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GENERIC DRUG REPURPOSING FOR COMMON DISEASES: PROPOSAL AND DESIGN OF A PULL MECHANISM

Report

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Background

As research and development (R&D) costs for novel drugs have increased, some view drug repurposing as a faster and cheaper option. Drug repurposing seeks to identify new indications through research on already-approved drugs. Estimates of the average cost of bringing a new drug to market range from $1.5 billion to $2.5 billion.[1,2] Conducting clinical trials and getting a drug to market can take on average 10.5 years — often longer when discovery and preclinical phases are included.[3] In contrast, research and marketing for repurposed drugs may cost around $300 million and can be completed in as few as three years.[4,5] Drugs targeted for repurposing have demonstrated safety in people through clinical trials and have amassed substantial real-world evidence while on the market. The combination of evidence generation during clinical trials and in real-world settings establishes well-defined safety and efficacy profiles. Therefore, developers of repurposed drugs may bypass early stages of testing and instead focus on demonstrating efficacy for a new indication.

Drug repurposing has recently seen an increase in interest especially for diseases with unmet medical needs and poor commercial markets such as rare diseases, neglected diseases, and emerging public health threats. There is also interest in repurposing generic drugs to find cheaper, accessible alternatives for expensive brand therapies. As the price of new branded drugs continues to rise, broader access to alternative therapies is becoming a more pressing need among patients, payers, and health systems. In 2023, the median annual list price for 47 new drugs was $300,000 according to a *Reuters* analysis, up 35% from $222,000 in 2022.[6] Generic drug repurposing presents a unique opportunity to increase access to therapies and lower prescription drug spending.

Yet, while most drugs have more than one indicated use or benefit, many drugs are never researched for indications beyond their initial targets, especially after the drug loses market exclusivity. There are a number of challenges to generic drug repurposing. In a systematic review conducted on drug repurposing, several barriers were identified including the lack of financial incentives, data access, biases, and liability risks (i.e., revealing new adverse events or toxicities).[7]

In this paper, we examine the challenge of financial incentives for generic drug repurposing and propose a pull mechanism as a potential solution. We closely examine the market failures driving this challenge and present key design elements for a pull mechanism to reward repurposing of generic drugs for common diseases affecting the United States' (US) population. We present cost estimates for the pull mechanism and consider potential benefits for several examples of common diseases. Our aim is to present a proposal for a pull incentive to reward generic drug repurposing for common diseases in the US and build a case for establishing and funding such a mechanism.

The Case for Action

Drug development is an expensive and risky endeavor. Drug developers must weigh the business risks against opportunities for success and profit when deciding where to direct their resources. For-profit companies are willing to take on risks if there is potential that the drug will reach patients and generate a sufficient return on investment. A primary incentive in the pharmaceutical market for ensuring profit after investment is patents. Patents provide market exclusivity — a guaranteed monopoly — for a set time period. However, once a drug loses market exclusivity, in many cases, generic competitors enter the market and the innovator drug's price is lowered substantially. For example, within 5 years, the prices of oral generics can be about 80% lower than the brand-name drug.[8,9]

Although pursuing second medical use patents for generic drugs is possible, it is generally not considered a viable solution as these patents can be difficult to acquire.[10] Acquiring these patents can also be risky because the developer may have to publicly disclose information related to ongoing clinical trials while waiting for the generation of sufficient evidence to file their patent. Even if a developer invested in expensive clinical trials for a new use of a generic drug and filed a patent for the new indication, the patent is essentially unenforceable. Other firms can still produce and sell the drug for other approved indications and prescribers and pharmacists can still provide patients with the cheaper generic versions. Pharmacists do not have information on the indication for which a certain drug is dispensed, and they are reimbursed at a fixed rate, incentivizing them to dispense the cheaper generic option. The knowledge generated from the developer-sponsored clinical trials therefore "spills over" to other entities, which represents a public goods problem. Clinical trial data on repurposed drugs is societally valuable since it can reveal effective new uses for existing drugs. However, as incentives currently exist, firms cannot guarantee a return on their investment for undertaking expensive clinical trials. Therefore, once a drug has generic competition there is a disincentive for pharmaceutical firms to invest in additional research.

While generic drug repurposing is expected to cost less than innovative development, late-stage clinical trials can still be expensive and can involve several risks. The biggest risk is that the drug fails to demonstrate meaningful benefit or efficacy for the new intended use. Another risk for developers is that new safety data or adverse effects may be identified, which may impact the use of the drug for already approved indications and drug sales.

Since for-profit companies lack incentives, most generic drug repurposing studies are conducted by academic institutions.[11] However, universities typically conduct studies that generate enough evidence to inform off-label use and are not positioned to sponsor regulatory submissions for label expansion or promotional activities. The regulatory approval process for repurposed generic drugs is difficult to navigate as there is no one-size fits all approach and approval requires a combination of new and existing clinical trial data. Regulatory approval does have important advantages for drug uptake, inclusion in treatment guidelines, coverage, and reimbursement.

Other health system stakeholders, such as public and private payers, stand to benefit from generic drug repurposing but are also faced with challenges that prevent them from financing clinical trials. In areas of unmet medical need, drug repurposing may increase medical care spending for payers in the short term, and long-term cost-savings may not be a large enough draw as initial payers may not accrue them.

It is difficult to compare the price for an existing drug versus a new drug, as the amount paid by the patient and insurer for any specific drug includes rebates, discounts, and copay programs. Therefore, there is limited visibility into potential cost-savings.

In order to encourage companies to take on risks associated with drug repurposing, incentives are necessary. Policies can create financial incentives to overcome market failures and have been impactful for a number of drug development challenges. There are two categories of financial incentives: push and pull. *Push incentives* offer upfront funding for R&D costs to de-risk the innovator's investments. A common example of push incentives is government funding for research. *Pull incentives*, on the other hand, reward innovators for successful drug development. These rewards can take various forms such as one-time cash payments, milestone payments, a guaranteed market upon approval (e.g., advanced market commitments), or a voucher of sufficient value to encourage development (e.g., priority review voucher).

Some push incentives are already in place to support generic drug repurposing efforts. US Federal agencies such as the National Center for Advancing Translational Sciences (NCATS) and the Biomedical Advanced Research and Development Authority (BARDA) provide up front funding for researchers conducting drug repurposing studies.[12,13] Push funding approaches have been used by the United Kingdom National Service and foundations such as the Bill and Melinda Gates Foundation and Open Philanthropy.[14,15] However, push funding approaches have limitations. Push funding does not ensure that organizations with the most relevant expertise, such as private information about potential uses, receive funding for research. Firms often have private information about potential new uses for specific generic drugs but chose not to study those uses in clinical trials due to a lack of financial incentive.[16]

Pull funding mechanisms, on the other hand, offer a promising complement to existing push funding. Pull funding does not pick winners and, instead, can reward firms that discover new uses first. A pull mechanism incentivizes the firms best placed to research new uses for a drug to do so. We posit that the creation of a pull incentive for generic drug repurposing can help spur investment in research on new uses of generic drugs.

Target Profile of a Generic Drug Repurposing Candidate

Before we propose a design of a pull incentive for generic drug repurposing, we must first set out a clear description of what exactly we are aiming to incentivize. Clear definitions are needed to guide developers and ensure there is a shared understanding of what constitutes generic drug repurposing, and which drugs may be potential targets.

Generic drugs are those that have lost all market exclusivity by the originator company. The emphasis on exclusivity rather than patent expiration captures drugs that may have received some form of exclusivity extensions as part of another incentive program that block competitors from the market. Eligible drugs for a generic drug repurposing pull mechanism should be those that either already have follow-on competitors or which could legally have competitors at the time of initiating clinical trials. As we described above, the presence of generic competitors drives the market failure for repurposing of generic drugs.

There are different types of studies on generic drugs that may be considered drug repurposing. Types of studies may include dose de-escalation, additional target populations, new drug combinations, or new indications. For common diseases, all these study types could generate value or health benefits. Pediatric or neonate populations, for instance, present a significant opportunity for addressing unmet medical need. Most drugs used for treatment in the NICU are used off-label and new drugs are often delayed in reaching pediatric populations because pediatric clinical trials are more costly than traditional trials and face significant challenges with recruitment. There are also conditions where the available therapies are very expensive and create a cost burden for both payers and patients. Dose de-escalation and new drug combinations present opportunities for more cost-effective treatment such as by determining the optimal dosage, and improving treatment outcomes and quality of life, especially in the cancer space.[17,18] The funder's goals will determine whether all categories of generic drug repurposing are considered or whether the scope is limited to determining a new indication only.

There are meaningfully different benefits generic drug repurposing can offer that a funder may want to consider in the mechanism. (1) A repurposed drug may offer improvement in care (either compared to current treatments or because there is an unmet medical need) but may not necessarily provide cost savings. (2) The repurposed generic drug may offer cost savings compared to existing treatments but no improvement in care (*i.e.*, is non-inferior compared to other treatment options but does not demonstrate added health benefit). (3) A repurposed generic also has the potential to offer both improvements in care and cost savings. All three categories of benefit have value to the health system and demonstrate the wide range of potential in drug repurposing. With so many opportunities for potential value add, we recommend keeping a broad scope for a pull mechanism design that is disease agnostic and open to all types of repurposing studies.

Design of the proposed pull mechanism

We propose a pull mechanism that rewards successful repurposing of generic drugs for common diseases in the US. The mechanism we propose includes the following design elements:

1. The reward will take the form of a cash prize linked to the use of the generic drug for the new indication and paid out in installments over a set period of time. Payment amounts will also be linked to the value of the repurposed therapy.
2. The prize will be paid to the firm that conducts the repurposing studies and achieves success.
3. Success will be defined as regulatory approval for the new indication (i.e., label expansion).
4. The mechanism will be disease agnostic, therefore any common disease affecting the US population is eligible as the target indication for a repurposed generic drug.

Here we go into further detail on each of these elements:

Element 1: At the outset, the funder would commit to paying firms up to a certain amount for each successfully repurposed generic drug. This “cap” could be considered the size of the pull fund. The funder would also agree to a specific $/disability-adjusted life years (DALYs) averted metric. The funder could list examples of how they intend to estimate DALYs but could not practically do this for all possible

treatments of all possible diseases. Therefore, specific DALYs averted details would need to be determined on a disease and treatment-specific basis. This determination could be made prior to firms investing in later stage clinical trials to help create certainty for firms prior to significant investments in development.

DALYs averted would be assessed relative to the standard of care as determined by the funder. Funders and 3rd party organizations would estimate DALYs averted for each increment of payment (i.e., year). Linking payments to DALYs would incentivize firms to discover high-value applications.

The funder may make payments for either a certain period of time (based on estimated time to reach the prize fund amount) or continuously until the prize fund amount is reached. Payments may be made on an annual basis, based on the prior year's prescriptions. Reliable data on the use of the drug is required to operationalize the mechanism. National level data drug prescriptions for the new indication may be obtained through a health data company such as IQVIA. IQVIA has access to claims data, across both public and private payers, and can use these claims to track drug prescriptions tailored to the disease or condition of use. Reports generated from claims data can capture the total prescriptions of the repurposed drug for the new indication across the US each year. This amount can be multiplied by the amount per use to determine how much of the cash prize will be awarded after each year.

Element 2: The funder will reward firms that conduct drug repurposing studies and achieve success (i.e., label expansion with FDA). Only the firm that sponsors the trials and regulatory submission will be eligible for the prize. However, it is important to note that exclusivity is not a component of the mechanism. This means all generic firms making the drug (in the same dose and formulation as approved for the new indication) may continue selling their versions on the market; however other generic firms are not eligible for any of the prize fund. There may be some spillover effect as demand for the drug may increase and boost overall sales. The lack of exclusivity here also has the added societal benefit of maintaining access and affordability and supporting expanded manufacturing capabilities to avert drug shortages.

Element 3: We recommend regulatory review and label expansion be a requirement for receiving the prize fund. This requirement provides a clear target for success, which will trigger the payment of the prize fund. Regulatory approval may be considered a high bar and challenging for some developers, but it has several advantages including encouraging promotion and uptake of the drug for the new indication and supporting coverage by payers. Firms can only market drugs for indications if they are approved by the FDA. With a label expansion, the sponsor may promote the repurposed treatment to prescribers, patients, and use other pharmaceutical marketing tools. Since the pull mechanism is linked to use (i.e., number of prescriptions), the sponsoring firm will benefit from the ability to promote the drug to prescribers and patients. Having FDA approval dramatically increases the likelihood of coverage by major health plans. For example, CMS generally does not cover off-label uses of drugs. The only exception is in cases where off-label use is deemed medically appropriate and necessary following an authorization process.[19,20] Payers may be open to reimburse for off-label use when a drug is included in clinical guidelines established by physician-led groups and societies (e.g., American Academy of Family Physicians). Inclusion in clinical guidelines may be considered a reasonable alternative to regulatory

approval for some diseases and conditions. Our preference is for label expansion to be the prize-awarding requirement.

Element 4: We suggest that the mechanism should remain disease agnostic, as limiting the reward to a narrow set of diseases may exclude conditions that can be treated with an existing generic drug. With a high degree of unknowns in drug development, there is no guarantee that a generic drug may be repurposed for any specific disease. We argue that keeping the mechanism disease agnostic allows more opportunities for successful drug repurposing that is led by research into treatment common diseases rather than what will be eligible for a reward. We realize this also opens the door for multiple potential reward recipients, which could be financially burdensome to a funder. The implementor/funder may consider putting a cap on the number of generic drug repurposing successes they are willing to reward. Although we recommend the disease agnostic approach, we also realize that it may be in the funders' interest to establish some guidelines targeting specific diseases or treatments. Using emerging AI tools for drug development could inform a targeted list of diseases and conditions for a pilot of the pull mechanism.

Benefit-cost analysis

Demonstrating that the benefits of a pull mechanism for generic drug repurposing would justify costs is essential for securing funding and implementing a program. We selected three diseases/conditions impacting patients in the US to perform a benefit-cost analysis: stroke, preterm birth, and Long COVID. Stroke is a major contributor to death and disability in the US, while preterm birth represents a major area of unmet medical need with no approved drugs currently on the market.[21] Long COVID represents a newly identified source of health care costs and disability in the US.[22,23] Benefits are estimated in DALYs and monetized DALYs. Costs – a function of DALYs, as described in the "Design" section – are estimated for each disease using a $/DALY value and the estimated DALYs averted for each disease. However, we also estimated the costs necessary to induce firms to repurpose generic drugs for two repurposing scenarios (i.e., simple and complex repurposing). These cost estimates are used to determine (a) if firms would attempt to repurpose a generic drug for each disease, given our assumptions, and, if so, (b) what the benefit-cost ratio (BCR) is for the funder.

Benefits estimates

For each of the three diseases, we calculated the number of deaths and disability-adjusted life years (DALYs) averted. The analysis adopted a time horizon of 27 years (2024-2050) in which the accrual of health benefits began once the repurposed drug completed all R&D and clinical trials (assumed to be 2033 for simple drugs and 2042 for complex drugs).

The health impact model used a few assumptions when calculating the outputs, including (1) upon market entry a new repurposed drug will increase treatment coverage by five percentage points per year with treatment coverage reaching no higher than 95%, (2) following market entry of a new repurposed drug the standard of care will be phased out at a rate of five percentage points per year until an equilibrium is reached in which 50% of treated cases receive the standard of care and 50% receive the new drug, and (3) a new repurposed drug will be 10% more effective than the standard of

care at reducing morbidity and mortality. Assumption (1) has been used in previous modeling studies and is considered an achievable annual incremental rate of coverage.[24–26] Assumptions (2) and (3) are demonstrative but are thought to be conservative characterizations of the market dynamics and potential incremental effectiveness of new pharmaceuticals.

Using these assumptions, we calculated deaths and DALYs averted over our analysis timeline as the difference between deaths and DALYs accrued in a base case scenario – with no repurposed drug entry into the market – versus a new drug scenario in which a new repurposed drug enters the market.

We made a few modifications when modeling for preterm birth. To calculate the DALYs averted by introducing a new drug for preterm birth, we assessed DALYs for both the mothers and children impacted by preterm birth. For mothers, post-partum depression served as a proxy for health impact assessment. For children, neurodevelopmental disorders within the first five years of life were considered. Furthermore, a new preterm birth drug would prevent new cases of the condition (reduce incidence), going beyond the reduction of disease severity or duration. Consequently, the preterm birth health impact model did not model a pre-existing medication (because there are none currently approved by the FDA), so no drug was phased out over time and the assumption related to efficacy over the standard of care was not used. Assumption 1 regarding drug coverage remained consistent with those previously described.

All inputs used within the model including incidence rates, US population estimates, disease durations, disability weights, case-fatality rates, and treatment coverage estimates were collected from peer-reviewed literature. Equations 1-11 in the appendix show how all inputs and assumptions that were used to calculate incidence cases, cases not treated, cases treated, deaths, years of life lost to disability (YLDs), years of life lost to death (YLLs), and DALYs for both the no repurposed drug and new drug scenarios, along with the realized values for each parameter adverted by the introduction of the repurposed drug. The inputs and their sources can also be found in the appendix.

Table 1 shows the health benefits accrued over our 20-year time horizon for each disease-drug combination. A simple repurposed drug for stroke would treat 3.13 million cases over 27 years thereby averting 43,891 deaths and 2.35 million DALYs. A simple repurposed drug for Long COVID would reach 16.78 million cases over 27 years, averting 1,670 deaths and 0.34 million DALYs. A simple repurposed drug for preterm birth would reach 3.45 million cases over 27 years, averting 2,034 deaths and 0.44 million DALYs. A complex repurposed drug would necessitate a longer duration in the R&D pipeline compared to a simple repurposed drug. Consequently, this would lead to notably less time available on the market and fewer health benefits gained for each disease within our 27-year timeframe.

Table 1. Health benefits by disease

Disease	Drug type	Number of cases treated with new drug (millions)	Deaths averted	DALYs averted (millions)
Stroke	Simple	3.13	43,891	2.35

Long COVID	Simple	16.78	1,670	0.34
Preterm Birth	Simple	3.45	2,034	0.44
Stroke	Complex	1.11	16,937	1.08
Long COVID	Complex	6.12	609	0.14
Preterm Birth	Complex	0.87	515	0.11

In this report, we monetize DALYs to provide a standardized economic measure of health impacts. This approach allows us to communicate the value of health improvements in financial terms that policymakers and funders can readily understand and use in comparisons to other health interventions. For our analysis, we use a value of $15,080 per DALY, which is equivalent to the annualized minimum wage in the United States.[27] We chose this figure as it represents a conservative estimate of the economic value of a year of healthy life, based on the minimum amount a person might earn in a year of full-time work in the U.S.

Cost estimates

As proposed in the design section, this mechanism is designed to pay firms per estimated DALY averted. The cost model uses the DALY estimates from the benefit model to estimate the program costs for each disease-use combination. The $/DALY value that our cost model assumes funders will pay is $3,770, which is 25% of the $/DALY used to estimate the monetized health benefits.[27] This 25% figure was chosen to create enough incentive that firms will want to enter but is meaningfully below 100% to ensure society at large does not yield all the benefits associated with the innovation to the drug developer.

To understand if the rewards are reasonably sized, the team estimated the costs necessary to induce firms to enter. More specifically, we estimate the costs necessary to induce enough R&D attempts such that there is a 66% chance of developing and gaining approval for one or more new indications for a generic drug.

We acknowledge that developing drugs for different diseases and in different therapeutic areas can vary significantly in cost and probability of success. For example, common diseases that affect a larger patient population require a large patient sample in clinical studies, which is costly. Thus, one should interpret our results as the *average* costs necessary to induce enough firms to yield the 66% threshold. We chose to use average costs given that our mechanism is meant to incentivize repurposing efforts on a broad range of diseases. However, it is possible that funders may choose to vary reward sizes by broad disease or therapeutic categories in order to increase the efficiency of the reward.

This estimate of the necessary reward size can be used to estimate if firms would develop drugs for the different disease categories we modeled and to help avoid the funder overpay. If the estimated reward for a specific drug-disease combination, we assume firms would not attempt to develop a drug for this combination. On the other hand, paying for each DALY risks paying firms far more than is necessary to induce them to perform R&D and beyond what is fiscally feasible for any funder. Therefore, the team

"caps" the reward size at 1.5 times the estimated costs necessary to induce firms to perform R&D on a specific drug-indication combination.

The team estimated the necessary reward size using the average cost of clinical development, probability of success, phase duration, and expected rate of return by pharmaceutical firms. Phase cost, probability of success, and phase duration figures were derived from two sources: the Portfolio-To-Impact Model ("P2I") tool (2018) and a *Nature* article published by Paul, et al.[28,29] The P2I tool estimates the costs and likelihood of success for different phases of drug development across various therapeutic areas using historical data. The tool has estimates specific to repurposed drugs. The *Nature* article was used when P2I did not have available data. Specifically, it was used for the discovery phase cost, discovery phase probability of success, new drug application probabilities of success, and new drug application duration assumptions. To account for firms' expected rate of return, we selected the real cost of capital rate of 10.5% per year, as used in other studies estimating cost of trials.[30,31]

We model two repurposing cost scenarios: "simple" and "complex." One reason costs and probabilities of success for generic drug repurposing may vary is the availability of prior data and research. For some diseases, potential repurposing candidates have already been identified and may have been tested in smaller studies. Such generic drug candidates may skip early stages of clinical research and begin at Phase 2 to demonstrate efficacy. We have defined this as the "simple" repurposing pathway. For other diseases, researchers may need to start at the discovery or pre-clinical phase to identify potential generic compounds that could be a match for the target disease or symptoms. Some investment would be needed for the discovery and preclinical phase before moving on to clinical trials, and therefore we have defined this as the "complex" pathway. Another example of a complex pathway may include changes in dose or patient population, which may require Phase 1 studies to demonstrate safety. See the appendix for a full list of phase cost, probability of success, and duration assumptions.

We applied these inputs to a model developed by researchers at Harvard University and Boston University. The model was originally developed for calculating the necessary size of prize funds for antibiotic development with funding from Arnold Ventures. The Duke University and University of Chicago teams made adjustments to the model to fit our specific cost modelling needs for generic drug repurposing.

The team estimates that a reward size of **$368 million** is required in order to induce firms to engage in "simple" repurposing and nearly **$3 billion** in order to induce firms to engage in "complex" repurposing for one drug-use combination. Therefore, our maximum (i.e., 1.5 times the necessary amount to induce firm entry) is **$551 million** for simple repurposing and **over $4 billion** for complex repurposing.

In addition to the total prize, monitoring is required to assess the uptake of the generic drug for the relevant indication. We estimate monitoring costs as involving a $124,000 upfront payment, followed by annual payments of $130,000. These estimates are derived from stakeholder interviews. Total funder costs, reflecting both the $/DALY prize – capped at 1.5x the size necessary to induce firm entry – and monitoring costs are listed in Table 2.

Table 2. Total funder costs

Disease	Drug type	Funder cost (USD billions)
Stroke	Simple	$0.55
Long COVID	Simple	$0.55
Preterm Birth	Simple	$0.55
Stroke	Complex	$0.77
Long COVID	Complex	$2.02
Preterm Birth	Complex	$0.04

Note: All values are expressed in present value and are rounded to the nearest decimal.

Benefit-cost ratios

For each disease, we calculated a BCR defined as the monetary value of DALYs averted divided by the total funder cost (reward plus monitoring costs). The BCR therefore represents the monetary returns to society for each USD $1 invested by the funder for the development of a new repurposed drug. We monetized DALYs averted using an income-based approach (see Equation 12 in the appendix). All monetary costs and benefits were discounted at an annual rate of 3.0%.

Table 3 shows the monetary value of health benefits, funder cost, and BCR for each disease-drug combination. A simple repurposed drug for stroke, Long COVID, and preterm birth would result in societal returns amount to USD $38.0, USD $5.5, and USD $6.7, respectively, for each USD $1.0 invested by the funder towards incentivizing the development of a new repurposed drug. Societal returns per USD $1.0 invested by the funder for the development of a complex repurposed drug would be substantially lower – USD $2.1, USD $2.0, and USD $2.0 for stroke, Long COVID, and preterm birth, respectively – due to less simulated time on the market because of the longer clinical trial development timeline.

Table 3. Monetary value of health benefits and benefit-cost ratios

Disease	Drug type	Monetary value of DALYs averted (USD billions)	Funder cost (USD billions)	Benefit-cost ratio
Stroke	Simple	$20.97	$0.55	38.0
Long COVID	Simple	$3.01	$0.55	5.5
Preterm Birth	Simple	$3.69	$0.55	6.7
Stroke	Complex	$8.45	$0.77	2.1
Long COVID	Complex	$1.06	$2.02	2.0
Preterm Birth	Complex	$0.84	$0.03	2.0

Note: All values are discounted using a discount rate of 3%. Rows are “grayed-out” for disease-drug combinations that do not yield a sufficient reward size in order to induce firm entry.

Sensitivity analysis

To account for uncertainty around our model assumptions and inputs, we conducted three sensitivity analyses described in Table 4. Each sensitivity analysis focuses on a different component of our benefit-cost model and captures the health benefits or costs resulting from the use of less conservative assumptions and or inputs. In summary, the sensitivity analyses model: (1) R&D efficiencies resulting from the use of artificial intelligence and adaptive clinical trials, (2) variation in the cost of capital, or (3) higher treatment coverage and drug adoption rates. For each sensitivity analysis we report the resulting BCRs. Additional information on deaths averted, DALYs averted, monetary value of health benefits, and funder costs for each sensitivity analysis can be found in Tables 9-10 of the appendix.

Table 4. Description of each sensitivity analysis

Sensitivity analysis (SA)	General effect modeled	Specific effects modeled (all effects are modeled together)	Relevant industry or area
SA 1[32]	Use of AI and adaptive clinical trials	30% reduction in the cost of preclinical trials 25% reduction in the cost of clinical trials 10% increase in the success probability of clinical trials 1 year reduction in the duration of preclinical trials	Pharmaceutical companies, R&D
SA 2	Reward system – exploration of the minimum and maximum cost of capital for pharmaceutical R&D	Annual cost of capital rate of 8% (lower bound)	Funder
SA 3	Health impact – exploration around changes to treatment coverage, adoption rates, and treatment efficacy	Treatment coverage increases by 10 percentage points per year New repurposed drug phases out standard of care until an equilibrium is reached such that 100% of treated cases receive new drug and 0% of treated cases receive standard of care	Population

		New repurposed drug is 15% more effective than the standard of care at reducing morbidity and mortality*	

**Note: drug efficacy was not varied for preterm birth due to no existing standard of care currently existing.*

Table 5 shows the BCRs for each disease-drug combination and sensitivity analysis. Each sensitivity analysis results in a higher BCR across all disease for simple drugs-drug combinations due to the use of less conservative inputs and assumptions, while BCRs for complex drugs were mostly unchanged. Sensitivity analysis two – decreased annual cost of capital – produces the largest increase in the BCR for each disease-drug combination except for preterm birth where sensitivity analysis three – faster treatment coverage expansion, larger overall adoption of the new repurposed drug, and higher drug effectiveness – produced the highest BCR.

Table 5. Benefit-cost ratios from each sensitivity analysis

Disease	Drug type	SA 1	SA 2	SA 3
Stroke	Simple	44.6	52.5	38.0
Long COVID	Simple	6.4	7.5	5.5
Preterm Birth	Simple	7.8	9.2	6.7
Stroke	Complex	2.6	3.1	2.1
Long COVID	Complex	2.0	2.1	2.1
Preterm Birth	Complex	2.0	2.0	2.0

Note: All values are discounted using a discount rate of 3%. Cells are "grayed-out" for disease-drug combinations that do not yield a sufficient reward size in order to induce firm entry.

Path to implementation and funding

Implementation of the mechanism

Implementing the mechanism would require several key actions. First, the implementing agency will need to establish a committee of expert advisors, who will determine the criteria for the mechanism. The committee must weigh the interests of the funders and the US public health needs. The implementer must provide clear objectives and criteria for the mechanism to guide interested developers. As a first step, the advisory committee may propose a pilot program focused on promising lead examples for generic drug repurposing. Establishing narrow criteria to target opportunities with strong likelihood of success that align with the funder's interests could be used as an early demonstration of the mechanism. If the mechanism proves successful as an incentive and provides the anticipated benefits, the committee may propose expansion of the program. The qualifying criteria the implementer and its advisory committee may want to set forth are outlined in the appendix.

Most importantly, the implementer will need to make payments to the successful firm on a regular basis – we recommend annually. The implementer will also need administrative support to determine the total prize fund amount. Above, we proposed a necessary size for the prize fund and also showed how the amount may vary with other considerations in the sensitivity analyses. The implementer must make a final determination on the size of the prize fund. Adjustments to the payment amount may be needed to incorporate realized value, as we've proposed above. If the implementer decides to reward value, internal or third-party analysts will be needed to assess the value of the repurposed generic drug based on clinical trial data and determine the appropriate additional value payment. Analysts can also determine the payment amount per prescription. A contract may be established to stipulate the amount to be paid per prescription, the schedule for payments, and the award duration.

Tracking prescriptions for the new indication is another integral component of the proposed mechanism. The agency will need to partner with a health care data and analytics partner to aggregate and analyze data on a national level. There are various firms to consider for this partnership. For example, an organization like IQVIA has access to a comprehensive set of claims data from across public and private payers and can generate reports with the necessary prescription data. The reports supplied by the health care data company will inform the annual prize payout amounts.

Funding agencies could limit the number of repurposing initiatives they fund in order to control their total costs. This strategy, though, would necessitate adjusting the prize fund size forecasts because companies would theoretically seek increased per-discovery payments to mitigate the uncertainty of securing funding within a specific year.

Identifying an implementer and funder

To identify an appropriate implementer for this mechanism, we must consider the various roles and expectations required. The implementer needs capabilities to provide the reward funds to the successful developer, calculate the payment amount per prescription including value adjustment, track the annual prescription data to determine annual payout amount, and offer strategic consulting to interested firms. The implementer would ideally reap some benefits of successful drug repurposing to encourage their investment in the mechanism. Finally, an implementer must also be well positioned to work across sectors.

There are multiple potential funders and implementers for the common diseases' generic drug repurposing pull mechanism, depending on interests. **Philanthropic funders** may have interest in implementing this mechanism if it were to align with their disease or population area interests. This would limit the scope of the mechanism but may present an opportunity to demonstrate how the mechanism may support generic drug repurposing and be considered for further adoption. Narrowing the disease scope comes with some risks, as there is no guarantee a repurposed drug can be identified for any specific disease.

Private payers or accountable health systems in the US may also be interested in the mechanism, since they stand to benefit from cost savings from generic drug repurposing. The specific criteria and goals of the mechanism would need to align with the payers' interests, such as reducing costs or improving the quality of care. These interests may allow for a broader disease scope for the mechanism. The fractured commercial payer market in the US poses a challenge, as payers would need to work together or pool

funds to support a mechanism. However, they may be disincentivized from collaborating because of the "free rider" challenge. Payers, who choose not to contribute to the mechanism could still benefit from the new indications for generic drugs and receive financial benefits from lowered prescription drug costs without having made any investment. This challenge may be overcome though if the benefits are large enough and the cost for each payer to contribute to the prize fund is low enough.

Consequently, we focus our recommendations for a funder and implementer on the US F**ederal government.** The US Federal government may also have interest in supporting or funding the prize mechanism and could play a pivotal role in its implementation. Government direct payers, such as the Department of Veteran Affairs (VA) or Department of Defense (TriCare), pay for care for millions of Americans and stand to benefit from cost savings and outcome improvements of drug repurposing for diseases that affect the populations they serve. The Department of Defense (DoD) already provides significant funding for R&D of treatments likely to be of particular benefit to the military. Furthermore, the broader societal benefits of drug repurposing are more aligned with the interests of the US Federal government than portions of the private sector. The US Federal government is also best positioned to implement a disease agnostic drug repurposing mechanism and to work with the many necessary stakeholders.

There are precedent proposals for US Federal government funding of rewards. For example, the PASTEUR Act is a proposed incentive program for antimicrobial drug development. The proposed bill gives authority to the US Department of Health and Human Services (HHS) to enter into subscription contracts with manufacturers for antimicrobial drugs.[33] The bill proposes the creation of an office with the Administration for Strategic Preparedness and Response (ASPR) to administer the contracts. While this bill has not yet been passed by Congress, it demonstrates the challenge of implementing incentive programs in the Federal government and the shared consideration of the concepts we are underwriting in our proposed pull mechanism.

HHS would be the most likely home for this proposed mechanism, but determining which agency is best positioned to fund and implement the incentive program is less straightforward. Several agencies, including the National Institutes for Health (NIH), NCATS, ASPR, and the Advanced Research Projects Agency for Health (ARPA-H), have already shown interest in advancing repurposing efforts, largely in the form of push funding (i.e., grants) for research. However, there are limitations and challenges when considering any of these agencies as a potential implementer. ASPR is well positioned to support generic drug repurposing, through both push and pull funding but only for public health emergencies or national security threats. NIH typically provides push funding for drug development through supporting many phases including pre-clinical and clinical trials. While NIH does not currently implement pull funding, it could be considered a plausible extension. However, extramural research funds are typically dispersed through institutes within NIH, such as NIAID or NCATS.[34] Although NCATS has been engaged in efforts to support drug repurposing, its efforts are currently restricted to rare diseases. The newly established ARPA-H has a broad scope to support transformative biomedical breakthroughs by investing in various potential solutions.

Another operating division of HHS to consider is the Centers for Medicare and Medicaid (CMS). CMS's role as a payer makes it a potential implementer for this mechanism, as Medicare and Medicaid beneficiaries (and Federal spending) could benefit from such a drug repurposing mechanism. However, we identified several challenges to implementing our proposed mechanism within CMS. One challenge is

the separate management of and payment models for drugs under different parts of Medicare. Part A covers drugs administered as part of inpatient hospital care and Part B covers prescription drugs that are administered in outpatient healthcare settings. Part D covers all other prescription drugs; however, it is optional under Medicare and is provided through contracted private insurance companies. Creating a generic drug repurposing pull incentive that can reward drugs used in all settings – inpatient, outpatient, and pharmacy-dispensed – would be significantly difficult to achieve. Drugs under part D are particularly challenging since the payers are federally approved private insurance companies. Yet another, greater challenge is that CMS only makes payments directly to providers or health facilities for Parts A and B drugs and to private plans in Medicare Part D. There is currently no existing pathway or authority for CMS to make direct payments to drug developers or manufacturers. This poses a crucial issue to our proposed mechanism.

While CMS does not have the legislative authority to implement such a drug development incentive program, there is precedent for support through CMS to develop innovative methods for lowering drug costs and health care costs more generally. The Inflation Reduction Act (IRA) included multiple provisions aimed at lowering prescription drug costs, including granting CMS the authority to negotiate Medicare prices for high-cost drugs with no generics or biosimilars on the market and to impose penalties on drug makers that increase prices faster than inflation. The IRA also took measures to reduce costs to Medicare beneficiaries such as capping out-of-pocket (OOP) insulin costs and removing OOP costs for adult vaccines.[35] To complement these efforts, President Biden also signed an Executive Order in October 2022 directing the Center for Medicare and Medicaid Innovation (CMMI) to consider a new payment and delivery models that could lower prescription drug costs.[36] One new payment model CMMI is implementing is the Cell and Gene Therapy (CGT) Access Model. In this model, rather than making payments directly for cell and gene therapies, CMS is coordinating and supporting multi-state Medicaid agencies to establish outcomes-based agreements with manufacturers by creating standard terms and implementing the agreed upon outcomes measures.[37] It is possible that CMS could play a similar supportive role in collaboration with other HHS agencies to support a pull mechanism. CMMI may also be tasked with considering a model that could support the generic drug repurposing pull mechanism.

Recommendations for implementation within the US Federal government

As mentioned above in the implementation overview, a pilot of the mechanism may be a beneficial starting point to demonstrate the value of the mechanism and generate greater interest among potential implementers. ARPA-H could develop or prime a pilot program, to help leverage other funding sources from within HHS or from philanthropic organizations or private payers. ARPA-H recently announced nearly $50 million in funding to support the development of an AI platform to identify new uses for existing drugs.[38] A generic drug repurposing incentive program could further complement existing efforts to reduce drug prices and unlock the full potential of existing treatments. In particular, ARPA-H could help organize a bidding or contribution mechanism for funding the reward, either from potentially interested parties for a particular promising drug or condition, or from its own analysis of examples where federal and/or private savings would be expected to offset the reward costs. Indeed, ARPA-H could potentially solicit bids for such a demonstration of the feasibility and generalizability of this approach, using a lead example. For a pilot, ARPA-H may choose to commit to funding a certain number of repurposed generic drugs – perhaps two or three as a proof of concept.

If an ARPA-H run pilot program can demonstrate success, this may open the door for a legislative proposal to establish a more permanent program within HHS. Similar to how the PASTEUR Act proposes an office with ASPR to administer subscription contracts, a generic drug repurposing proposal could suggest an implementing office within NIH. There may also be support steps CMS can take, which could be explored by CMMI. If the ARPA-H pilot can provide evidence of strong cost savings and/or health benefit for patients, this may encourage CMMI to explore this option.

Conclusion

Generic drug repurposing holds substantial potential as a cheaper alternative to drug development and for identifying lower cost therapies. The current market incentives are misaligned to encourage developers to explore these options. In this paper we have proposed a pull incentive mechanism that could address this challenge. Our proposed mechanism aims to reward developers for their investment in R&D while also encouraging promotion and uptake of the new repurposed therapy. Initial benefits demonstrate that a funders' costs may be justified and could reap social benefits. The US Federal government may consider funding and implementing such a mechanism to support efforts to lower drug costs for patients and advance new therapies to meet health needs. A pilot program with a promising lead may be a practical first step to demonstrate the value of the pull mechanism. Implementing this mechanism could allow the untapped potential of generic drugs to be more thorough explored for the benefit of US patients.

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APPENDIX

A. Draft outline contract or regulation

Qualifications

Types of firms: Any firm who sponsors the trials and label expansion with the FDA. This includes pharmaceutical companies, manufacturers, academic institutions, or not-for-profit drug developers.

Drugs: Any small molecule drug that has lost all exclusivity; in other words, any generic drug. Biosimilars are excluded from this mechanism.

Diseases: The mechanism will be disease agnostic, but aims to reward common diseases impacting the US population.

Target product profiles: The repurposed generic drug should either meet an unmet medical need, offer cost savings and at least equivalent efficacy, or superior efficacy (even if not offering cost savings).

Type of repurposing studies: As long as studies meet the characteristics described under target product profile, any type of repurposing study qualifies for the prize. This includes new indications, formulations, patient populations, dosing, or drug combinations.

Reward trigger: Regulatory approval by the US FDA to update the drug label is required to trigger the prize payout. Payout timelines will begin on the date of FDA approval.

Process for rewarding the firm

1. The funder promises a reward for generic drug repurposing.
2. Firms (and private venture capital) will invest in R&D for generic drug repurposing with the goal of submitting data to the FDA for label expansion.
3. The generic drug receives FDA approval for a new use.
4. The funder (i.e., government) will determine the payout amount by assessing value of drug based on clinical trial data.
5. The developer will begin promoting the drug for the new use to providers and patients.
6. Health providers will begin prescribing the generic drug to patients for the new use.
7. A third-party health data analytics firm will track the prescriptions of the drug for the new use.
8. The developer will receive payments from the funder scaled to the prior year's prescription data.
9. The government makes the payments to the developer annually until the prize fund amount has been reached.

B. B. Model equations

Incident cases **Equation 1**

$$N=\sum nx=1(Rx*Px) N=\sum x=1n(Rx*Px)$$

Where x is year, n is number of years, R is incidence rate per hundred thousand population, and P is population size in hundred thousands.

Cases not treated **Equation 2**

$$N=\sum nx=1(Ix*(1-Cx)) N=\sum x=1n(Ix*1-Cx)$$

Where x is year, n is number of years, I is disease incidence, and C is treatment coverage.

Cases treated **Equation 3**

$$N=\sum nx=1(Ix*Cx) N=\sum x=1n(Ix*Cx)$$

Where x is year, n is number of years, I is disease incidence, and C is treatment coverage.

Deaths **Equation 4**

$$N=\sum nx=1[(Ix*(1-Cx)*CFR)+(Ix*Cx*CFRt)] N=\sum x=1n[Ix*1-Cx*CFR+Ix*Cx*CFRt]$$

Where x is year, n is number of years, I is disease incidence, C is treatment coverage, CFR is case-fatality rate without treatment, and CFRt is case-fatality rate with treatment.

Years of life lost to disability (YLD) **Equation 5**

$$N=\sum nx=1[(Ix*(1-Cx)*D*DW)+(Ix*Cx*Dt*DWt)] N=\sum x=1n[Ix*1-Cx*D*DW+(Ix*Cx*Dt*DWt)]$$

Where x is year, n is number of years, I is disease incidence, C is treatment coverage, D is duration of disease without treatment, Dt is duration of disease with treatment, DW is disability weight without treatment, and DWt is disability weight with treatment.

Years of life lost to death (YLL) **Equation 6**

$$N=\sum nx=1[(Ix*(1-Cx)*CFR*LE)+(Ix*Cx*CFRt*LE)] N=\sum x=1n[Ix*1-Cx*CFR*LE+Ix*Cx*CFRt*LE]$$

Where x is year, n is number of years, I is disease incidence, C is treatment coverage, CFR is case-fatality rate without treatment, CFRt is case-fatality rate with treatment, and LE is life-expectancy (in years) at the average age of death among individuals with the disease.

Disability-adjusted life years (DALYs) **Equation 7**

N=∑nx=1[((Ix∗(1−Cx)∗D∗DW)+(Ix∗Cx∗Dt∗DWt))+((Ix∗(1−Cx)∗CFR∗LE)+(Ix∗Cx∗CFRt∗LE))]$N=\sum x=1n[Ix*1-Cx*D*DW+Ix*Cx*Dt*DWt+Ix*1-Cx*CFR*LE+Ix*Cx*CFRt*LE]$

Where x is year, n is number of years, I is disease incidence, C is treatment coverage, D is duration of disease without treatment, Dt is duration of disease with treatment, DW is disability weight without treatment, DWt is disability weight with treatment, CFR is case-fatality rate without treatment, CFRt is case-fatality rate with treatment, and LE is life-expectancy (in years) at the average age of death among individuals with the disease.

Deaths averted **Equation 8**

N=∑nx=1(Dx−Dtx)$N=\sum x=1n(Dx-Dtx)$

Where x is year, n is number of years, D is deaths in base case scenario, and Dt is deaths in scenario with new repurposed drug.

YLDs averted **Equation 9**

N=∑nx=1(YLDx−YLDtx)$N=\sum x=1n(YLDx-YLDtx)$

Where x is year, n is number of years, YLD is years of life lost to disability in base case scenario, and YLDt is years of life lost to disability in scenario with new repurposed drug.

YLLs averted **Equation 10**

N=∑nx=1(YLLx−YLLtx)$N=\sum x=1n(YLLx-YLLtx)$

Where x is year, n is number of years, YLL is years of life lost to death in base case scenario, and YLLt is years of life lost to death in scenario with new repurposed drug.

DALYs averted **Equation 11**

N=∑nx=1[(YLDx−YLDtx)+(YLLx−YLLtx)]$N=\sum x=1n[YLDx-YLDtx+YLLx-YLLtx]$

Where x is year, n is number of years, YLD is years of life lost to disability in base case scenario, YLDt is years of life lost to disability in scenario with new repurposed drug, YLL is years of life lost to death in base case scenario, and YLLt is years of life lost to death in scenario with new repurposed drug.

Monetary value of DALYs averted **Equation 12**

$$N=\sum nx=1[((YLDx-YLDtx)*E*M)+((YLLx-YLLtx)*E*M)]N=\sum x=1n[(YLDx-YLDtx)*E*M+(YLLx-YLLtx*E*M)]$$

Where x is year, n is number of years, YLD is years of life lost to disability in base case scenario, YLDt is years of life lost to disability in scenario with new repurposed drug, YLL is years of life lost to death in base case scenario, YLLt is years of life lost to death in scenario with new repurposed drug, E is employment rate within the defined working age group, and M is annual minimum wage.

C. Incidence rates

Table 1. Disease-specific incidence rates

Disease	Incidence rate per hundred thousand population*	Average annual percent change in incidence rate between 2000 and 2021	Source
Stroke	123.86	-0.02%	Global Burden of Disease Collaborative Network, 2024
Long COVID[+]	632.96	--	Calculation
Preterm Birth	148.16	-1.51%	Global Burden of Disease Collaborative Network, 2024

*Incidence rate per hundred thousand population was used for year one of our analysis and then the annual percent change in incident rate was applied for each subsequent year. No average annual percent change in incidence rate was calculated for Long COVID due to data availability.

[+] The Long COVID incidence rate was calculated by multiplying the United States' incidence rate per hundred thousand population for COVID-19 infection from 2021 (Source: Global Burden of Disease Collaborative Network, 2024) by 53.68% (Source: Ma, 2021) to obtain the incidence rate for symptomatic COVID-19 infection. Next, the incidence rate for symptomatic COVID-19 infection was multiplied by 6.2% (Source: Global Burden of Disease Long COVID Collaborators, 2022) in order to obtain the incidence rate for Long COVID.

D. Population estimates

Table 2. United States population size over time

Year	United States population	Source
2024	341,814,420	United Nations Department of Economic and Social Affairs, 2024
2025	343,603,404	United Nations Department of Economic and Social Affairs, 2024

2026	345,364,937	United Nations Department of Economic and Social Affairs, 2024
2027	347,098,261	United Nations Department of Economic and Social Affairs, 2024
2028	348,804,850	United Nations Department of Economic and Social Affairs, 2024
2029	350,493,332	United Nations Department of Economic and Social Affairs, 2024
2030	352,162,301	United Nations Department of Economic and Social Affairs, 2024
2031	353,802,974	United Nations Department of Economic and Social Affairs, 2024
2032	355,412,200	United Nations Department of Economic and Social Affairs, 2024
2033	356,991,059	United Nations Department of Economic and Social Affairs, 2024
2034	358,528,776	United Nations Department of Economic and Social Affairs, 2024
2035	360,016,420	United Nations Department of Economic and Social Affairs, 2024
2036	361,456,574	United Nations Department of Economic and Social Affairs, 2024
2037	362,841,838	United Nations Department of Economic and Social Affairs, 2024
2038	364,161,174	United Nations Department of Economic and Social Affairs, 2024
2039	365,420,860	United Nations Department of Economic and Social Affairs, 2024
2040	366,616,240	United Nations Department of Economic and Social Affairs, 2024
2041	367,749,399	United Nations Department of Economic and Social Affairs, 2024
2042	368,832,202	United Nations Department of Economic and Social Affairs, 2024
2043	369,853,049	United Nations Department of Economic and Social Affairs, 2024
2044	370,815,336	United Nations Department of Economic and Social Affairs, 2024
2045	371,715,154	United Nations Department of Economic and Social Affairs, 2024
2046	372,551,915	United Nations Department of Economic and Social Affairs, 2024
2047	373,335,573	United Nations Department of Economic and Social Affairs, 2024
2048	374,064,084	United Nations Department of Economic and Social Affairs, 2024

2049	374,749,589	United Nations Department of Economic and Social Affairs, 2024
2050	375,391,963	United Nations Department of Economic and Social Affairs, 2024

E. Disease durations

Table. Disease durations in years

Disease	Duration without treatment	Duration with treatment	Source (without treatment)	Source (with treatment)
Stroke	15.300	15.300	Peng, 2022	Peng, 2022
Long COVID	0.456	0.310	Global Burden of Disease Long COVID Collaborators, 2022 *	Calculation †
Antihistamines				
Fatigue	--	0.296	--	Salvucci, 2023
Brain Fog	--	0.283	--	Salvucci, 2023
Low Dose Naltrexone	--	0.206	--	Tamariz, 2024
Steroids				
Fatigue	--	0.368	--	Goel, 2021
Respiratory Symptoms	--	0.359	--	Goel, 2021
SSRI S1R agonist	--	0.350	--	Rus, 2023
Preterm Birth^				
Infant	5.000	5.000	Soleimani, 2014	Soleimani, 2014
Mother	1.000	1.000	National Institutes of Health, 2020	National Institutes of Health, 2020

* Long COVID disease duration without treatment was calculated by using reported Long COVID disease durations for those hospitalized and non-hospitalized for COVID assuming 29.4% of those with long covid were hospitalized within 30 days of initial covid diagnosis (Source: Ioannou, 2022).
† Duration with treatment for Long COVID was calculated by taking the average of reported existing medication outcomes from peer-reviewed literature.
^ Preterm births – Duration of disease for preterm birth calculations are independent of treatment administration. A 5-year term was used for the calculation of DALYs for preterm birth children while a one year – average duration of post-partum depression in mothers – was used for mothers.

F. Disease disability weights

Table. Disease disability weights

Disease	Disability weight without treatment	Disability weight with treatment	Notes	Source
Stroke	0.316	0.051	Weight is for Acute ischemic stroke severity level 3, without heart failure; Stroke, long-term consequences, moderate plus cognitive problems	Global Burden of Disease Collaborative Network, 2024
Long COVID	0.222	0.222	Weight is the average of all 3-symptom cluster and severity	Global Burden of Disease Long COVID Collaborators, 2022
Preterm Birth				
Infant	0.168	0.168	Represents the average disability weight of preterm birth children with neurodegenerative disorders	Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019)
Mother	0.399	0.399	Represents the average disability weight of mothers who experience post partum depression	Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019)

G. Disease case-fatality rates

Table. Disease case-fatality rates (CFR)

Disease	CFR without treatment	CFR with treatment	Sources
Stroke	0.1390	0.1110	Zhang, 2020
Long COVID	0.001	0.001	Ahmad, 2022
Preterm Birth			
Infant	0.014	0.014	Centers for Disease Control and Prevention, 2024
			March of Dimes, 2024
Mother	0.000317	0.000317	Hagatulah, 2024

			Burkhard, 2024

H. Disease treatment coverage

Table. Disease specific treatment coverage

Disease	Treatment coverage	Notes	Source
Stroke	0.91	Proportion of the US population within 60 minutes of an emergency department in a stroke center	Zachrison, 2022
Long COVID	0.88	Average percentage of having a usual place of health care for adults aged 18 and over from 2019 to 2023	National Center for Health Statistics, 2024
Preterm Birth	--	No treatment coverage rate was used for preterm birth due to no current standard of care drug existing	--

I. Inputs for monetizing DALYs

Table 7. Percent of cases within working age, percent of deaths within working age, and life expectancy at average age of death

Disease	Percent of cases ages 15 to 69 years*	Percent of deaths ages 15 to 69 years*	Life expectancy at average age of death**
Stroke	47.2%	21.0%	15.7
Long COVID[+]	68.7%	21.5%	19.3
Preterm Birth			
Infants	0%	0%	70.0
Mothers[^]	100%	100%	53.0

*Source is Global Burden of Disease Collaborative Network, 2024;For Long COVID, cases by age group were found by finding the COVID-19 incidence rate by age group (Sources: Centers for Disease Control & Prevention, 2023 & Global Burden of Disease Collaborative Network, 2024) and multiplying each age group by 53.68% (Source: Ma, 2021) to obtain the incidence rate for symptomatic COVID-19 infection by age group. Next, the incidence rate for symptomatic COVID-19 infection by age group was multiplied by 6.2% (Source: Global Burden of Disease Long COVID Collaborators, 2022) in order to obtain the incidence rate for Long COVID by age group.
**Source: United Nations Department of Economic and Social Affairs, 2024

[+] Due to data availability for Long COVID cases and deaths, working age was considered to be 18-64 years of age
^ Assumption based on the average age of US mothers at first birth (27.5 years)

Table 8. Employment rates and minimum wage

Disease	Employment rate among 15- to 69-year-olds*	Annual min wage (2024 USD)*
Stroke	72.7%	$15,080.40
Long COVID	72.7%	$15,080.40
Preterm Birth	72.7%	$15,080.40

*Source: International Labour Organization

J. Additional results of sensitivity analyses

Table 9. Health benefits for each sensitivity analysis

Disease	Drug type	Sensitivity analysis (SA)	Number of cases treated with new drug (millions)	Deaths averted	DALYs averted (millions)
Stroke	Simple	SA 1	1.53	22,573	1.34
Long COVID	Simple	SA 1	250.86	24,968	5.43
Preterm Birth	Simple	SA 1	1.41	832	0.18
Stroke	Complex	SA 1	0.10	2,117	0.20
Long COVID	Complex	SA 1	17.69	1,761	0.54
Preterm Birth	Complex	SA 1	0.06	36	0.01
Stroke	Simple	SA 2	1.53	22,573	1.34
Long COVID	Simple	SA 2	250.86	24,968	5.43
Preterm Birth	Simple	SA 2	1.41	832	0.18
Stroke	Complex	SA 2	0.10	2,117	0.20
Long COVID	Complex	SA 2	17.69	1,761	0.54
Preterm Birth	Complex	SA 2	0.06	36	0.01
Stroke	Simple	SA 3	1.53	31,091	1.51
Long COVID	Simple	SA 3	252.20	37,653	7.26
Preterm Birth	Simple	SA 3	2.78	1,639	0.35
Stroke	Complex	SA 3	0.10	2,666	0.22
Long COVID	Complex	SA 3	19.08	2,848	0.74
Preterm Birth	Complex	SA 3	0.12	73	0.02

Table 10. Monetary value of health benefits and benefit-cost ratios for each sensitivity analysis

Disease	Drug type	Sensitivity analysis (SA)	Monetary value of DALYs	Funder cost (USD billions)	Benefit-cost ratio

			averted (USD billions)		
Stroke	Simple	SA 1	3.89	0.47	8.28
Long COVID	Simple	SA 1	24.79	0.47	52.75
Preterm Birth	Simple	SA 1	1.25	0.47	2.65
Stroke	Complex	SA 1	0.56	0.77	0.72
Long COVID	Complex	SA 1	2.23	2.02	1.10
Preterm Birth	Complex	SA 1	0.05	0.03	1.68
Stroke	Simple	SA 2	3.89	0.40	9.73
Long COVID	Simple	SA 2	24.79	0.40	62.02
Preterm Birth	Simple	SA 2	1.25	0.40	3.12
Stroke	Complex	SA 2	0.56	0.77	0.72
Long COVID	Complex	SA 2	2.23	2.02	1.10
Preterm Birth	Complex	SA 2	0.05	0.03	1.68
Stroke	Simple	SA 3	4.21	0.55	7.64
Long COVID	Simple	SA 3	32.82	0.55	59.46
Preterm Birth	Simple	SA 3	2.46	0.55	4.45
Stroke	Complex	SA 3	0.58	0.81	0.71
Long COVID	Complex	SA 3	3.04	2.77	1.10
Preterm Birth	Complex	SA 3	0.10	0.06	1.68

Note: All values are discounted using a discount rate of 3%. Rows are "grayed-out" for disease-drug combinations that do not yield a sufficient reward size in order to induce firm entry.

K. Necessary Reward Size Inputs

Phase costs estimates

Drug type	Hit identification	Hit-to-Lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	New Drug Application	Total
	$m	$m	$m	$m	$m	$m	$m	$m	$m
Repurposed, simple	$0	$0	$0	$0	$0	$7	$22	$2	$31
Repurposed, complex	$1	$4	$14	$6	$3	$7	$22	$2	$59

Source: Portfolio-To-Impact Model ("P2I") tool (2018), Paul, et al. (2010), FDA FY2023 user fee table (2022)

Note: Results are rounded to the nearest million-dollar value. All dollars are in 2024 terms. Paul, et al. (2010) was used when P2I did not have available data. Specifically, it was used for the hit identification, hit-to-lead, and lead optimization costs. The 2023 New Drug Application costs from 2023 were used to estimate New Drug Application costs.

Phase duration estimates

Drug type	Hit identification	Hit-to-Lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	New Drug Application	Total
	years	years	years	years	years	years	years	years	years
Repurposed, simple	0.00	0.00	0.00	0.00	0.00	2.25	2.25	1.50	6
Repurposed, complex	1.00	1.50	2.00	2.50	1.75	2.25	2.25	1.50	15

Source: Portfolio-To-Impact Model ("P2I") tool (2018) and Paul, et al. (2010)

Note: Results are rounded to the nearest quarter year. Paul, et al. (2010) was used when P2I did not have available data. Specifically, it was used for the new drug application duration assumptions

Phase probability of success estimates

Drug type	Hit identification	Hit-to-Lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	New Drug Application	Compounded
	%	%	%	%	%	%	%	%	%
Repurposed, simple	100%	100%	100%	100%	100%	46%	46%	91%	19%
Repurposed, complex	80%	75%	85%	75%	59%	46%	68%	91%	6%

Source: Portfolio-To-Impact Model ("P2I") tool (2018) and Paul, et al. (2010)
Note: Results are rounded to the nearest percentage point. Paul, et al. (2010) was used when P2I did not have available data. Specifically, it was used for the hit identification, hit-to-lead, lead optimization, and new drug application probabilities of success.

Discount rate
The base scenario's discount rate was 10.5%.
Source: DiMasi, et al. (2016)

Monitoring costs

	Monitoring, fixed	Monitoring, variable
	$	$/quarter
Value	$124,000	$32,299
Dollar year	2024	2024

Source: Private quote, high estimate (May, 2024)

L. Description of each sensitivity analysis

Sensitivity analysis (SA)	General effect modeled	Specific effects modeled (all effects are modeled together)	Relevant industry or area
SA 1	Use of AI and adaptive clinical trials	30% reduction in the cost of preclinical trials 25% reduction in the cost of clinical trials 10% increase in the success probability of clinical trials 1 year reduction in the duration of preclinical trials Source: The Center for Policy Impact in Global Health at Duke University	Pharmaceutical companies, R&D
SA 2	Reward system – exploration of the minimum and maximum cost of capital for pharmaceutical R&D	Annual cost of capital rate of 8% (lower bound)	Funder
SA 3	Health impact – exploration around changes to treatment coverage, adoption rates, and treatment efficacy	Treatment coverage increases by 10 percentage points per year New repurposed drug phases out standard of care until an equilibrium is reached such that 100% of treated cases receive new drug and 0% of treated cases receive standard of care New repurposed drug is 15% more effective than the standard of care at reducing morbidity and mortality	Population