cancer diagnosis was observed in patients prescribed metformin (Xu et al., 2015). The number of new drugs approved per billion US dollars spent for drug research and development was halved every 9 years since 1950, decreasing about 80-fold from 1950 to 2012 after adjustment for inflation (Scannell, Blanckley, Boldon, & Warrington, 2012). It was recently estimated that the average cost for developing a new drug ranges from US $2 billion to $3 billion, while on average 13–15 years are required for its

approval (Xu et al., 2020). These numbers illustrate the need for considering drug repurposing for drastically reducing development costs, improving success rates, and reducing toxicity risks, as the latter are, for most drugs, already established.

As of late April 2020, the National Institutes of Health (NIH) website for clinical trials (ClinicalTrials.gov) lists over thousand registered trials in COVID-19 patients. Some of these trials examine the potential to repurpose (reposition) therapeutics approved for other conditions for COVID-19 patients; notable examples are listed in Table 1. However, clinical trials typically take many months to complete, require high level of funding, and are usually done with small cohorts (fewer than 100 patients in each study arm) and at a single site. A by far faster and more efficient method for rapidly identifying approved therapeutics and repurpose them for COVID-19 patients is data mining of electronic health and prescription records of COVID-19 patients. Electronic health records (EHRs) of COVID-19 patients were already useful for identifying and assessing hypertension and diabetes as its major fatality risks (T. Chen, Wu et al., 2020; Li et al., 2020). Health records were also useful for studying infectivity among children (Qiu et al., 2020) and in embryos of infected pregnant women (H. Chen, Guo et al., 2020; Li et al., 2020), and COVID-19 neurological manifestations (Mao et al., 2020).

TABLE 1 Interventional clinical trials in COVID-19 patients with current therapeutics

NCT	Therapeutic	Drug family (major indication; repurposing reference)
NCT04280705	Remdesivir	Antiviral (Grein et al., 2020)
NCT04304313	Sildenafil	PDE5 inhibitor (erectile dysfunction)
NCT04317092	Tocilizumab	Immunosuppressive (rheumatoid arthritis)
NCT04321174	Lopinavir-ritonavir	Antiviral (Stower, 2020)
NCT04335123	Losartan	ARB (Gurwitz, 2020)
NCT04335786	Valsartan	ARB (Acanfora, Ciccone, Scicchitano, Acanfora, & Casucci, 2020)
NCT04341675	Sirolimus	Rapamycin (organ transplant rejection; Zhou et al., 2020)
NCT04342663	Fluvoxamine	SSRI antidepressant drug (major depressive disorder)
NCT04348695	Simvastatin	Statin (cholesterol lowering; Fedson, Opal, & Rordam, 2020)
NCT04350593	Dapagliflozin	Type 2 diabetes drug (Cure & Cumhur, 2020)
NCT04355026	Bromhexine	Mucolytic drug (respiratory disorders)
NCT04355936	Telmisartan	ARB (Rothlin, Vetulli, Duarte, & Pelorosso, 2020)
NCT04359329	Estradiol patch	Transdermal delivery for estradiol (La Vignera et al., 2020)

Note: As of May 6, 2020, there were 1,092 clinical trials registered at ClinicalTrials.gov concerning the treatment of COVID-19 patients. Of these, 316 trials were interventional and already recruiting. This table lists 13 examples for FDA approved drug trials in COVID-19 patients (arranged by their NCT codes). The most common approved drugs were hydroxychloroquine and chloroquine (not included in the table). References are included where relevant articles have been published.

Abbreviations: ARB, angiotensin receptor blocker; SSRI, selective serotonin reuptake inhibitor.

Many health providers maintain EHRs which include, in addition to detailed longitudinal clinical phenotypes, prescription records of their customers. For example, Maccabi Healthcare, the second largest Israeli healthcare provider, maintains such records and has utilized them for epidemiologic studies (Levkovitch-Verbin, Goldshtein, Chodick, Zigman, & Shalev, 2014). Drug prescription records data mining is also useful for identifying adverse events due to drug interactions (Hansen et al., 2016; Zhan, Roughead, Liu, Pratt, & Li, 2018). Making such prescription record datasets valuable for clinical and epidemiological research requires a common data collection and encryption modes that enable rapid, comparable, and systematic analyses across unrelated observational data sources for identifying and evaluating the safety and efficacy of therapeutics and their combinations for various clinical morbidities (Reisinger et al., 2010; Shabo, 2010: Shabo, 2014). This remains an unmet need for improved international collaboration of prescription records data mining.

Applying data mining of prescription records for COVID-19 patients for whom rich phenotypic information is available on the course of their disease, starting with early phase prior to hospital admission, seems a promising method for identification of drug candidates that can be repurposed for COVID-19 patients. Such combined data mining may assist in identifying the most suitable existing therapeutics, possibly including drug combinations, that may protect SARS-CoV-2 infected individuals from life-threatening symptoms.

2 | PRESCRIPTION RECORDS DATA MINING AND DRUG REPURPOSING FOR COVID-19

Table 1 lists examples for clinical trials registered with ClinicalTrials.gov and aimed at assessing the potential of drug repurposing for COVID-19. Some of such clinical trials may benefit from data mining prescription records: plans for such clinical trials may be modified to prescribe a different dosage, another approved therapeutic from the same drug family, or to change the inclusion and exclusion criteria, such as excluding patients with certain comorbidities or taking certain co-medications. Below, I discuss three examples among the repurposing trials listed in Table 1 for which data mining of prescription records seems in particular beneficial. The use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for COVID-19 patients has been debated, with some suggesting that it may offer protection from serious COVID-19

(e.g., Gurwitz, 2020; Rothlin et al., 2020) while others warning that ACE inhibitors and ARBs need to be carefully considered for COVID-19 patients due to potential risks (Zheng, Ma, Zhang, & Xie, 2020). The current consensus is to continue using ACE inhibitors and ARBs as prescribed for hypertensive patients, but not apply them as a COVID-19 therapeutic until their value and risks are clarified (Danser, Epstein, & Batlle, 2020; Patel & Verma, 2020; Vaduganathan et al., 2020). Indeed, several clinical trials registered with ClinicalTrials.gov will be assessing the value of ACE inhibitors and ARBs in COVID-19 (Table 1). Clearly, data mining of prescription records for COVID-19 patients taking ACE inhibitors or ARBs would be highly valuable for assessing their utility, as well as for optimal design of ongoing and planned clinical trials. Another example concerns transdermal estradiol patches, commonly used as hormone replacement therapy for post-menopausal women or other indications (La Vignera et al., 2020). Transdermal or oral estradiol are prescription drugs, thus health providers should have such records. Hence, trials such as NCT04359329 (Table 1) may benefit from data mining estradiol's prescription records for assessing the value of transdermal or oral estradiol. Lastly, anti-androgens, commonly used for treating acne or alopecia and sometimes applied for treating prostate cancer patients, were suggested as beneficial for reducing COVID-19 severity (Wambier & Goren, 2020). This suggestion is based on the well-established androgen-mediated upregulation of TMPRSS2, coding for a protease which is essential for ARS-CoV-2 cell entry subsequent to the binding of its spike protein to the ACE2 receptor (Clinckemalie et al., 2013). This suggestion is supported by the comparatively low rates of COVID-19 fatalities among children, whose androgen levels remain low until puberty.

3 | HUMAN LIVES MATTER

Access of health informatics researchers to EHRs, including to individual prescription records, is key for efficient and time-saving drug repurposing studies. An effective and fast response for reducing COVID-19 morbidity and fatalities requires novel expedited ways of applying information technologies for supporting clinical needs (Grange et al., 2020). In Taiwan, the success of combating COVID-19 was in part thanks to its advanced information technology capacity (Lin et al., 2020). As discussed above, applying health informatics is in particular valuable for drug repurposing (drug repositioning). During the ongoing pandemic, and as long as a safe and effective vaccines are not available, applying medical and prescription records data mining for drug repurposing requires a reasonable degree of easing current data access regulations, as summarized in Table 2. Some of these suggestions, in particular relaxing rules for institutional review board (IRB) approval for access to individual prescription records, may seem a risk of patients' privacy. However, relaxing IRB rules, including waivers for consent, are justified during emergencies (Dix, Esposito, Spinosa, Olson, & Chapman, 2004; McRae, Ackroyd-Stolarz, & Weijer, 2005); undeniably the current SARS-CoV-2 pandemic falls into this category. A policy that only allows the publication of finding as aggregated patient data should minimize such privacy risks. Moreover, privacy concerns pale in comparison with the serious privacy fears surrounding the tracking of citizens and residents by mobile phone location tracking applications during the current pandemic (Lenert & McSwain, 2020; Park, Choi, & Ko, 2020). A strong commitment of health providers for open collaboration with the biomedical research community is required, as health provides are often the sole owners of retrospective health and drug prescription records of their customers. Withholding these health records from the research community would be an unforgivable breach of their commitment to human health. Health records sharing is possible along with careful anonymization of identifiers for assuring patient privacy. As long as the SARS-CoV-2 pandemic is ongoing, saving lives matters the most, and drug repurposing could save lives by far faster and more efficiently than new clinical trials.

TABLE 2 Proposed protocol of utilization of prescription records for repurposing therapeutics for COVID-19 patients

- Applying prescription records for drug repurposing is far cheaper and faster compared with prospective interventional clinical trials. This approach has been successful for several drugs, for example, for metformin (Xu et al., 2015).
- Health and prescription records must be anonymized by removing any potential identifiers (e.g., date and place of birth, names of treating clinicians, etc.). Records should include rich phenotypic data, including age, sex, ethnicity, current comorbidities, BMI, and so forth (while all potential identifiers are removed).
- Access to raw data should be provided to registered qualified users following commitment to not breach patients' identity, not provide raw data access to third parties, and publish findings only as aggregated data. Publication of individual patient records must be strictly prohibited along with the policies for performing human genome research (Joly, Dyke, Knoppers, & Pastinen, 2016).
- To facilitate timely drug repurposing research, institutional review boards should consider waiving the informed consent of patients for accessing their recent prescription records.

Note added in proof: While this commentary article was in the proofs stage, a study by Montopoli et al. (Int J Mol Sci. 2020 Apr 22;21(8). pii: E2948. doi: 10.3390/ijms21082948.2020) was published, in which the authors reported that androgen-deprivation therapy (ADT) reduced the risk of SARS-CoV-2 infection by 4.05-fold in prostate cancer patients receiving ADT compared to patients who did not receive ADT. This study serves as a fine example of applying prescription records for COVID-19 drug repurposing.

CONFLICT OF INTEREST

The author declares no potential conflict of interest.

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