Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Response to: Broadbent 2020, Better the drug you know: Commentary on "Daughton 2020, Natural experiment concept to accelerate the re-purposing of existing therapeutics for Covid-19"

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The Commentary by Dr. Broadbent on "Natural Experiment Concept to Accelerate the Re-purposing of Existing Therapeutics for Covid-19" [1] provides a backstory and context for clarifying how the paper fits within the domain of epidemiology. This is very useful in communicating the concept's potential in the repurposing drugs for Covid-19 therapy - or for any future disease epidemic.

Worth reiterating is the reality underlying any new concept - the devil is always in the details. The details are always more demanding than the general. For this particular concept, which might be more simply termed "Drug Repurposing Epidemiology" (DRE), its actual implementation or deployment might be most challenged by the heavy-lift required in the collection of patients' drug usage data (and metadata) required by DRE. Data collection would often entail working closely with those performing the actual diagnostic or surveillance testing - an environment fraught with occupational risks of infection. There is no pretense - many complexities would have to be addressed. But simple and clever solutions to seemingly intractable problems always seem to emerge. And the collection of patients' drug usage data should already be an invaluable part of medical practice (but often is not). Public health organizations and clinical medicine need to embrace its full potential and encourage its efficient collection and organization for promoting the mining of further knowledge. This will require nationally centralized, digital databases and the willingness to input the data in real time.

With this said, the following is recommended for those who wish to try and ground-truth the DRE concept. Starting with a pilot project at small scale (perhaps no larger than a small city) the focus should initially be on only one aspect (or mode) of DRE. Since Covid-19 serological antibody tests have yet to be validated for sensitivity and specificity and have not been formally approved for routine, widespread use in the U.S., it would be best to rely solely on drug usage data obtained during diagnostic testing. Even though rt-PCR is the most specific and sensitive diagnostic test currently available, effort should be made to consider a less-costly and faster SARS-CoV-2 antigen test. Even though antigen tests are less sensitive that PCR, positive results are very reliable. This would allow DRE to focus on the mode that relies solely on cases yielding positive tests. This mode would be used to reveal those drugs with unusually high or unusually low usage distributions that are associated with poor Covid-19 outcomes. Drugs with lower-than-expected usage distributions would be attractive candidates to further explore as possibly protective. Drugs with higher-than-expected usage distributions would deserve attention as possibly contraindicated for therapeutic use. This mode would represent the low-hanging fruit for DRE.

Fortunately, natural experiments involving pandemics arise infrequently. But for that very reason, it behooves investigators to be ready with testable hypotheses when the opportunities arise. With this in mind, it is important to recognize that other natural experiments involving Covid-19 are ripe for picking. One class of potential experiments could prove especially useful in enhancing the utility of DRE or in groundtruthing its findings. This class of experiments would involve the application of wastewater-based epidemiology (WBE), which is used for fast, large-scale community-wide monitoring of numerous types of chemicals or biomolecules (e.g., [4,5,10]).

One example pertinent to DRE would involve implementing WBE for the following. (1) Using current virus outbreak data and WBE, locate communities with unusually high and low incidence of Covid-19. (2) Use the drug distribution data from DRE that point to drugs associated with good and with poor Covid-19 medical outcomes. (3) Groundtruth these DRE data by monitoring for both groups of drugs (drugs in low- and high-incidence distributions) according to their association with community-wide Covid-19 levels as measured by WBE rather than with clinical diagnostic testing. This type of approach using WBE could provide further corroboration of DRE results.

WBE could also be explored as a standalone or complementary alternative approach, functioning analogously to DRE as described in the paper but on a much larger population scale. WBE could possibly be implemented more readily and for less cost than DRE that relies on clinical diagnostic testing and the onerous collection of case-by-case drug-usage data. The downside of WBE is that it would require more advanced mass spectrometric laboratory capabilities for the non-targeted quantitation of drugs in sewage. In contrast to monitoring markers of SARS-CoV-2 in sewage, many drugs (and especially their

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unique metabolites) are excreted extensively in urine (as opposed to feces); this would simplify sewage sampling and preparation for analysis.

To even further streamline implementation of the DRE concept by using WBE, it could prove extremely useful to begin exploring the use of proxy-measures for Covid-19 infection. For WBE, there is no reason that the measures should be restricted to the methods of analysis that are used in clinical testing (PCR and antigen testing). An important alternative needs to be explored - namely, endogenous biomarkers that are excreted (preferably in urine) at elevated levels in the diseased state. Biomarkers (instead of virus-specific markers) might even be a better way to gauge the extent of Covid-19 when using WBE. While biomarkers are excreted by any number of medical conditions, they could serve as "excess" measures for an epidemic (much like excess deaths). For example, consider that Covid-19 often involves extensive inflammatory damage. The archetype biomarker for systemic inflammation is the class of prostaglandin-like compounds called isoprostanes [3,8]; a range of other biomarkers (e.g., see: [4,10]) might also be elevated with Covid-19. Any of these biomarkers might make excellent alternatives to targeting SARS-CoV-2 markers. Moreover, a number of other benefits could emerge, notably: (i) Biomarkers might be more universally excreted in excess by infected individuals and also have tighter ranges for per-capita excreted levels. This could afford more representative estimations of the number of infected individuals in a community. (ii) The total number of infected individuals can be measured in a community (because of logistical limitations, diagnostics testing fails to test an unknown but possibly large portion of the infected population). (iii) Biomarkers excreted extensively in the urine (as opposed to feces) could reduce analytical costs associated with sewage sampling and sample preparation. (iv) Biomarkers might serve as better leading indicators of infection. They might also be better indicators of continuing infection after diagnostic testing turns negative.

A possible complication for DRE not noted in the paper relates to a still-emerging realization regarding the large constellation of Covid-19 signs and symptoms. This disease seems to be manifesting with an expanding spectrum of symtomologies. Initially regarded primarily as a pulmonary disease, more recently it is also looking like a cardiovascular disease, with clotting becoming a major risk [9]. It might also possibly be associated with (or the cause of) previously uncommon conditions, such as Multisystem Inflammatory Syndrome in Children [2]. As a result, outcomes noted from infection with SARS-CoV-2 might be entangled with any number of other underlying morbidities, creating a broad spectrum of outcomes and making it difficult to categorize data. It might be extremely difficult to disentangle those drugs that appear to be associated with favorable or unfavorable outcomes as being associated with Covid-19 or with the underlying morbidities (e.g., [7]). It could all become rather murky (e.g., [6]). This can be seen from a scenario where a portion of those who eventually die might be a result of having not undergone medical treatment for their underlying morbidities rather than from the virus itself.

Regardless of the difficulties, there could be any number of other advantages to DRE (whether performed by clinical diagnostic testing or by WBE). DRE could be a useful tool in quickly pushing back against unfounded claims and even disinformation that certain drugs are useful in therapeutic treatments - simply by showing that such drugs have no association with favorable therapeutic outcomes (or even possibly associated with poor outcomes) (e.g., [11]). DRE could also help resolve ambiguities in the outcomes of clinical trials involving drug repurposing.

It is hoped that this paper will capture the interest of others like Dr. Broadbent. Some could serve to shepherd or champion the advancement or eventual deployment of the DRE/WBE concepts in fighting Covid-19, as well as future epidemics.

Declaration of Competing Interest

The author declares no conflict of interest. The work had no affiliation with any public or private agency. The concept and ideas presented did not originate from any prior published works.

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