EXPERT OPINION ON DRUG DISCOVERY
https://doi.org/10.1080/17460441.2021.1854221

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SPECIAL REPORT

Drug development post COVID-19 pandemic: toward a better system to meet current and future global health challenges

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ABSTRACT

Introduction: Despite advances in drug research and development, our knowledge of the underlying molecular mechanisms of many diseases remains inadequate. This have led to limited effective medicines for several diseases. To address these challenges, efficient strategies, novel technologies, and policies are urgently needed. The main obstacles in drug discovery and development are the mounting cost, risk, and time frame needed to develop new medicines. Fair pricing and accessibility is another unmet global challenge.

Areas covered: Here, the authors cover the pace, risks, cost, and challenges facing drug development processes. Additionally, they introduce disease-associated data which demand global attention and propose solutions to overcome these challenges.

Expert opinion: The massive challenges encountered during drug development urgently call for a serious global rethinking of the way this process is done. A partial solution might be if many consortiums of multi-nations, academic institutions, clinicians, pharma companies, and funding agencies gather at different fronts to crowdsource resources, share knowledge and risks. Such an ecosystem can rapidly generate first-in-class molecules that are safe, effective, and affordable. We think that this article represents a wake-up call for the scientific community to immediately reassess the current drug discovery and development procedures.

ARTICLE HISTORY
Received 5 October 2020
Accepted 18 November 2020

KEYWORDS
Alzheimer's disease; cancer; clinical trials; COVID-19; drug development; drug failure; effective drugs; infectious diseases; malaria; rare diseases

1. Introduction

The ongoing COVID-19 pandemic has imposed a heavy toll on human life, health care, global economy and almost every aspect of human life [1,2]. Yet despite its devastating effects, it has also mobilized and united many elements of the drug discovery and development process to seek therapies to address this most pressing public health emergency. In a record time frame, 36 vaccines have entered in clinical trials and 89 are in preclinical phase [3]. While it usually takes 10–15 years to develop a vaccine, in less than a year, promising results from phase III clinical trials of the Pfizer/BioNTech vaccine were recently announced with results from trials by other pharma companies expected to follow soon (Figure 1) [4].

This momentous foot is a testament to the collective human resolve and can only be achieved in the presence of a global will, collaboration, and available resources needed to tackle a global health crisis of this scale. Yet as the world remains focused on COVID-19 pandemic, the humankind still faces several intricate diseases many of which do not obey the standard Mendelian rules of inheritance such as infectious diseases [5], cancer [6], rare diseases [7], and dementia [8]. Despite skyrocketing technological advances, the impression has gained ground that we are clueless about most of the diseases' etiologies, progression and molecular mechanisms. Solving unmet medical needs is still a distant dream and there is a pressing need to develop new and effective medicines for several existing diseases. To successfully address these challenges, developing efficient strategies, novel technologies, and policies are paramount. The mounting cost, risk, and timely process are significant obstacles that hinders the drug discovery and development processes. As global momentum continues to materialize in an effort to address the ongoing pandemic, valuable lessons and perhaps plunders can be learned and applied to address other global health-related challenges humankind faces. In the following sections, major perplexing challenges to the health of humankind, the hurdles facing drug discovery and development and frontiers for potential solutions, are addressed.

2. Unmet needs

2.1. Alarming pace of deadly diseases

Death rates due to diseases largely depend on access to health care and availability of effective medicines. The vast majority of the deadliest diseases are partially preventable

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Article highlights

- Patients desperately want effective affordable drugs and they want them quickly.
- Drug development needs massive changes in the currently followed procedures.
- Despite the advancement of technology, there are many unmet needs for the treatment of many diseases including infectious diseases, CNS diseases, Alzheimer's, rare diseases and cancer.
- Despite the alarming pace of serious diseases, the drug development community has not yet embraced pooling the crowd sources of science to implement new reforms in drug development.
- Lack of enough global alliance, secrecy, duplication of efforts, cost, pace and reproducibility elements are among the mitigating factors that need to be addressed.

This box summarizes key points contained in the article.

with better access to preventive procedures and quality healthcare delivery. With the advancements in medical sciences, we have seen a drastic reduction in death rates for many devastating diseases in developed nations and to a lesser extent in developing countries. A brief summary of the global medical challenges the humankind continues to face is presented below.

2.1.1. Infectious diseases

Malaria is an ancient scourge as old as humanity itself. There are over 200 million new infections and around half a million deaths reported every year [5]. Despite many attempts to design effective vaccines, none has been successful at providing long-lasting benefits at a population level [9]. Tuberculosis (TB) remains one of the top 10 causes of death worldwide, with 10,000 million infections and 1.5 million deaths in 2018 according to the world health organization [10]. Likewise, viruses continue to compromise the lives of tens of millions of people. Globally, influenza virus infects a 1 billion people and causes up to 650,000 deaths every year despite the availability of the flu vaccine [11]. Viral infections inflict heavy societal and economic burdens beside their morbidity and mortality tolls. The past half century has witnessed deadly outbreaks of novel viruses of animal origin other than SARS-CoV2 such as Nipah, Hendra, Hanta, Ebola, several influenza

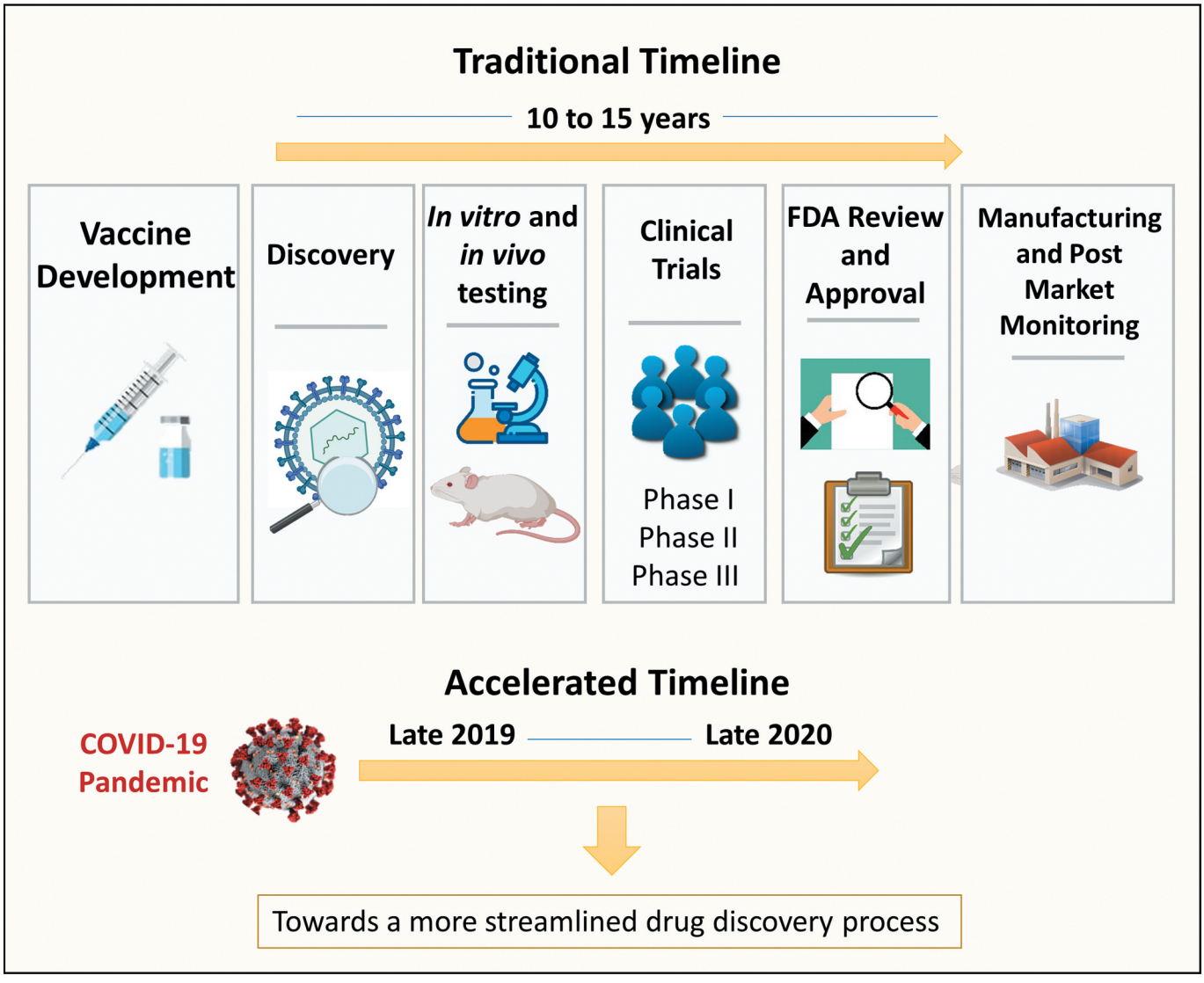

Figure 1. Comparison between the traditional vaccine development timeline and the accelerated development time line in response to the COVID-19 pandemic.

subtypes, SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) [12]. These outbreaks warn the urgency of understanding the factors influencing viral diseases emergence and spread as well as global preparedness to halt these epidemics from becoming a full-blown pandemic [13]. Multidrug resistance is yet another emergent global public health threat [14]. The emergence and spread of antimicrobial resistance (AMR) among bacterial pathogen are responsible for more than 700,000 deaths per year, and is projected to cause a 10 million deaths per year by 2050 [15]. The World Health Organization along with several other organization have called an urgent action to tackle the spread of antimicrobial resistance and invest in development of new antibiotics [16].

2.1.2. Cancer

Cancer remains as the second leading cause of mortality worldwide. In 2018, cancer have affected an estimated 18.1 million people and caused 9.6 million deaths [17]. A close watch at the statistics reveals that cancer kills around 10 million people every year; which is about 20,000 people every day; that correlates to one person every second. The number of cancer deaths in the United States alone is predicted to increase to 946,833 in 2030 from 595,690 in 2016 [18]. These disturbing figures desperately calls for the need to develop early diagnostics, novel, and effective medicines as well as new drug development strategies. Partial solutions to this challenge by precision medicine and immunotherapy has been firmly established, merits to the recent inventions in cancer genomics and immunology [18].

2.1.3. CNS diseases

Another significant growing healthcare need with a major economic and medical impacts is Dementia [19]. Globally, dementia affects around 50 million people, and over the past 18 years, the percentage of death among Alzheimer's patients doubled while deaths resulting from stroke, and heart diseases have decreased [20]. In the US alone the number of Alzheimer's dementia cases is expected to shoot up to 13.8 million and impose a health care burden of 1.1 trillion dollars by 2050 [20]. As of today, there are no medications known to reverse the progression of Alzheimer's disease [21].

2.1.4. Rare diseases

Although individual occurrence is rare, collectively rare diseases is a problem affecting 6–8% of the world population [7]. The Rare Diseases Clinical Research Network was established by The National Institutes of Health (NIH) to address these unique challenges. Among the 7,000 rare diseases, treatments are available only for 5%. Altogether across the globe, there are 350 million people diagnosed with rare diseases and half of them are children, a third of which are below 5-years old [22]. There is a great disparity in access to orphan medicinal products (OMPs) and healthcare services among world countries despite mounting international initiatives [23].

3. Challenges facing the current drug development process

The lack of ample effective and affordable medicines is one of the vexing challenges faced globally. It is imperative to generate novel treatment strategies, however, fair pricing and quick access to medicines remain a massive global challenge. Chronic shortages and rising demands for critical drugs affect patient community with many dying from easily curable diseases [24]. To a large extent, present day drug development and discovery is controlled oftentimes by private entities which are driven by vested economic interests and boundary conditions. This leads to the burden trickling down to patients, their families and carers either through lack of effective medicines or mounting financial costs. Addressing these global issues is the need of the hour and a plausible solution could be devising new tools and technologies, novel methodological approaches, and infrastructural changes to streamline the drug discovery review processes. On the other hand, the desperate need for new effective drugs raises a concern over the efficacy of many of the currently marketed drugs. A study examining efficacy of solid tumors therapies approved by the FDA between 2002 and 2014, found only 30 out of 71 therapies (42%) to have modest clinically meaningful improvements [25]. Sluggish data sharing and irreproducibility of published research remains as another major challenge. A 2016 survey of 1,576 researchers by the journal Nature found that over 70% of researchers have failed to reproduce other scientist's experiments [26].

The challenges in drug discovery and development for academics, research communities, and pharma industries needed for successful drug development can be broken down to cost, risk as well as pace.

3.1. Cost and risk

The amount spent to develop an individual drug largely depends on the costs to conduct safety and efficacy studies and also to secure regulatory approvals. Estimates for the cost for Drug development range from ~ 1 billion to whopping 11.8 billion for a single drug [27,28]. However, around 90% of drugs in development for human use do not reach the market due to safety or efficacy concerns. Such failures can be due to lack of efficacy, safety issues, or a lack of funding to complete a trial [29]. In other cases, failing to maintain good manufacturing protocols and follow FDA guidance, as well as problems with patient recruitment, enrollment, retention and follow up can all compound to both complicate and increase the cost needed for drug development [29]. Given this mounting cost with little success due to high attrition rates, it is obvious that the drug development as a business model is very risky purely from an economical and financial sense. Aside from the high cost/high attrition rates nature of the drug discovery process, other drugs, like antibiotics or orphan drugs, are often abandoned and don't reach the market due to little or no commercial interest [30].

3.2. Pace

The process of drug research and development is extremely slow taking at least 7 to 10 years for a lead candidate to reach the marketplace [28]. This is mainly due to the rigorous process needed to ensure safety and efficacy through clinical human trial and as well as obtaining regulatory approvals. Duplication and reproducibility are other factors that also contributes to the slow pace of drug discovery. While duplication and reproducibility can be seen as a squander of time and resources, they remain essential to provide more data and evidence and ensure the safety and efficiency before they are prescribed to the population. The devastating malformations of children born to women prescribed 'Thalidomide', to treat morning sickness is a stark reminder of the important of independent rigorous evaluation of a drug's safety profile before its release for population [31]. A more recent example, hydroxychloroquine as a treatment for COVID-19, highlights the importance of multiple and independent studies needed to demonstrate a drug's safety and efficiency [32]. Other factors include, suboptimal collaboration or lack of meaningful collaborative efforts among academia, industry, and government institutions despite several effort to encourage collaboration [33]. This have led, on many instances, to academics and pharma sectors working on similar ideas in parallel, in secret, and often in competition. Therefore, the establishment of a trusted and fair framework of collaboration and data sharing can both speed up the pace and improve the outcome of successful drugs.

3.2. Limitations and more of the same

A large number of drugs approved by the FDA in the past 10 years are new formulations of existing drugs referred to as 'me too drugs'. While in some cases these drugs have offered some improvements over older versions, in many cases improvements remain marginal with slight changes in side effects or activity profiles [34]. Since these drugs have identical mechanism of action to older versions their innovative value and overall benefit is oftentimes insignificant [35]. Additionally, the molecular effects of several marketed drugs remain unknown despite their proven effectiveness. For example, acetaminophen is used by millions to treat mild to moderate pain while lithium is a first-line treatment for biopolar disorder. Yet the exact molecular target and mechanism of action remain unknown [36,37]. Many diseases particularly those affect the nervous system like Alzheimer, Parkinson's, and depression lack accurate biomarkers [38,39]. While progress is being made, the lack of reliable biomarkers remains another impediment for the accurate diagnosis, prognosis and effective drug development against these diseases.

4. From bench to bedside translational research: the breakthrough of the hour

The combination of basic research and innovation is arguably one of the greatest catalysts in creating a paradigm shift in drug discovery. From the accidental discovery of penicillin by Alexander Fleming's and Warfarin by Karl Link while investigating hemorrhaging cattle to the more recent discovery and development of the CRISPR/Cas9, basic research and innovation are fundamental to the drug discovery process. No one could have envisioned that a routine effort to sequence bacterial genomes to improve yogurt production would ultimately lead to the development of CRISPR/Cas9, the revolutionary gene-editing tool with its seemingly endless utilities and applications [40]. Basic research continues to expand our understanding of fundamental biological processes which in turn paves the way to innovation in translational research and opens up exciting new arenas in personalized and targeted therapies such as gene and cell-based therapies [41]. While these innovations are still in their infancy [42] and come with a high cost [43], they hold significant promise with some exciting trial reports beginning to roll in [44]. With at least 5 clinical trials evaluating cell-based therapy to treat COVID-19, this approach along with gene therapy are likely to transform treatment options as we move into the future [45].

5. Conclusion

In summary, inefficient data sharing, irreproducibility of published work, high cost, high failure rates, and slow pace remain as significant challenges for the drug discovery and development process. Over the past few years, many research institutions around the world have developed an infrastructure in collaboration with pharma companies, peer research laboratories/institutions, government/philanthropy organizations to crowdsource resources, share knowledge and assess risk. The idea was mooted with the formation of the Academic Drug Discovery Consortium (ADCC) that aims at nurturing the academic drug discovery centers in the USA [46]. ADCC initiated a collaborative network to facilitate exchange of expertise and technical know-how, and the formation of partnerships among the participating organizations including industry. In addition to academic drug discovery centers, independent researchers around the globe have registered from various organizations, including universities, pharmaceutical companies, government institutions and diseases foundations. Many companies have also approached the ADDC for assistance in designing specific disease/ drug research areas [46]. The success of ADCC emphasizes the need for networking/ collaboration to harness the best possible avenues in the most cost-effective way for the rapid discovery of novel and effective medicines.

Very recently, an unprecedented effort, as ever in the history, has been made to avert the COVID-19 pandemic by the National Institutes of Health (NIH) [47]. The NIH in collaboration with major drug companies and funders has announced a plan to conduct clinical trials employing drugs and vaccines to treat COVID-19. Priorities have been designated for testing and development of selected drugs/vaccines to avoid duplication and wastage of time, money and resources. The partnership called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) is a collaborative network of NIH, government agencies in the U.S, pharma/biotech companies, academia and nonprofit

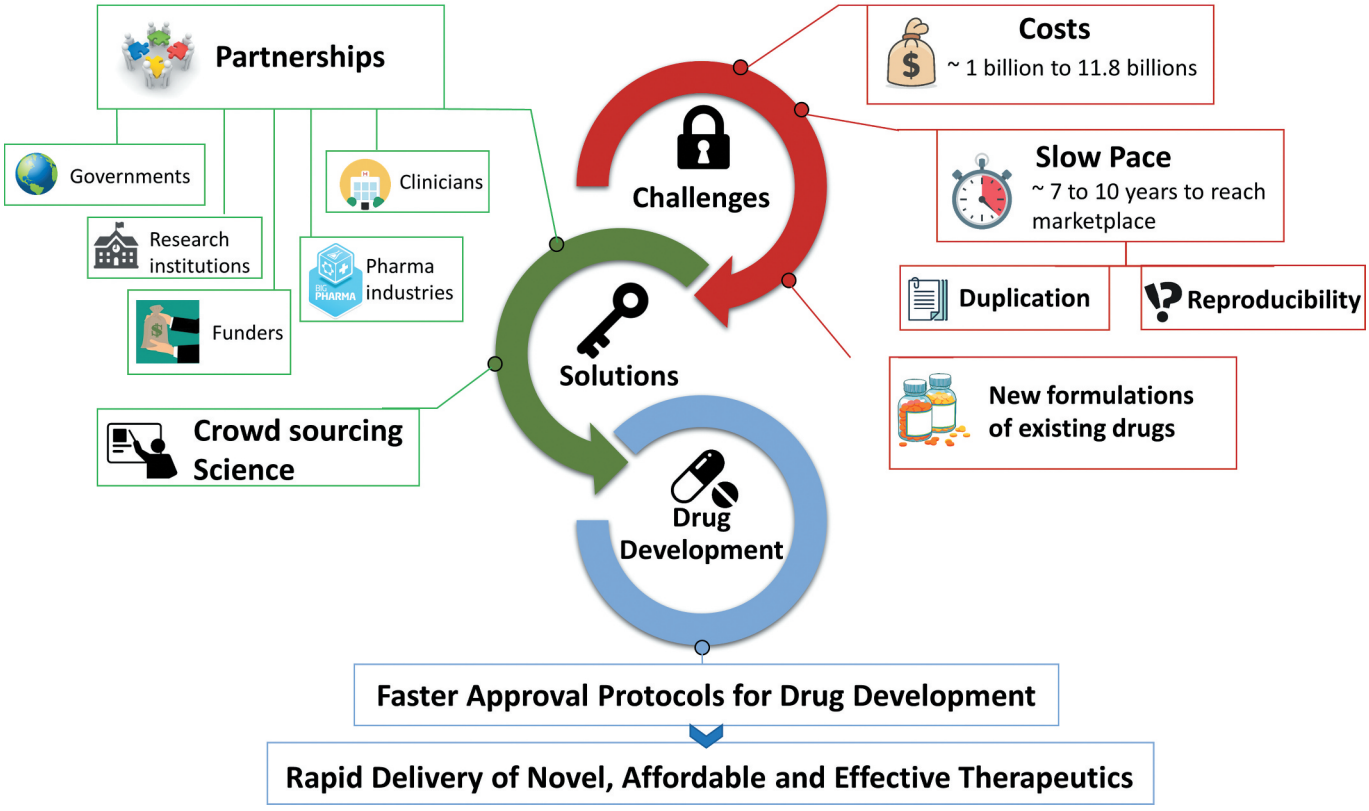

Figure 2. Schematic representation depicting the challenges facing the current drug development process and proposed solutions toward rapid delivery of novel, affordable and effective therapeutics.

Foundations of the National Institutes of Health (FNIH). ACTIV is defined as an international strategy to evaluate data on most promising early drug candidates for clinical trials by efficient use of NIH funding. The alliance will also study and analyze the genome of all SARS-CoV-2 strains, and how the virus infects various cell types and patients with different, underlining conditions, ages and genetic makeups. This is what the whole world looks forward to, a global alliance for the benefit of the humankind. Public–private partnerships, adaptive trial designs, and big data offers excellent avenues for innovating drug discovery and design process but face several challenges which must be met [27].

6. Expert opinion

We propose the need for establishing a consortium of various nations, academic institutions, clinicians, pharma companies, and funders to pave the way for efficient strategies to tackle the world's major health challenges. The consortium could bring in collaborative ideas that can quantify the benefits of open research to create a new ecosystem for the discovery and development of first-in-class effective and affordable medicines (Figure 2).

Additionally, to maximize the opportunity from scientific advancements and to bring in the right therapies to the concerned patients in a timely manner, we propose the following imperative actions: enriched collaboration, crowdsourcing, data sharing, improved patient access, and recruitment to clinical research, faster protocols for drug approval models. The effort would bring in the best of global minds which would effectively contribute the success of this venture. In addition, the above-mentioned scheme will also bring in various advancements in the field of scientific technology which would provide the necessary impetus to the sustainability and continuity of this idea. In this desperate time ever, public–private partnerships and the extension of the precompetitive space among academia, industry, and government could offer solutions to the global health challenges and to rapidly deliver novel therapeutics that are effective and affordable (Figure 2). And finally, what if a tiny fraction of the multi-trillion-dollar stimulus packages allocated by many nations to overcome the recession the world is experiencing now due to COVID-19, is apportioned for the proposed collaborative research? We will leave it to the reader to imagine the potential benefit such an initiative can reflect on the global humankind well-being.

Funding

The authors gratefully acknowledge the Research Funding Department at the University of Sharjah [Grant number: 1801110125-P] and the Aljalila Foundation [Grant number: AJF 202058] for funding this project.

Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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