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Drug Repurposing During The COVID-19 Pandemic: Lessons For Expediting Drug Development And Access

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ABSTRACT The COVID-19 pandemic created a large, sudden unmet public health need for rapid access to safe and effective treatments. Against this backdrop, policy makers and researchers have looked to drug repurposing—using a drug previously approved for one indication to target a new indication—as a means to accelerate the identification and development of COVID-19 treatments. Using detailed data on US clinical trials initiated during the pandemic, we examined the trajectory and sources of drug repurposing initiatives for COVID-19. We found a rapid increase in repurposing efforts at the start of the pandemic, followed by a transition to greater de novo drug development. The drugs tested for repurposing treat a wide range of indications but were typically initially approved for other infectious diseases. Finally, we documented substantial variation by trial sponsor (academic, industry, or government) and generic status: Industry sponsorship for repurposing occurred much less frequently for drugs with generic competitors already on the market. Our findings inform drug repurposing policy for both future emerging diseases and drug development in general.

Expedient and affordable access to safe and effective medicines is vital for improving patient health outcomes.¹ This has been salient during the COVID-19 pandemic, whose onset created a large, sudden unmet public health need for rapid access to safe and effective treatments for a condition with no proven therapeutics.² Although the public health needs were immediate, drug development typically occurs over much longer periods. The development of a new drug from preclinical testing to regulatory approval generally takes ten years, on average, costs between \$300 million and \$2.8 billion, and has more than a 90 percent failure rate.³⁻⁷ In the context of an emerging disease pandemic, delays in therapeutic development can lead to significant morbidity, mortality, and economic costs that might otherwise be avoided by faster development processes.

During the COVID-19 pandemic, drug repurposing—using a drug previously approved for one indication to target a new indication—has provided a potential means to accelerate the identification and development of novel treatments.⁸ As the pandemic led to remarkable efforts to quickly develop new therapeutics—notably vaccines developed in record-setting times—researchers simultaneously focused on the treatment possibilities from repurposing.

Broadly, drug repurposing is seen as offering three key advantages over de novo drug development. First, because repurposing starts with medicines that have already undergone clinical studies and regulatory scrutiny, repurposed drugs are often considered safer by avoiding the risk of exposing patients to a drug with unknown adverse effects.⁹ In the context of drug repurposing, the tolerable safety profile for a repurposed drug depends on whether the repur-

posed indication increases risk levels or lowers the acceptability of risks.¹⁰ For regulators, the benefit and safety considerations for de novo drug development and drug repurposing are similar in general, except that more will frequently be known about expected adverse effects when developing repurposed as opposed to de novo drugs. A second advantage is that investigators may leverage prior experience with a drug to expedite and lower the costs of development. For example, investigators may begin at later stages of development, use smaller clinical trials, and experience higher success rates in achieving approval for additional indications.¹¹ Finally, to the extent that repurposed drugs already have generic competitors, they may be available to patients at lower price points and help improve access to pharmaceutical innovations.

The medical and economic benefits associated with repurposing extend beyond COVID-19. The use of drug repurposing to identify treatments for various diseases has accelerated in recent years.¹² With the advance of novel techniques based on machine learning, artificial intelligence, or in silico screens, plus new data sources such as large-scale electronic health records, repurposing may play an increasingly important role in the future.^{13,14}

Despite the high level of interest, much remains to be learned about what policies and institutions may best support safe, effective, expedient, and accessible drug repurposing. There are long-standing concerns that current regulatory and market systems do not provide sufficient incentives for repurposing.^{9,12,15,16} For drugs that already face generic competition—precisely those drugs that potentially offer the greatest economic benefit from repurposing—pharmaceutical companies may have a limited ability to recoup the costs of developing additional indications. Repurposing during a pandemic presents unique challenges as well, including greater difficulty maintaining high scientific standards, communicating results clearly and frequently to the public, and ensuring ethical trial design.¹⁷⁻¹⁹

To date there has been relatively little empirical evidence documenting drug repurposing for COVID-19. The handful of studies exploring this have been case studies, have focused on the underlying science rather than policy, or occurred very early in the pandemic.^{20,21} Similarly, limited systematic knowledge exists to inform drug repurposing policy more generally. Prior research has leveraged case studies,^{22,23} bibliometric data,²⁴ and Food and Drug Administration (FDA) approvals.²⁵

We contribute to the existing literature by using the universe of US clinical trials to provide

systematic empirical evidence on the scale and scope of drug repurposing efforts for COVID-19. In addition to informing policy for future emerging diseases, we used COVID-19 as a “natural experiment,” providing an external shock to drug development investments to derive lessons for nonpandemic repurposing policy that would otherwise be difficult to investigate. For example, in the absence of such a natural experiment, it would be difficult to determine why any observed repurposing activity occurred when and where it did, as it may have resulted from scientific advances, policy changes, or firms’ rent-seeking behavior, among other potential explanations. In this study we examined the time course of drug repurposing trials during the pandemic, the profile of drugs tested, and variations in repurposing efforts by both trial sponsor (academic, industry, or government) and the presence of generic competition.

Study Data And Methods

COVID-19 TRIALS To systematically measure COVID-19 clinical research efforts, including both successful and unsuccessful development efforts, we identified clinical trials related to COVID-19 using ClinicalTrials.gov and the Cortellis Clinical Trials Intelligence database. We categorized the medical conditions studied in each trial with the International Classification of Diseases, Ninth Revision (ICD-9), coding system; we selected trials listing “coronavirus” as the primary condition being studied for inclusion in our sample. For each trial we also relied on additional information specifying trial characteristics, including the intervention, phase, and start date, and in our analysis we considered the sponsor as a proxy for trial funding.²⁶

We identified 847 unique COVID-19 clinical trials launched between January 1, 2020, and December 31, 2021. We restricted the sample to 531 trials specifically focused on assessing drug efficacy—trials testing small molecules, biologics, or combination products.²⁷ We also excluded phase 0 studies ($n = 9$), phase IV studies ($n = 35$), and studies missing phase status ($n = 2$). This resulted in our final analytic data set of 485 trials.

REPURPOSED DRUGS To determine whether a studied drug was approved by the FDA, we obtained approval dates and approved indications from the FDA website²⁸ and through manual review. As with the trials, FDA-approved indications were classified using ICD-9 codes. We defined *repurposed drugs* as those having an initial FDA approval date before March 11, 2020 (the date the World Health Organization [WHO] declared COVID-19 a pandemic). A diagram of the

sample selection process and a list of all repurposed drugs used in the trials are provided in online appendix exhibits 1 and 2.²⁹ To understand the roles of market exclusivity and competitive dynamics in incentivizing drug repurposing, we manually identified whether each repurposed drug had any generic competitors in the US marketplace as of January 1, 2020. To further explore the use of repurposed drugs for COVID-19 treatment, including off-label use without FDA approval or emergency use authorization, we also identified all drugs recommended for use as of March 2022 by either the National Institutes of Health (NIH)³⁰ or Infectious Diseases Society of America³¹ guidelines on COVID-19 treatment.

LIMITATIONS Our study was subject to several limitations. First, as mentioned above, we focused on interventional trials that listed coronavirus as the primary condition. This might not include other conditions closely associated with COVID-19 or observational studies without a supporting trial. For example, roughly 2 percent of the 485 clinical trials in our final sample also tested for multisystem inflammatory syndrome in children, a condition closely linked to COVID-19.

Second, our definition of *drug repurposing* excluded drugs that may have been previously developed, including having prior clinical trials, but that did not receive FDA approval. A prominent example of this is remdesivir, which was initially developed for Ebola but had not received FDA approval before the COVID-19 pandemic. In our data, sixteen drugs with a previous phase III trial but without FDA approval before the pandemic were tested against COVID-19. Although many policy considerations for such “recycled” drugs will be similar to those for repurposed drugs with prior FDA approval, there are also differences. These include the extent of prior testing and the strength of firms’ incentives to pursue new indications. For instance, use patents may provide robust financial incentives for drugs previously unapproved for any indication.³²

Third, our study is limited in the extent to which it informs the amount of repurposing that drug policy should support. Although repurposed drugs have led to substantial benefits for patients with COVID-19, we did not observe the costs of these development efforts. In line with this, although many treatments studied for repurposing had strong scientific rationales for testing their use in COVID-19, others were viewed as having much weaker scientific rationales or approaching pseudoscience.^{33–35}

Finally, our study analyzed repurposing for COVID-19 at a particular snapshot in time. It is possible that some repurposed therapeutics cur-

Repurposing seems to have lived up to its promise of quickly leading to the development of effective COVID-19 therapeutics.

rently in development will ultimately be found effective and that some currently recommended therapeutics may hold less promise as additional studies evaluate their use. Yet at three years since the start of the pandemic and as COVID-19 transitions from a pandemic to an endemic disease, sufficient experience with COVID-19 has accrued to reflect on what lessons may be learned.

Study Results

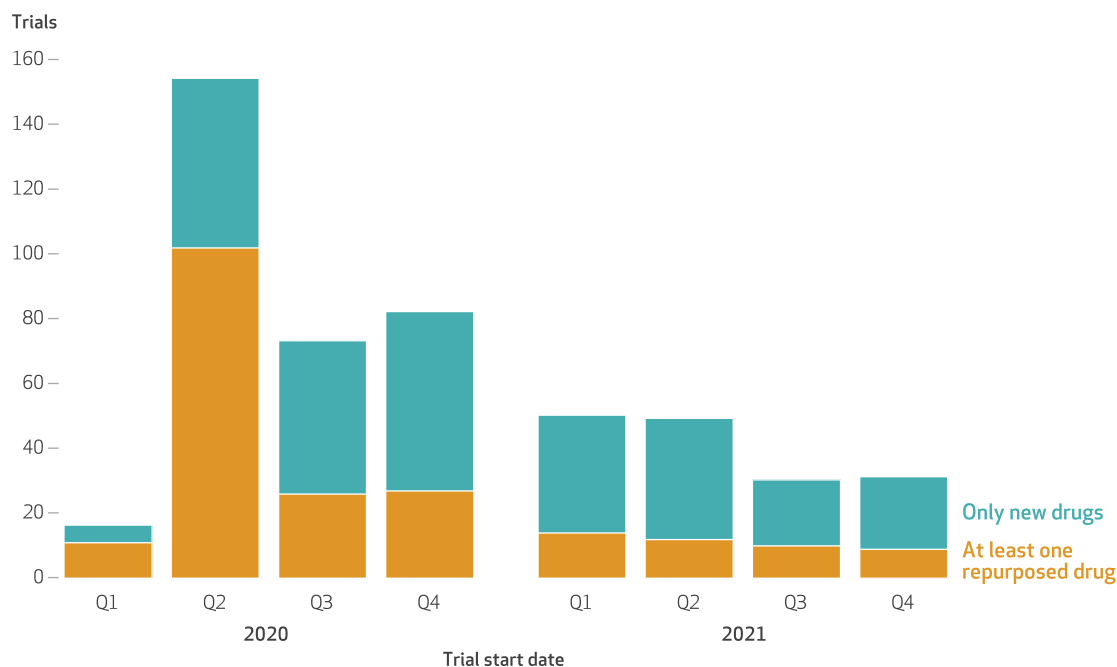
Of the 485 clinical trials in our final analytic sample, 211 trials (44 percent) tested at least one repurposed drug; in total, these trials tested 101 distinct repurposed drugs.³⁶

TIME COURSE OF DRUG REPURPOSING Although a small number of trials began in the first quarter of 2020, the largest number of total trials began in the second quarter of 2020, the first full quarter after the WHO declared COVID-19 a pandemic (exhibit 1). The overall number of trials per quarter decreased after that point: There were 154 trials in the second quarter of 2020 but only 31 by the fourth quarter of 2021. Initially, a majority of COVID-19 trials tested repurposed drugs, but as the pandemic progressed, trials testing *de novo* drugs represented a larger share of trials. During the first half of 2020, roughly two-thirds of COVID-19 trials tested a repurposed drug (69 percent in the first quarter of 2020 and 66 percent in the second quarter of 2020). However, from the third quarter of 2020 through the fourth quarter of 2021, only 31 percent of trials tested at least one repurposed drug.

SOURCES OF REPURPOSED DRUGS Exhibit 2 presents the disease categories for which repurposed drugs tested in COVID-19 trials were approved by the FDA. Drugs tested for repurposing were commonly motivated by purported anti-inflammatory activity to reduce virus-mediated pathology, direct antiviral activity against

EXHIBIT 1

US clinical trials for COVID-19 treatments, by drug repurposing status and quarter, 2020-21



SOURCE Authors' analysis of clinical trial data from ClinicalTrials.gov and the Cortellis Clinical Trials Intelligence database. **NOTES** The full height of each bar represents the total number of trials in the quarter indicated. The total number of trials is 485.

COVID-19, or the potential to treat complications from COVID-19 such as the increased risk for thromboembolic disease. In line with this, we found that drugs studied for COVID-19 repurposing were approved most often for infectious diseases or musculoskeletal issues, with the latter including many anti-inflammatory agents initially developed for rheumatologic diseases. Several tested drugs also treat diseases much more distantly related to viral infections, such as obstetric or mental health drugs. The mean age of repurposed drugs, measured from year of first approval, was 32.1 years, with a range from three to ninety-five years (appendix exhibit 3).²⁹

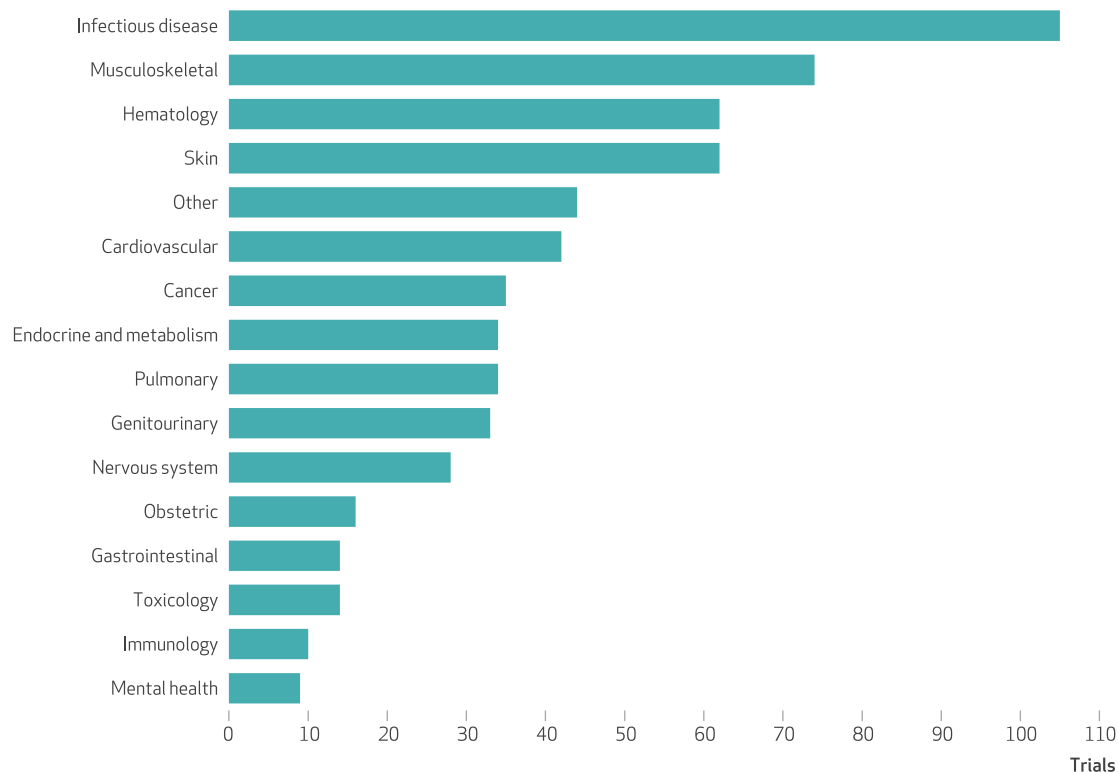
Exhibit 3 provides additional details on the most frequently tested repurposed drugs in the COVID-19 trials. Although the rationales for testing in COVID-19 among this group were diverse and sometimes multifactorial or poorly understood, many had proposed anti-inflammatory activity. Hydroxychloroquine, which was initially approved in 1955 for the treatment of malaria, was tested in the largest number of trials (forty-four trials, or 21 percent of trials testing repurposed drugs). Azithromycin, which was initially approved for pneumonia and skin infections, was the next most commonly tested drug, appearing in fifteen separate trials (7 percent). Several of the most frequently tested drugs are used in the treatment of rheumatoid arthritis

(hydroxychloroquine, tocilizumab, dexamethasone, and baricitinib).

REPURPOSING BY TRIAL SPONSORS AND GENERIC COMPETITION Exhibit 4 provides details on trial sponsors.³⁷ Among the 485 trials, 33 percent were sponsored by an academic institution alone, 40 percent by industry alone, and 3 percent by the government alone. Breaking down the trials by whether the tested drugs were new or repurposed revealed striking patterns: Trials testing only new drugs were more likely to be sponsored by industry. Of the 274 trials testing only new drugs, 59 percent were sponsored by industry alone and 13 percent by academia alone. These trends are almost exactly reversed when one looks at those that tested at least one repurposed drug (17 percent by industry and 60 percent by academia). Accounting for the availability of generics magnified the differences in sponsorship type: The majority (78 percent) of trials testing drugs that were repurposed and available as generic were sponsored by academic institutions alone. Looking at whether a trial had any academic, industry, or government sponsorship reveals similar trends as described above. Of trials testing only new drugs, 84 percent had at least some industry sponsorship, whereas 78 percent of trials testing repurposed drugs had academic sponsorship. Of trials testing only repurposed drugs with generic availability, more than

EXHIBIT 2

Disease categories of repurposed drugs tested in US clinical trials for COVID-19 treatments, 2020-21



SOURCE Authors' analysis of clinical trial data from ClinicalTrials.gov and the Cortellis Clinical Trials Intelligence database. **NOTES** The information in this figure is at the trial level, consisting of drugs' International Classification of Diseases, Ninth Revision (ICD-9), categories for trials with at least one repurposed drug. Because a given trial may test multiple drugs and because each drug may have multiple ICD-9 codes associated with it, trials may appear in more than one disease category. However, each trial is counted only once per disease category (that is, if a trial tests multiple drugs in the same disease category, the trial is counted only once for that disease category). The total number of trials is 211.

90 percent had an academic sponsor.³⁸

As a complement to this, we examined whether drugs recommended for use by the NIH or Infectious Diseases Society of America treatment guidelines^{30,31} had FDA approval, had an emergency use authorization, or were used off label for COVID-19 (appendix exhibit 5).²⁹ We found similar patterns: All repurposed drugs with generic competition (eight of eight) were recommended for use off label without an emergency use authorization or FDA approval. In contrast, one-third of repurposed drugs without generic competition (two of six) had FDA approval or an emergency use authorization for use in COVID-19.

Discussion

Repurposed drugs have offered an important potential source of pharmaceutical innovation against COVID-19. The majority (66 percent) of trials that we examined tested repurposed drugs as early as the second quarter of 2020, in line

with the idea that repurposed drugs may shorten required clinical development times compared with de novo drugs.

We also saw evidence that drugs not only were studied for repurposing but also made their way into the standard of care for patients with COVID-19, as evidenced by their inclusion in NIH or Infectious Diseases Society of America COVID-19 guidelines.^{30,31} These trends suggest that drug repurposing seems to have lived up to its promise of quickly leading to the development of effective COVID-19 therapeutics.

Notably, the drugs studied for repurposing had a mean age of thirty-two years and were initially developed for a wide breadth of initial indications. This emphasizes the difficulty in predicting the ways in which medical innovations may ultimately be used, as well as demonstrating the long-term returns to both the private and public efforts that supported these drugs' initial development.³⁹

In line with concerns that industry may have lower incentives for repurposing because of re-

EXHIBIT 3
The most frequently tested repurposed drugs in US clinical trials for COVID-19 treatments, 2020-21

Drug	No. of COVID-19 trials	Initial FDA approval year	Initial sponsor for approval	Selected prior uses
Hydroxychloroquine	44	1955	Advanz Pharma	Malaria, ^a systemic lupus erythematosus, rheumatoid arthritis
Azithromycin	15	1991	Pfizer	Community-acquired pneumonia, ^a skin infections ^a , acute otitis media
Tocilizumab	12	2010	Genentech	Rheumatoid arthritis, ^a giant cell arteritis
Dexamethasone	9	1958	Merck	Rheumatoid arthritis, ^a adrenal insufficiency, cerebral edema
Nitric oxide	8	1999	INO Therapeutics	Pulmonary hypertension in neonates ^a
Colchicine	7	1961	Merck	Gout, ^a familial Mediterranean fever
Famotidine	6	1986	Bausch	Gastroesophageal reflux disease, ^a gastric ulcer, Zollinger-Ellison syndrome
Losartan	6	1995	Merck	Hypertension, ^a diabetic nephropathy
Acetylcysteine	5	1963	Mead Johnson	Mucolytic, ^a acetaminophen toxicity
Baricitinib	5	2018	Eli Lilly	Rheumatoid arthritis ^a
Heparin	5	1939	Roche/Organon	Thromboembolism, ^a consumptive coagulopathies, atrial fibrillation
Naltrexone	5	1984	DuPont	Opioid dependence, ^a alcohol dependence

SOURCE Authors' analysis of clinical trial data from ClinicalTrials.gov, the Cortellis Clinical Trials Intelligence database, the Food and Drug Administration (FDA) website, and manual review. **NOTE** Table contains repurposed drugs used in at least five trials. ^aInitial indication or indications.

duced profits once drugs face generic competition, we found that industry sponsorship played a limited role in supporting drug repurposing. Instead, most sponsorship for clinical trials of repurposed drugs came from academic institutions, especially for drugs with generic competitors already on the market.

Policy Implications

Although we focused on trials for a specific disease, the COVID-19 pandemic experience may shed light on drug repurposing in other settings. First, when viewed within the broader landscape of treatment development, our results indicate that drug repurposing may be an important com-

plement to (rather than a substitute for) de novo drug development. Exhibit 1 indicates that as the pandemic progressed, research efforts increasingly turned toward de novo drug development. We attribute this change over time to several factors, including rising care standards making it more difficult for drugs to demonstrate superiority versus the current standard of care and many low-hanging ideas for both de novo and repurposed drugs having already been explored.

Second, the design of regulatory institutions to support future pandemic drug repurposing will need to balance the trade-off between moving expeditiously and maintaining high scientific standards. Our sample included 211 trials testing 101 different repurposed drugs. At con-

EXHIBIT 4
Breakdown of sponsorship type for US clinical trials for COVID-19 treatments, 2020-21

Sponsorship type	All trials (N = 485)	All trials (full sample)			Trials testing only repurposed drugs		
		Trials testing only new drugs (n = 274)	Trials testing at least one repurposed drug (n = 211)	Absolute difference ^a	Trials testing only drugs with generic availability (n = 117)	All other trials (n = 65)	Absolute difference ^a
Only academic	33.2%	12.8%	59.7%	46.9	77.8%	35.4%	42.4
Only industry	40.4	58.8	16.6	42.2	6.8	29.2	22.4
Only government	2.7	1.5	4.3	2.8	0.9	4.6	3.8
Any academic	54.2	35.8	78.2	42.4	92.3	63.1	29.2
Any industry	60.8	83.9	30.8	53.1	17.1	52.3	35.2
Any government	9.5	8.4	10.9	2.5	5.1	15.4	10.3

SOURCE Authors' analysis of clinical trial data from ClinicalTrials.gov and the Cortellis Clinical Trials Intelligence database. **NOTES** Percentages are given with respect to the total number of trials for the column. Absolute differences are calculated between the prior two columns. Appendix exhibit 4 shows detailed counts of trials by sponsorship type (see note 29 in text). ^aPercentage points.

ventional thresholds of statistical significance, a nontrivial fraction of initial positive results may be due to chance alone; early reports of efficacy might not hold up to further scrutiny. The challenge of false-positive study results is exacerbated by the difficulties of running high-quality clinical studies during a pandemic, as well as the unique costs of such findings in an emerging disease pandemic.^{18,40} These include early off-label use exposing patients to adverse effects before definitive clinical evaluation, emergency use authorization withdrawals shaking public confidence, the time and expense of running higher-quality follow-on studies, and declines in the pace of scientific progress as effort is made to disprove spurious initial results instead of pursuing other promising research avenues. Hydroxychloroquine provides a case in point: Limited initial evidence led to a large spike in demand, exposing patients to adverse effects, incurring significant direct costs, and spurring many follow-on studies before it was ultimately found to be ineffective.⁸ This emphasizes the importance of focusing on drugs with strong rather than marginal treatment effects and compelling, well-documented biologic mechanisms underlying their use.

Third, it is widely documented that efforts to repurpose drugs face headwinds from weak incentives and organizational barriers.^{9,12,15,41} From an industry perspective, even if it is cheaper than de novo drug development, drug repurposing remains a high-risk, expensive investment that also may identify new adverse effects threatening existing approved indications. Policies such as patent extensions for new indications may provide additional incentives but must be balanced with the costs of extended monopoly pricing by pharmaceutical companies and the possibility of gaming via low-value additional indications. If a generic competitor is already present, firms may have only a very limited ability to recoup investments in further development, significantly reducing incentives to repurpose drugs.

However, drug repurposing efforts led by academics with government funding face their own challenges as well. Academics and grant-making bodies might not have the expertise or time to navigate FDA approval processes; instead, clinical trials may be performed to study potential repurposed drugs, and providers may choose to use them off label. This is reflected in appendix exhibit 5,²⁹ where not a single repurposed drug for which a generic was on the market had received FDA approval or an emergency use authorization. Rather, these medications were recommended for off-label use in the NIH or Infectious Diseases Society of America guidelines.^{30,31} Although off-label use avoids the time

The COVID-19 pandemic experience may shed light on drug repurposing in other settings.

and expense of formal regulatory approval, it has limitations and costs as well. Off-label use, even though it is common, frequently has little or no scientific basis, emphasizing the value of rigorous regulatory review.^{41,42} In addition, restrictions on advertising off-label pharmaceutical use may slow the diffusion into practice of effective repurposed drugs for a new indication.^{43,44}

More generally, given that drug repurposing makes up a significant fraction of drug approvals and pharmaceutical revenue, great care must be taken in making adjustments to corresponding policy and regulation.⁴⁵ Moreover, the optimal policy and institutions to support drug repurposing will differ across contexts. For instance, repurposing during a pandemic to swiftly develop new treatments versus repurposing as part of a planned market expansion strategy for a de novo drug will have distinct considerations that need to be weighed.

Several initiatives to support drug repurposing have been developed in recent years, including the Discovering New Therapeutic Uses for Existing Molecules program launched by the NIH National Center for Advancing Translational Sciences in the US and the Developmental Pathway Funding Scheme by the Medical Research Council in the United Kingdom. Many possible policy solutions to the weak incentives for pharmaceutical companies to repurpose drugs have been suggested over the years, including direct government funding, contract research, prizes, patent extensions, adjustments to use patent rules, pharmaceutical tax incentives, and tradeable vouchers such as for priority review.^{8,9,46,47}

Conclusion

Data from trials initiated early in the COVID-19 pandemic provide insights into the role of repurposed drugs in expediting the identification of safe and effective treatments in both pandemic and nonpandemic settings. The results of this study suggest that efforts to repurpose drugs

to treat COVID-19 were an important complement to de novo drug development. Further policies to encourage drug repurposing efforts that can work in tandem with de novo development may be warranted. For example, centralized efforts to evaluate, fund, and coordinate clinical trials may help maintain high quality standards, minimize duplicative research efforts, and ultimately speed access to effective therapeutics for future emerging pandemic diseases.⁸

Given the potential opportunities from drug repurposing, additional topics that merit future study include examining the relative benefits of regulatory approval and off-label prescribing. In particular, for drugs with generic competition, how much should off-label prescribing, with evaluation and education via professional medical societies and scientific publications, be relied on, versus promoting formal FDA approval for new indications?

Our results indicate that academic institutions are more likely than other sponsor types to sponsor trials that test drugs with generic competitors already on the market. To the extent that

policy makers view regulatory approval as providing more net benefits than off-label prescribing, institutions that provide support to academics testing repurposed drugs may be necessary, to shepherd these drugs from successful clinical trials to formal regulatory approval. This may include funding contract research organizations with specialized expertise to assist academic-led repurposing efforts.

Although open questions remain, data on COVID-19 clinical trials indicate that repurposed drugs have offered an important source of innovation during the pandemic, facilitating timely access to effective treatments for patients. We believe that future research that systematically examines clinical trials for drug repurposing and considers the risk-benefit trade-off associated with repurposed drugs in nonpandemic settings will provide complementary, policy-relevant insights.⁴⁸ The results of this study highlight the importance of public policies to further support repurposing initiatives for both existing and future emerging diseases, as well as treatment development more broadly. ■

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 - 38 The presence of a single generic competitor might not result in the same market pressures and price reductions as broad-based generic competition. However, we expect that the dynamics of investment decisions and potential for additional market entry will dampen incentives to repurpose drugs even when only a single generic competitor is present. This is because a firm must bear the substantial investment costs and risks of drug development, but given the lower entry barriers for additional generic manufacturers, successful repurposing efforts with a meaningful financial return would have only a short window before additional generic entrants would compete away their economic profits. In our sample, repurposed drugs facing a single generic competitor constituted a relatively small percentage: Using the number of FDA-approved abbreviated new drug applications as a proxy for market structure, we found that four (7 percent) of the fifty-nine repurposed drugs with generic competition at the pandemic start faced a single generic competitor; the remaining fifty-five drugs (93 percent) faced broad-based competition.
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