How Many Patients Does It Take to Repurpose a Cancer Drug? A Cohort Study of Post-approval Oncology Drugs

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Abstract

Background: Major codes of human research call for minimizing patient burden and maximizing knowledge gains. Some research activities may make better use of patients because their findings have a greater impact on care. In this report, we use a metric of efficiency, the number of patients needed to achieve an FDA approval, to estimate the impact of post-approval research compared to initial drug development that required 12,217 patients.

Methods: We created a sample of anti-cancer drugs approved by the FDA between 2012 to 2015. We searched clinicaltrials.gov to identify drug development trajectories launched after FDA approval. We identified the number of trajectories producing the following milestones: secondary FDA approvals, NCCN off-label recommendations and FDA approvals of substantial benefit by ESMO-MCBS. Using enrollment, we estimated the number of patients needed to obtain each milestone.

Results: Forty-two cancer drugs were approved, leading to 451 post-approval trajectories enrolling 129,548 patients. Fourteen secondary FDA approvals were identified, of which 4 met the ESMO-MCBS definition of substantial clinical benefit. Fourteen NCCN off-label recommendations were obtained. A total of 9253; 32,387 and 4627 patients were needed to attain an FDA approval, an approval with substantial clinical benefit on ESMO-MCBS, and an NCCN guideline recommendation, respectively. The number of patients needed to obtain a first secondary FDA approval was 16,596.

Conclusion: The number of patients needed to extend the label of approved drugs is comparable to developing new drugs. Our findings suggest that public policy and research oversight should not favour post-approval research since whatever advantages are present

regarding prior knowledge about safety and pharmacology do not translate to lower patient burden or high research efficiencies.

Résumé

Contexte : Les principaux codes de la recherche sur l'homme préconisent de minimiser la charge pour le patient et de maximiser les gains de connaissances. Certaines activités de recherche peuvent faire un meilleur usage des patients, car leurs résultats ont un impact plus important sur les soins. Dans ce rapport, nous utilisons une mesure de l'efficacité, le nombre de patients nécessaires pour obtenir une approbation de la FDA, afin d'estimer l'impact de la recherche post-approbation par rapport au développement initial du médicament qui a nécessité 12 217 patients.

Méthodes : Nous avons créé un échantillon de médicaments anticancéreux approuvés par la FDA entre 2012 et 2015. Nous avons effectué des recherches sur le site clinicaltrials.gov pour identifier les trajectoires de développement de médicaments lancées après l'approbation de la FDA. Nous avons identifié le nombre de trajectoires produisant les jalons suivants : approbations secondaires de la FDA, recommandations hors indication du NCCN et approbations de la FDA d'un bénéfice substantiel par l'ESMO-MCBS. En utilisant les données d'inscription, nous avons estimé le nombre de patients nécessaires pour obtenir chaque jalon.

Résultats : Quarante-deux médicaments anticancéreux ont été approuvés, ce qui a conduit à 451 trajectoires post-approbation impliquant 129 548 patients. Quatorze approbations secondaires de la FDA ont été identifiées, dont 4 répondaient à la définition ESMO-MCBS de bénéfice clinique substantiel. Quatorze recommandations NCCN hors indication ont été obtenues. Au total, 9253, 32 387 et 4627 patients ont été nécessaires pour obtenir respectivement une approbation de la FDA, une approbation avec un bénéfice clinique substantiel selon l'ESMO-MCBS et une recommandation du NCCN. Le nombre de patients nécessaires pour obtenir une première approbation secondaire de la FDA était de 16 596.

Conclusion : Le nombre de patients nécessaires pour élargir l'étiquette des médicaments approuvés est comparable au développement de nouveaux médicaments. Nos résultats suggèrent que la politique publique et la surveillance de la recherche ne devraient pas favoriser la recherche post-approbation, car les avantages éventuels liés à la connaissance préalable de la tolérance et de la pharmacologie ne se traduisent pas par une réduction de la charge pour les patients ou par une efficacité élevée de la recherche.

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Contribution of Authors

Chapter 1: CO conducted the literature review and wrote Chapter 1. JK provided editorial assistance for the entire chapter.

Chapter 2: JK conceived the main conceptual ideas for this project. JK, CO, NH developed the methodologies, with input from CM. CO conducted the pilot to verify the study's feasibility. Data was collected by CO. Double coding was conducted by CW and clinical benefit evaluations of approvals were conducted by JDP. CO analyzed the data and wrote the manuscript and supplementary materials. The manuscript was reviewed and edited by CO, JK, NH, CM, CW and JDP and is now under review for publication.

Chapter 3: CO conducted the literature review and wrote Chapter 3. JK provided editorial assistance for the entire chapter.

Introduction

Cancer is one of the leading causes of death worldwide. [1] Despite the urgent need for pharmaceutical advances, most drugs put into testing for cancer fail to demonstrate safety and efficacy sufficient to support regulatory approval. [2] Drug repurposing has the potential to aid in uncovering new therapeutic options for patients in a research landscape where *de novo* drug development is slower than expected. In cancer, drug repurposing or label extension research, which entails finding new uses for an already approved drug, accounts for 29% of all clinical trials. [3] Due to an existing foundation of clinical data concerning the study intervention, drug repurposing clinical trials involve less uncertainty concerning safety. [4] Thus, therapeutic applications have the potential to be uncovered with fewer clinical trials involved. Consequently, drug repurposing can be fruitful and has led to important new applications in many disease areas. However, such progress isn't without costs which include funnelling patients away from other branches of research in which their altruistic contribution might be better utilized. An ethical research enterprise should prioritize avenues of research that present the highest probability of societal benefit with the lowest possible cost. To inform such research oversight, the efficiency of drug repurposing should be evaluated and compared to other avenues of research.

Prior work has evaluated the efficiency of drug development from an economic standpoint. Many recent analyses focus on the financial costs of obtaining regulatory approval. [5-7] While such analysis provides insight into the fiscal efficiency of certain avenues of research, it fails to attend to the most morally relevant inputs and outputs of drug development – patients.

Patients play a fundamental role in clinical development. They undertake risks and expenses which are essential to the development of any new drug. Not only must patients endure the side effects of treatments in research settings, but they attend frequent disruptive clinic visits

and undergo invasive procedures above those required in the standard of care. While some of the research burdens may be redeemed by the prospect of personal clinical benefit, the principle of clinical equipoise establishes that trial participation is likely to present limited direct benefit. [8]

One way to evaluate the burden born by patients in drug development is to evaluate the number of patients required to obtain regulatory approval. We previously reported that 12,217 patient-participants are needed to bring a new cancer drug to market. [9] However, the per-patient efficiency of drug repurposing has yet to be uncovered.

The objective of this thesis is thus to determine the number of patients needed to successfully repurpose an FDA-approved cancer drug. To do this, we conduct a retrospective cohort study of all FDA-approved cancer drugs approved between 2012 and 2015. We also examine the number of patient-participants needed to achieve an off-label recommendation in clinical practice guidelines and to obtain a secondary approval that is deemed to present substantial clinical benefit. Our results highlight the magnitude of the burden borne by patients in drug repurposing efforts in cancer compared to the clinical gain. We provide a discussion of how our findings have several implications for cancer drug repurposing oversight and research prioritization.

Chapter 1: Drug Repurposing in Cancer

Introduction to Drug Repurposing in Cancer

Cancer is one of the leading causes of death worldwide, accounting for 9.6 million deaths globally in 2018. [1] The economic and societal burden of cancer is expected to increase with the aging of the population and improvements in survival. [10] Despite the urgent need for pharmaceutical advances, the translation of new drugs for cancer has been slower than expected. [2] Only 1 in every 5000 to 10 000 prospective anticancer agents get approved. [11] One in 20 oncology drugs tested in phase I trials receive FDA approval. [12] In part, because new drug development is so costly, and new drugs often target mechanisms that are implicated in other diseases, many clinical trial efforts are directed at finding new uses for existing drugs. Such an approach to research is called post-approval drug repurposing or label extending research. In cancer, it accounts for 29% of clinical trials. [3] Drug repurposing can be productive and has led to important new applications in many cases. However, it isn't without costs, which include diverting patients away from other clinical trials or activities. A key task for policy and ethics is getting the best value for the research conducted. This thesis will provide information that will aid in addressing the question – does post-approval drug repurposing delivery good value for patients and research systems?

Overview of Drug Repurposing

Drug repurposing has a long and productive history in pharmaceutical development. It has historically been an opportunistic and serendipitous endeavour. [13] Drug repurposing is increasing in popularity due to genomic and proteomic technologies which increase the precision of clinical hypothesis. [14] A notable example of drug repurposing in cancer is imatinib, which was

originally approved for chronic myeloid leukemia and was later approved for hypereosinophilic syndrome, chronic eosinophilic leukemia, and dermatofibrosarcoma. [15] Other examples of cancer drugs that were repurposed for other indications include trastuzumab (originally approved for HER2 positive breast cancer), which later received approval for HER2 positive gastric cancer. Another example is sunitinib (originally approved for gastrointestinal stromal tumours and renal cell carcinoma), which later received approval for pancreatic neuroendocrine tumours. [16]

When pursuing drug repurposing research efforts, researchers have access to existing clinical data for the study drug from prior clinical trials. The pharmacokinetics, pharmacodynamics and toxicology profiles are already established in preclinical and phase I studies. [4,17] This means that information already exists on the dose, side effects and interactions with other drugs. [18] For this reason, drug repurposing stands to require fewer clinical trials to uncover new therapeutic applications since early-phase clinical trials don't need to be repeated. With such existing clinical information, drugs can rapidly progress to phase II and III trials when tested in new indications. [19,20] This can result in repurposed drugs being approved in a shorter time period—3 to 12 years for repurposed drugs compared to 10 to 17 years for a novel drug. [21] Since label-extending research is performed with previous safety data in its arsenal [4,18,22], advocates argue label extending is an efficient and safe avenue of research for patients – providing additional treatment options which are especially important to patients who are refractory to primary treatment or have rare diseases. [2,19] Such advances could have a significant impact on care as rare diseases are much more prevalent than perceived in cancer. Approximately 20% of people with cancer in the US are diagnosed with rare cancer, defined as cancer with an incidence of fewer than 6 cases per 100,000 individuals per year. [23] Drug repurposing has the potential to aid a large, underserved patient population in cancer.

Since more is understood about the safety, pharmacology, and targets of approved drugs, the marginal cost of drug repurposing should be lower than *de novo* drug development. Although the regulatory and phase III costs may remain more or less the same for repurposed drugs as for new drugs in the same indication, drug repurposing is likely to present substantial savings as a result of not needing to conduct preclinical and phase I trials. [24,25] As well, at the point where repurposing is pursued, the costs of establishing new formulations and manufacturing are nil. [16] Some estimations suggest that the average associated cost of repurposing is estimated to be US$300 million on average, compared to an estimated US$2-3 billion for a new chemical entity. [4] Other estimates suggest that drug developers can bypass 40% to 60% of the costs of bringing a drug to market by eliminating much of the toxicological and pharmacokinetic assessments. [26,27] Lower marginal costs also translate to less patient burden and fewer resources needed to achieve a clinical gain suggesting that drug repurposing might be attractive for both economic as well as moral reasons.

Despite the maturity of pharmacological knowledge at the point where repurposing is pursued, post-approval drug repurposing faces hardships akin to any drug development process. Even in repurposing, cancer trials are expensive and failure rates are potentially even higher than in *de novo* drug development. [18] One study showed that secondary indications are less likely to advance to FDA submission when compared to primary indications (46.2% vs 67.6%). [12] In parallel, another study showed that for cancer drugs approved from 2005 to 2017, 75% of secondary FDA approvals originated from pre-approval research vs 15% from post-approval research. [28] Drug repurposing hypotheses are just as likely to demonstrate a lack of sufficient clinical evidence as traditional drug development programs and have their phase II and III trials not meet their primary endpoint. [29,30] For example, one study found that in a cohort of twelve

cancer drugs, none of the post-approval repurposing efforts resulted in a new FDA approval despite the 69 unique drug repurposing hypotheses explored post-approval, illustrating the high volume of clinical trials that lead to dead ends, even in repurposing research. [15] Similarly, a study of imatinib revealed that 67% of indications tested before initial approval went on to receive approval, where 6% of trajectories started after initial approval resulted in an FDA approval or positive randomized control trial within 8 years. [31]

With reduced marginal costs, available safety information and studies suggesting diminished returns from investment in drug repurposing, the overall societal advantage of drug repurposing compared to other forms of research is unclear. We have limited both financial and moral resources to invest in research. The most morally sound research enterprise should strive to maximize efficiency while minimizing societal burden. To obtain this goal, we must first understand how different avenues of research compare in terms of resource input and therapeutic output before research oversight can prioritize the type of research that requires the least global burden for the greatest societal gain. One way of assessing some of the most morally important relationships between research inputs and outputs of the entire research enterprise is to estimate the moral efficiency of research. This entails comparing various types of research, like pre-approval and post-approval research, for the trade-off between patient-participants invested in clinical trials and the clinical gains. A proxy for moral efficiency is how many patients are needed to successfully obtain a regulatory approval. Previous work uncovered the moral efficiency of *de novo* drug development in cancer. [9] How many patients are needed to successful repurpose a cancer drug remains to be studied. Such information could aid in comparing the moral merit of drug repurposing research to other forms of research to better inform research oversight and prioritization.

Policy Rationale for Balancing a Research Portfolio

How should research systems balance investing in de novo drug development against investing in drug repurposing? When physicians recruit for cancer trials (or disease charities highlight research opportunities), to what degree should they direct patients toward one avenue of research versus the other? Does our research system currently underfund drug repurposing efforts? The present thesis will focus on one morally significant question that lies at the heart of addressing these questions; to what degree do post-approval drug repurposing efforts utilize patients?

How efficiently patient participants are utilized in drug repurposing is relevant for several reasons. Firstly, clinical advances rest on the shoulders of patients who bear the burdens of clinical research. Evaluating the volume of patient participants necessary for research helps render visible the size of a moral economy that private drug development relies on to function. Despite prior information, drug repurposing clinical trials are not riskless for patients as drugs do not have complete safety profiles when approved. [32,33] Such incomplete safety profiles are pronounced in repurposing research since treatments are often hastily directed toward patients who are difficult to treat and refractory to available treatments. [34,35] Basic principles of research ethics entail that clinical development should strive to minimize patient burden while maximizing research efficiency. By quantifying patient volunteerism, the research enterprise can appreciate and acknowledge the sacrifice patients make which is essential for societal advance in clinical care.

Secondly, evaluating patient volumes can also help inform patients of the likelihood that their participation leads to changes in cancer care. When patients enroll in trials, they are in part

motivated to participate since they are told that their participation may advance science. [36] They are rarely given information that allows them to assess the probability their participation may advance medical science. The number of patients needed to obtain additional therapeutic options for patients could be included in the informed consent process and help patients evaluate a clinical trial's potential to provide the type of societal benefit they seek to contribute to.

Thirdly, there is a finite pool of patients available for research participation and research systems ought to get the greatest value from this pool. Clinical trials should save human and economic resources by discounting ineffective treatments as efficiently as possible. [37] Developing policies that prioritize research most likely to provide value requires evidence concerning the impact of various research strategies. Little is known about the volume of patient participants required for drug development. Previous studies have restricted their analysis to drugs obtaining regulatory approval. [38,39] Such studies fail to evaluate the total number of patients participating in research, including those participating in unsuccessful research trajectories. The value of drug repurposing is not guaranteed since there may be dynamics within drug repurposing efforts that frustrate the ability to deliver good value. For example, many drugs that are evaluated post-approval are never evaluated rigorously leading to what some commentators have called "clinical agnosticism" being the uncertainty concerning the clinical value of a therapeutic option. [40] Others have commented that post-approval drug repurposing employs a "more shots on goal" approach to research where many hypotheses are tested without testing their inherent validity resulting in many patients participating in fruitless avenues of research. [29] More work needs to be done before we can comment on the value of drug repurposing and understand whether this research avenue is where researchers should direct our most morally important resource – patients.

The research enterprise should strive to make the best use of the limited stock of human participants and maximize the extent to which their aims of contributing to medical advances are gratified when balancing our research portfolio. According to our prior work, 12 217 patients are needed to bring a new cancer drug to licensure but we have yet to evaluate the efficiency of post-approval drug repurposing. [9] The present work sets out to compare this estimate with the number of patients needed to achieve a label extension for an already approved drug in cancer.

Chapter 2: Manuscript, Supplementary Material

Objective

The goal of this thesis will be to estimate the number of patients needed to repurpose a cancer drug. We define successful drug repurposing as when an FDA-approved cancer drug obtains a secondary regulatory approval resulting from research that was initiated after the initial licensure of the drug. Our approach will identify all post-approval research trajectories – defined as a series of clinical trials testing the same drug-indication pairing initiated after the initial licensure of a drug – and will determine the proportion of trajectories that result in a secondary FDA approval. We will determine the proportion of trajectories that result in an off-label recommendation in clinical practice guidelines and a secondary approval that is deemed to present substantial clinical benefit for patients. Using the total enrollment in all post-approval research trajectories, we will estimate the number of patients needed to extend the label of an approved drug, obtain an off-label recommendation in clinical practice guidelines, and obtain a label extension presenting substantial clinical benefit for patients. Our study will also probe the quality of evidence supporting label extension approvals.

The results of our study will bring to light the burden born by patients in drug repurposing. The patients needed to obtain a secondary FDA approval based on post-approval research will be compared to the number of patients needed to obtain initial licensure in cancer. Such information will help regulators better balance their research portfolios. It will inform patients as to the probability that their participation in clinical research aiming to repurpose a drug will result in additional approvals.

Submitted Manuscript

How Many Patients Does it Take to Repurpose a Cancer Drug? A Retrospective Cohort Study of Post-approval Oncology Drugs

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Abstract

Background: Patients endure risk and uncertainty when they participate in clinical trials. We previously estimated that 12,217 patient-participants are required to bring a new cancer drug to market. However, many research efforts are aimed at extending the label of already approved drugs. Herein, we estimate the number of patients required to extend the indication of an FDA approved cancer drug.

Methods: We identified all anti-cancer drugs approved by the FDA 2012 to 2015. We searched clinicaltrials.gov to identify all drug development trajectories (i.e., a series of one or more clinical trials testing a unique drug-indication pairing) launched after FDA approval for each drug. We identified which trajectories produced the following milestones: secondary FDA approvals, secondary FDA approvals achieving substantial clinical benefit in ESMO-MCBS, and recommendations in NCCN clinical practice guidelines. Using the total enrollment, we estimated the number of patients needed to reach each milestone.

Results: Forty-two drugs were approved by the FDA between 2012-2015, leading to 451 post-approval trajectories enrolling 129,548 patients. Fourteen secondary FDA approvals were identified, of which 4 met the ESMO-MCBS definition of substantial clinical benefit. Fourteen NCCN off-label recommendations were obtained. A total of 9253; 32,387 and 4627 patients were needed to attain an FDA approval, an approval with substantial clinical benefit on ESMO-MCBS, and an NCCN guideline recommendation, respectively. The number of patients needed to obtain a first secondary FDA approval was 16,596.

Conclusion: Large numbers of patients are needed to extend the label of prior FDA approved drugs. Extra knowledge available to researchers about a drug's safety and pharmacology after

FDA approval does not appear to translate into reduced patient demand for discovering new cancer applications.

Introduction

Pharmaceutical firms bear risks and costs when they develop new drugs. [1] Much of this derives from the high rates of failure and the lengthy timelines required to conduct clinical trials. [2,3]

Patients play a vital role in supporting clinical development, and they too bear some of the risks and expenses associated with clinical trials. Patients participating in trials are required to make frequent clinic visits, undergo invasive procedures (e.g., phlebotomy, repeat biopsies), and endure side effects of treatments which, at the point of testing, are unproven. Some of these research burdens may be offset by the prospect of clinically meaningful benefits, for both themselves and for future patients. Yet, the principle of clinical equipoise establishes that any direct benefits from trial participation are likely to be limited. [4]

One metric that illustrates the magnitude of the burden borne by patients in successful drug development is the number of patients required in novel drug development. We previously reported that 12,217 patient-participants are needed to bring a new cancer drug to market. [5] However, almost a third of clinical trials in cancer involve efforts aimed at extending the label of approved drugs – an approach to research called drug repurposing. [6] While label-extension studies involve less uncertainty concerning the safety of study interventions [7], their efficiency, measured in terms of patient volume needed for a new FDA approval, has yet to be established. This information may help policymakers, academic medical centers, and researchers balance their research portfolios. It can also be used to help patients and patient advocates maximize the value of their research participation.

In what follows, we report the results of a retrospective cohort study estimating the number of patients needed to extend the label of an approved FDA cancer drug. Secondarily, we

examine the number of patient-participants needed to achieve an off-label recommendation in the National Comprehensive Cancer Network clinical practice guidelines (NCCN CPG) and those secondary approvals that are deemed to be of substantial clinical benefit defined by the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS).

Methods

Objectives and Definitions

Our primary objective was to estimate the number of patients needed to obtain a secondary approval after a new cancer drug has already received its first FDA approval based on a post-approval trajectory. We defined "secondary approvals" as indications added to the FDA label after the first approval of a drug. A "trajectory" is a series of one or more clinical trials testing a unique drug-indication pairing. We defined a "post-approval trajectory" as a trajectory that started after the first FDA-approval of the drug (i.e. secondary approvals might result from pre-approval or post-approval trajectories; we focused on the latter). Secondary objectives included estimating the number of patients needed to obtain a more permissive development milestone (a new recommendation in the NCCN clinical practice guidelines), and a more stringent milestone (secondary approval with substantial clinical benefit using the ESMO-MCBS[8]) based on post-approval research.

Our study was pre-registered on OSF (see https://osf.io/upe4h/); all deviations from and adjustments to our protocol are described in the supplementary materials.

Creation of FDA Approved Drug Cohort

We identified all anti-cancer drugs approved from January 1st, 2012 to December 31st, 2015 by searching Drugs@FDA for new molecular entities (NMEs) receiving a first approval for cancer (see Supplementary eMethods1 online). Supportive medications used for symptom management in cancer were excluded. The 2015 cut-off was selected to allow for 6 years of follow-up for secondary approvals. Six years of follow-up were selected based on previously unpublished work in which we found that 78.6% of secondary approval for oncology drugs approved between 2005 and 2017 occurred within 6 years. [9] All drugs were classified as either cytotoxic therapy, targeted therapy, immunotherapy, or other (see Supplementary eMethods2 online).

Capture and Characterization of Post-Approval Trajectories

We next identified all drug development trajectories launched after FDA approval for each drug in our sample. This involved searching ClinicalTrials.gov using drug name synonyms to capture all clinical trials initiated after the drugs' initial FDA approval and assembling the trials into trajectories (see Supplementary eMethods3 online), using the NCCN broad indication categories (see Supplementary eMethods4 online). All trial records were updated on December 10th, 2021. Trials within trajectories that began before the initial approval of a drug but continued after initial approval were excluded (see Supplementary eFigure1 online). A trajectory was deemed biomarker-enriched if the patient population was selected based on a biomarker directly related to the mechanism of action of the drug (see Supplementary eMethods5 online). Trajectories were classified as industry-initiated if the first trial in the trajectory was sponsored by industry. The enrollments of all clinical trials in eligible trajectories were recorded. Only clinical trials and FDA approvals beginning within 6 years of each original approval were

considered to ensure that every drug in our sample had an equivalent amount of time to reach a milestone.

Milestone attainment

We assessed the number of trajectories attaining each of the three development milestones. For our primary endpoint, we determined whether trajectories led to an FDA approval by identifying all secondary approvals that occurred within 6 years of initial FDA approval (accelerated or full) for all the drugs in our cohort and searching backward to see if the indication-drug pairings matched any of the post-approval trajectories. From this, we obtained the number of secondary approvals stemming from post-approval trajectories.

Second, we determined whether trajectories led to an FDA approval with substantial clinical benefit, as measured by ESMO-MCBS. [8] Many FDA approvals are of uncertain or limited clinical impact. [10] To assess the benefit of each FDA approval, we identified the pivotal trial cited in Section 14 of the FDA label of each secondary approval and found the published ESMO-MCBS scorecards. [11] An oncologist (JDP) performed the grading evaluation for all trials without an available scorecard. For secondary indications that were approved via the accelerated approval pathway, if an updated pivotal trial was available up to 5 years after the initial approval of the given indication, this trial was used as part of the ESMO-MCBS grading evaluation.

Third, using the method described above, we determined whether trajectories led to a recommendation in NCCN CPG by searching all NCCN CPG from 2012-2021 for instances in which an off-label recommendation for a drug in our sample originated from a post-approval trajectory.

In consultation with a leader of a patient advocacy organization (CM), we also assessed the number of patients needed to attain three additional patient-centered research milestones: a secondary FDA approval supported by a pivotal trial that a) used randomization, b) used a clinical endpoint (e.g.: overall survival), c) measured quality of life. For indications that were approved via the accelerated approval pathway, we evaluated the same trials which were identified for the ESMO-MCBS assessment. For drugs with off-label NCCN recommendations resulting from a post-approval trajectory, the cited supporting evidence was identified and examined for the above properties.

Analysis

Our primary outcome was calculated by dividing the number of patients enrolled in all post-approval trajectories by the number of secondary FDA approvals. The same calculation was conducted for our secondary outcome milestones. We also evaluated the number of patients needed per approval for industry-initiated vs non-industry initiated trajectories. We performed a descriptive analysis of all the outcomes performed in this study. Due to the limited number of drugs obtaining secondary approvals, we did not calculate confidence intervals. A 15% sample of clinical trials was double coded for inclusion/exclusion, biomarker enrichment and trajectory assignment, resulting in a cohen kappa of 0.81. This agreement was deemed acceptable, and the remainder of the sample was single-coded as per the protocol. All drug types were double-coded by CO and CW and disagreements were resolved through discussion. FDA approval information and off-label NCCN recommendations were singly extracted.

A planned sensitivity analysis that restricted our sample to drugs with longer post-approval follow-up time since FDA approval (8 years) could not be completed because none of the drugs achieved any secondary approvals beyond 6 years of initial approval. The maximum amount of time between initial approval and secondary approval was 5.8 years.

Post-Hoc Analyses

We performed a post-hoc analysis evaluating the proportion of approved indications for rare diseases. An indication is "rare" if it has an incidence of less than 6 per 100 000. [12] Cancer.net was used to find the projected number of cases for 2021 for each indication. When unavailable, we obtained estimates from recent publications. Incidence was calculated using the population of the United States on December 10th, 2021 (332 328 876). [13]

To enable a direct comparison with prior work evaluating the number of patients needed to obtain an initial FDA approval [5], we also determined the number of patients needed to obtain a first (as opposed to all) secondary approval.

Results

We captured 42 cancer drugs that received their first FDA approval between January 2012 and December 2015. Over three quarters were targeted agents (36/42, 86%); 3 were immunotherapy (7%), and 3 were cytotoxic therapy (7%). Four drugs (9.5%) in our cohort received at least one secondary FDA approval resulting from a post-approval trajectory, amounting to 14 secondary approvals (see Table 1). Of these, four (29%) were deemed to present substantial clinical benefits using ESMO-MCBS. Another 14 drug-indication pairings for 5 different drugs were recommended for off-label use in NCCN CPG (see Supplementary eTable1

online), based on trajectories started within 6 years of approval. The median patient enrollment per drug was 579 patients, with the maximum being 53,547 for Pembrolizumab and the minimum being 6 patients for Omacetaxine mepesuccinate. None of the secondary approvals originated from a biomarker-enriched trajectory. Our findings did not indicate that secondary approvals were restricted to rare diseases; 50% of approvals were indications in this category.

A total of 451 post-approval trajectories were recorded for all drugs in our cohort (see Table 2). Of these, 14 (3.1%) resulted in a secondary approval (see Figure 1). The median patient enrollment per trajectory was 47 patients.

Patient-Enrollment Needed to Obtain Milestones

A total of 129,548 patients participated in post-approval research trajectories for drugs in our sample. Our primary outcome, 9253 patients were needed in post-approval clinical trials to obtain a secondary FDA approval. When restricting analysis to only those secondary approvals deemed to have a substantial benefit by ESMO-MCBS, the figure was 32,387. We found that 4627 patients were needed to obtain either an NCCN off-label recommendation or a secondary FDA approval. A total of 16,596 patients were needed for a drug to obtain its first secondary approval.

Of all patients who enrolled in post-approval drug development trajectory trials, 13,440 (10%) were enrolled in trials within trajectories that advanced to one of the 14 FDA approval and 3683 (2.8%) in trajectories leading to secondary approvals with substantial clinical benefit. When only considering the patients enrolled in trajectories prior to the first secondary FDA approval for all the drugs in our cohort that experienced label extension, 5.4% of patients directly contributed to the 4 first secondary approvals.

Patient Enrollment by Research Strata and Evidence Quality Milestones

Of the 14 trajectories that resulted in a secondary approval, seven (50%) were industry initiated. A total of 8954 patients were needed per approval for industry-initiated trajectories vs. 9553 patients for non-industry-initiated trajectories.

By December 10th, 2021, 5 (63%) of 8 accelerated approvals reported the results of a confirmatory pivotal trial on the FDA label within 5 years of approval (see Supplementary eTable2 online). A total of 16,193 patients were needed to obtain a secondary approval that was based on a randomized clinical trial, 21,591 patients were needed to obtain an approval based on a trial that used a survival endpoint, and 32,387 patients were needed to obtain a secondary approval that was based on a clinical trial that measured health-related quality of life. None of the NCCN off-label recommendations that occurred within 6 years of initial approval were based on trials that used randomization, a clinical endpoint, or quality of life measures (see Supplementary eTable2 online).

Discussion

In this retrospective cohort study, we found that large numbers of patients are needed to extend the label of already approved cancer drugs. In particular, 9253 patient participants are needed to obtain a new label for a prior FDA-approved drug, and 32,387 patient participants are needed to obtain a secondary approval deemed to be of substantial clinical benefit by ESMO-MCBS. The number of patients needed to obtain either an NCCN recommendation for off-label use or a secondary FDA approval was considerably lower: 4627. Our findings do not suggest a difference in patient volume needed for a secondary approval for research efforts initiated by industry compared to non-industry-initiated efforts. They do suggest, however, that industry-

initiated trajectories are more fruitful: although 18% of trajectories are industry-initiated, 50% of approvals result from such trajectories.

Our analysis replicating methods used in our previous study suggests that the number of patients needed to obtain a first secondary approval based on post-approval research (16,596 patients) is similar to the number of patients needed to obtain a first FDA licensure (12,217 patients). [5] On a per-patient basis, 5.4% of patients in our sample directly contribute to the trajectories of a first secondary approval, as compared with 19% for the first approval of a new drug. [5] That post-approval research is likely to be no more efficient, on a per-patient basis, than in initial indication/drug discovery suggests that whatever efficiencies gained from greater knowledge of mechanism and safety are offset by lower prior probabilities of achieving regulatory approval when initiating testing of new clinical hypotheses after a drug is already approved. This aligns with prior studies of post-approval research. In a study of cancer drugs approved 2005-2007, no new FDA approvals were obtained from 69 disease-indication pairings that were launched into trials. [14] Another analysis found that of 60 secondary approvals occurring within 6 years of initial licensure for cancer drugs approved from 2005 to 2017, 9 (15%) resulted from post-approval research. [9] Another report suggested that label extensions are less medically impactful than initial drug approvals, as measured by effect sizes or disease prevalence of approved indications. [15] Our findings cannot answer the question of whether this reflects diminished prior probability on scientific hypotheses tested after approval, or diminished commercial investment in post-approval trials and regulatory submission.

Our study should be interpreted in light of several limitations. First, our measure of the relationship between volunteerism and impact is simple. The number of patients does not account for the intensity of research burdens, and FDA approval is a crude measure of practical

impact. However, we did evaluate the clinical benefit of secondary approvals using ESMO-MCBS to better understand the impact of the approvals we captured. Second, our cohort of cancer drugs is limited to those approved by the FDA from 2012 to 2015 and may not reflect the patient burden of recently approved cancer drugs. Third, we only consider secondary approvals and NCCN off-label recommendations that occur within 6 years of approval. We were unable to perform a planned analysis at 8 years as none of the drugs with 8 years of follow-up achieved label extensions based on post-approval research. Greater follow-up time would be expected to increase both the number of patients captured as well as the number of secondary approvals.

In summary, for cancer drugs receiving approval between 2012 and 2015, 129,548 patients participated in clinical trials initiated after approval to support drug label extension. Our findings reinforce that large numbers of patients enrolled in clinical trials are needed to achieve advancements in cancer clinical research. They also underscore that clinical development efforts pursued after drug approval are no more successful than pre-approval drug development efforts, despite relatively mature knowledge of a drug's safety and pharmacology. Opting for pre-approval trials may, therefore, be a better option for patients, physicians, and institutions wishing to maximize the per-patient gain of knowledge from clinical trials.

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Table 1: Secondary FDA Approvals Resulting from Post-Approval Research

Drug	Drug Class	Initial Approval	Secondary Approval	Patient Enrollment in Trajectory	ESMO-MCBS Score*
Trifluridine and Tipiracil	Cytotoxic	Colorectal Cancer	Gastroesophageal Junction Adenocarcinoma	259	3
			Gastric Cancer	259	3
Nivolumab	Immunotherapy	Melanoma	Urothelial Carcinoma	1139	A
			Malignant Pleural Mesothelioma	1463	3
Pembrolizumab	Immunotherapy	Melanoma	Head and Neck Squamous Cell Cancer	1691	4
			Hodgkin Lymphoma	545	4
			Primary Mediastinal Large B-Cell Lymphoma	481	3
			PDL1 (CPS ≥1) Cervical Cancer	309	4
			Hepatocellular Carcinoma	1632	1
			Merkel Cell Carcinoma	650	3
			Cutaneous Squamous Cell Carcinoma	797	3
			Endometrial Carcinoma	1875	3
			Tumor Mutational Burden-High (TMB-H) Solid Tumor	2104	3
Ibrutinib	Targeted therapy	Mantle Cell Lymphoma)	Graft vs. Host Disease	238	N/A

* See Supplementary eTable3 for PMID of the publications used for all ESMO-MCBS evaluations. An approval is deemed to present substantial benefit with a score of 4-5 or A-B.

Table 2: Properties of Post-Approval Trajectories

		Number of Trajectories
Trajectory Property	Industry Initiated	66 (18%)*
	Biomarker Enriched	107 (24%)
Trajectory Outcomes	Secondary FDA approval	14 (3%)
	NCCN off-label recommendation	14 (3%)
	Secondary FDA approval presenting substantial clinical benefit (ESMO-MCBS)	4 (1%)
Trajectory Drug Type	Immunotherapy	97 (22%)
	Cytotoxic therapy	15 (3%)
	Targeted therapy	339 (75%)

*Clinical trials for mixed malignancies were omitted from this calculation

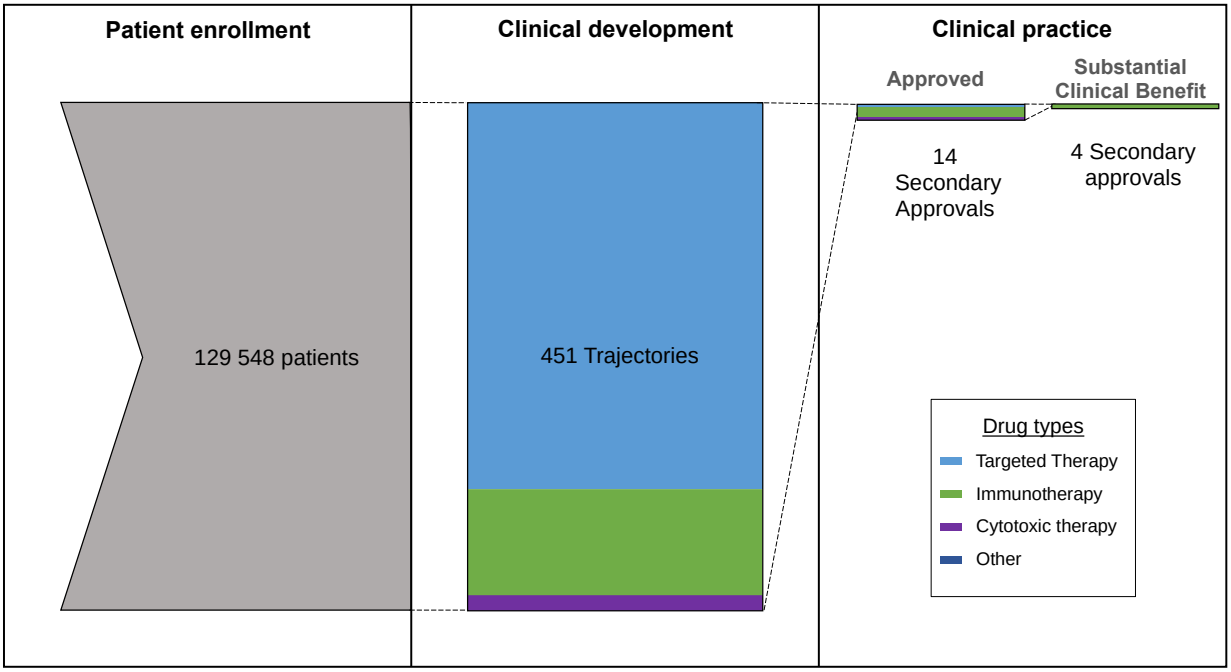

Figure 1: Patient Contribution and Clinical Success of Label Extension Efforts Post-Approval. The left panel represents the total patient enrollment in all eligible post-approval trajectories. The middle panel represents the trajectories all these patients participated in and the distribution of trajectories by drug type. The right panel represents the approvals that resulted from patient involvement in post-approval research.

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Data availability statement: Data will be made available upon request.

Conflict of interest: The author(s) declare no competing interests.

Supplementary Material

Supplementary Methods

eMethods1 - Search Details

We collected drug name synonyms using NCI thesaurus. If no entry was found in the NCI thesaurus, the search was re-performed in PubChem. If synonyms were found in FDA approval documents/clinicaltrials.gov entries, they were added to the list of synonyms. For each drug, the date of the original approval and all subsequent approvals was recorded. Withdrawn approvals were not included in our analysis.

eMethods2 - Screening Drugs

We examined the drug description provided on NCI thesauruses and used this information to classify each drug as either cytotoxic, immunotherapy, targeted or other. A drug that predominately stimulates or manipulates the immune system to recognize and/or target cancer cells, was classified as immunotherapy. Targeted drugs inhibit or activate specific molecular targets. Cytotoxic drugs affect all dividing cells and lead to cell death. The model we use is hierarchical which means that if a drug has characteristics for more than one drug class, it will be classified based on the more innovative mechanism. The order of drug classifications from most to least innovative is as follows: immunotherapy, targeted therapy, and cytotoxic therapy. Should a drug not fit into any of the three categories described above, then it was labelled as “other”.

eMethods3 - Screening Trials

We contended with instances in which a particular clinical trial tested either multiple drugs or multiple indications as follows: when a trial included 2 different indications, then the trial was treated as reflecting two trajectories (ex: trajectory 1A, trajectory 1B) and patients were evenly assigned to both trajectories. This technique was employed for up to 3 different malignancies. Beyond 3 indications, trials were labelled as either "mixed solid malignancies," "mixed hematological malignancies" or "mixed solid and hematological malignancies." Should one of two indications tested in a trial originate from pre-approval research, half of the patients were excluded from the analysis.

For master protocols or instances in which the drug of interest was used in fewer than 50% of the arms, only the patients enrolled in the arm(s) of interest were counted. To obtain an estimate for this number, then the trial enrollment was divided by the number of arms in the study and multiplied by the number of eligible arms.

In instances where a combination trial included two drugs from our sample, the trial was included in both trajectories, but each was considered as 50% of a trial and the number of patients was assigned 50% to one trajectory and 50% to the another to avoid overcounting patients. The same was true if 3 or more drugs are tested; the number of patients was divided by the number of drugs. Should a drug be in combination with a drug outside the scope of our study, then all patients were counted.

When a trial was labelled as a Phase1/2, then the trial was classified according to the indication tested in the Phase 2 section of the trial.

When a trajectory resulted in a secondary FDA approval, only patients enrolled in clinical trials that began before the date of secondary FDA approval were counted.

eMethods4 - Defining Cancer Indications

Because many trajectories start in broad indications and narrow to sub-indications as they progress, we assigned each indication to an indication category using the broad indication categories used by the National Comprehensive Cancer Network (NCCN) guidelines. For example, since the guidelines for treating follicular lymphoma and mantle cell lymphoma are provided in NCCN's guidelines for treating B-cell lymphoma, both these indications fall into the same indication category and are treated as one broad indication. Thus, a trial testing drug X in follicular lymphoma and a trial testing drug X in mantle lymphoma were part of the same trajectory.

eMethods5 - Biomarker enrichment

A trajectory was labelled as "biomarker enriched" if all the trials founding this trajectory were enriched. A trial would fulfill the criteria for enrichment if the mechanism of action of the drug tested was directly related to the biomarker for which the patient population was enriched. In this sense, our definition of enrichment resembled that of "predictive enrichment" proposed by the FDA in which a protein or genetic marker related to the drug's mechanism of action is used to select the patient population. [1] In instances where a specific drug-indication pairing was observed in both enriched trials and unenriched trials, then two separate trajectories were made for both avenues of research despite the same indication being tested in both.

Changes to Protocol

Some of our pre-specified analyses did not, on reflection, align with our main goals and were therefore excluded from the manuscript. This includes a Kaplan-Meier plot comparing time to secondary FDA approvals.

We had planned to assess the number of patients needed to obtain a secondary approval by drug class but did not perform this analysis due to the low number of secondary approvals for some drug classes. We also did not assess the number of patients needed to obtain a biomarker enriched approval since no biomarker enriched approvals originated from a biomarker enriched trajectory.

We had originally planned to exclude mixed malignancy trials from the calculation that is comparing the number of patients per approval for industry-initiated vs non-industry-initiated trajectories. Upon reconsideration, we classified mixed malignancies studies on a trial level as industry-sponsored or not and proceeded to include these patients in our calculations.

We planned to only double code 10% of the sample, but due to available personnel, we double coded 15%.

We had planned to include withdrawn off-label recommendations in NCCN guidelines in our study. For consistency, we chose not to include such recommendations since we did not consider withdrawn FDA approvals in our project.

Supplementary Analysis

eTable1: NCCN Off-label Recommendations Stemmed from Post-Approval Trajectories

Drug	**Drug Type**	**Indication**	**Patient Enrollment**
Cobimetinib	Targeted	CNS Cancer	36
Lenvatinib	Targeted	Head and Neck Cancer	304
Nivolumab	Immunotherapy	Anal Carcinoma	481
		Chronic Lymphocytic Leukemia	72
		T-cell Lymphoma	27
Pembrolizumab	Immunotherapy	Anal Carcinoma	32
		Chronic Lymphocytic Leukemia	53
		Malignant Pleural Mesothelioma	569
		Primary Cutaneous Lymphoma	58
		Soft Tissue Sarcoma	327
		T-cell Lymphoma	72
		Thymomas and Thymic Cancer	148
		Uveal Melanoma	412
Ibrutinib	Targeted	CNS Cancer	352

eTable2: Property of Pivotal Trials Cited to Support either Secondary FDA Approvals or NCCN Off-label Recommendations

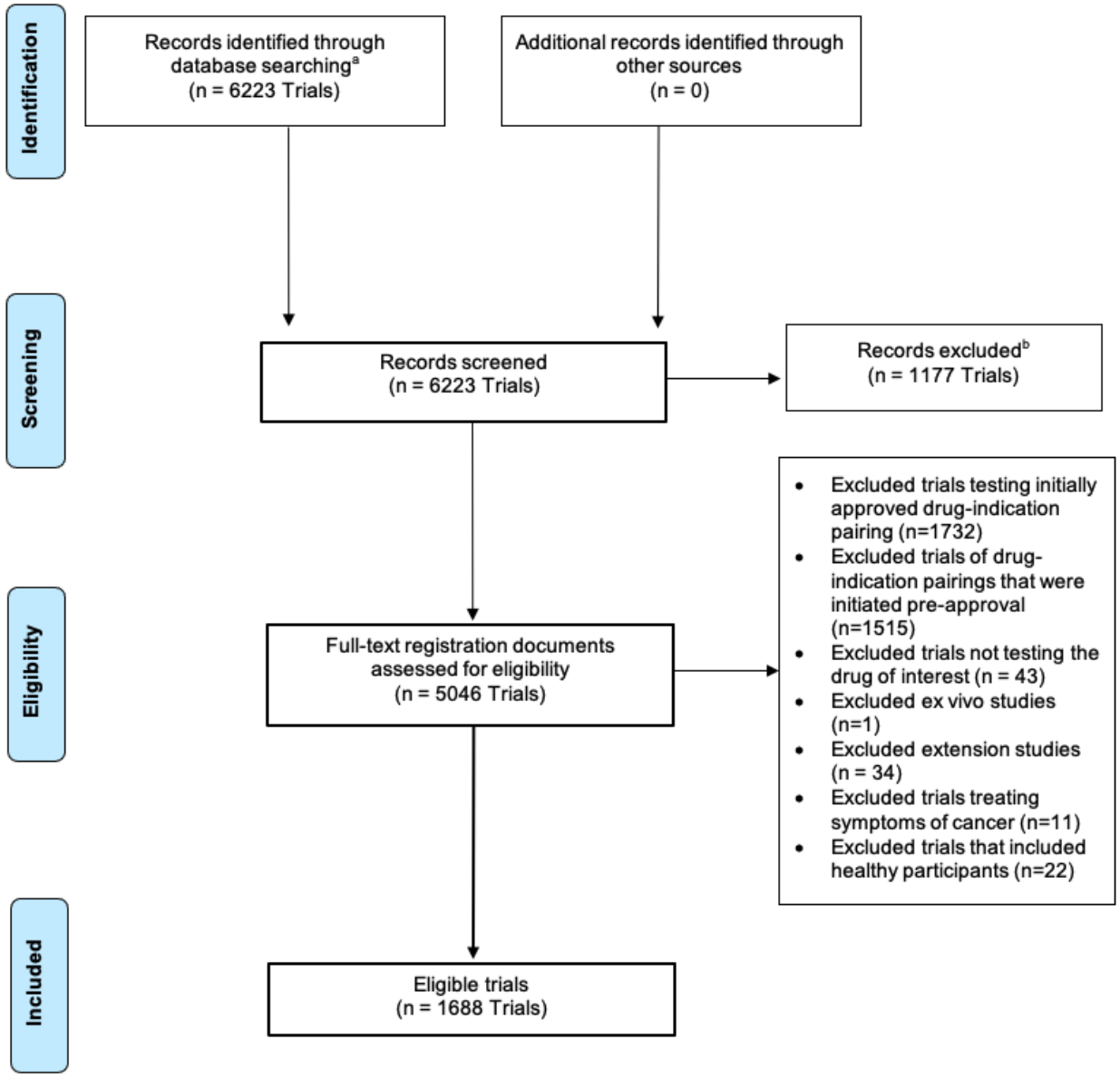
Property	**Original Pivotal Trial Supporting Secondary Approvals**	**Updated Pivotal Trials Supporting Secondary Approvals**	**Trials supporting off-label recommendations in NCCN CPG.**
Randomization	21%	57%	0%
Survival Endpoint	21%	43%	0%
Measure Quality of Life (QoL)	14%	29%	0%
Substantial clinical benefit (ESMO)	0%	29%	N/A

eTable 3: Publications used for ESMO-MCBS Score Evaluation

Drug	Secondary Approval	PMID First Pivotal Trial	Score	PMID Updated Pivotal Trial	Score
Trifluridine and Tipiracil	Gastroesophageal Junction Adenocarcinoma	30355453	3*	N/A	N/A
	Gastric Cancer	30355453	3*	N/A	N/A
Nivolumab	Urothelial Carcinoma	28131785	2	34077643	A
	Malignant Pleural Mesothelioma	33485464	3	N/A	N/A
Pembrolizumab	Head and Neck Squamous Cell Cancer	27646946	1	31679945	4*
	Hodgkin Lymphoma	28441111	3	33721562	4
	Primary Mediastinal Large B-Cell Lymphoma	31609651	3	Publication Pending	-
	PDL1 (CPS ≥1) Cervical Cancer	30943124	3	34534429	4
	Hepatocellular Carcinoma	29875066	1	Publication Pending	-
	Merkel Cell Carcinoma	33879601	3	Publication Pending	-
	Cutaneous Squamous Cell Carcinoma	32673170	3	N/A	N/A
	Endometrial Carcinoma	32167863	3	Publication Pending	-
	Tumor Mutational Burden-High (TMB-H) Solid Tumor	32919526	3	N/A	N/A

*Published scorecard

eFigure1 – PRISMA Flow Diagram for Identification of Cohort of Clinical Trials



a) Search of clinicaltrials.gov for clinical trials testing drugs from our cohort that were initiated after the date of initial FDA approval of each respective drug
b) We excluded trials that were initiated 6 or more years after the initial approval of each respective drug

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Chapter 3: Discussion

Clinical research exposes patients to risks and medical uncertainty with the primary aim of advancing ends external to the human volunteer. Accordingly, some commentators argue that clinical translation efforts should aim to minimize patient burden - either by minimizing per patient exposure to research burden in trials or by minimizing the number of patients needed to support major policy decisions like regulatory approval or drug reimbursement. [41] This thesis set out to benchmark the relationship between patient participation in clinical research and a major policy decision- in this case, regulatory approval- for a category of clinical research that constitutes a large proportion of trials - post-approval cancer trials. Post-approval clinical trials account for 29% of all cancer clinical trials. [3] Many policies are designed to encourage post-approval research. For example, additional market exclusivity is offered in the US for new uses of a previously approved drug. [42] While these policies may encourage new discoveries, the implications for how well research systems utilize patient participation have not been studied systematically.

We set out to address this gap by determining how many patient participants are needed to obtain a label extension for an FDA-approved drug and comparing that to previous figures for new drug development. In this chapter, we situate the findings from this thesis in the literature, address the question of whether post-approval drug repurposing delivers good value for research systems and patients, and identify further work that needs to be done to fully understand how patient investment can be best utilized in clinical research.

How Well does Post-Approval Cancer Research Utilize Patient Enrollment?

Our findings demonstrated that 9253 patients are needed to repurpose a cancer drug and 16,596 patients are needed to obtain a first secondary approval based on post-approval research. The latter estimate is comparable to our prior estimate of 12,217 patients for an initial FDA licensure. [9] That post-approval research is likely to be no more efficient on a per-patient basis than pre-approval research suggests that whatever efficiencies that are gained from greater knowledge of mechanism, pharmacology and safety with an approved drug are offset by other factors, such as a lower prior probability of success or a lack of economic incentive, that act as friction on efficient cancer drug repurposing.

The diminishing returns of post-approval research implied in the present study are consistent with other analyses of post-approval research. In a study of 12 cancer drugs approved from 2005 to 2007, no new FDA approvals were obtained from 69 disease-indication pairings that were launched into clinical testing. [15] Another analysis found that of 60 secondary approvals occurring within 6 years of initial licensure for cancer drugs approved from 2005 to 2017, 9 (15%) resulted from post-approval research efforts. [28] Another report suggested that label extensions are less medically impactful than initial drug approvals, as measured by effect sizes or disease prevalence of approved indications. [43] Forthcoming research from our laboratory suggests that, with each new indication put into testing, the probability of gaining an additional FDA approval diminishes significantly (data not shown).

The majority (90%) of patients who participated in post-approval clinical research were not enrolled in clinical trials testing indications that got approved. Five percent of patients directly contributed to a first label extension post-approval. Comparatively, 19% of patients enrolled in pre-approval research directly contribute to initial licensure. [9] This suggests that pre-approval research presents a higher probability of direct medical benefit for patient-participants.

The decreased probability of medical benefit post-approval may be explained by the fact that after a new drug receives approval, companies and public sponsors often run numerous small trials exploring the drug's activity in different indications and often fail to follow up with larger confirmatory trials. [40] Our findings support this hypothesis as the median enrollment in a research trajectory was 47 patients. This means that most patients undertake the burdens of clinical research post-approval without medically benefiting from their participation, or without their participation leading to changes in clinical practice. However, we must note the significant heterogenicity of enrollment per trajectory and drug suggesting that small clinical trials do not represent the entirety of the post-approval drug repurposing landscape.

Despite having a lower proportion of patients directly benefiting from research, the social value of post-approval research cannot be judged on this metric alone. For example, it might be the case that few approvals arise from post-approval research, but those that do are very responsive to the needs of patients and provide high clinical value. If this is the case, post-approval research merits further public investment despite it not being much more efficient at generating approvals than pre-approval research on a per-patient basis. The scope of impact generated from post-approval research must be evaluated to understand if this type of research is fulfilling the potential it holds for change valued by patients.

Impact of Clinical Care Generated Post-Approval

Our findings demonstrated that most patients who participated in post-approval clinical trials did not contribute to a trajectory that resulted in clinically impactful changes in care. Low-quality NCCN off-label recommendations and a few high ESMO approvals (e.g. n=4, 29% of all approvals) were generated. One factor that might mitigate this seeming decrement in efficiency (compared with pre-approval research) is that post-approval research might be directed toward

rare cancers. If this were the case, recommendations based on low evidence, or low ESMO-MCBS scores might simply reflect the limited ability to accrue sufficient patients for decisive randomized trials. However, our findings did not indicate that secondary approvals were restricted to rare diseases; 50% of approvals were for non-rare cancers.

Another factor that might mitigate the per-patient decrement of efficiency post-approval is if the approvals generated utilize biomarker-selected trials. Biomarker-selected approvals are associated with improved efficacy outcomes for patients. [44] If post-approval research generates biomarker-selected approvals, it could stand to challenge pre-approval research in terms of value. However, we did not observe such a trend. None of the FDA approvals captured in our study resulted from biomarker-selected trajectories. Meanwhile, 15% of initial approvals resulting from pre-approval research originate from biomarker-selected trajectories. [9] Another study examining all new therapeutics and biologics approved by the FDA between January 1st, 2013 and June 30th, 2017 found that 39% of oncology approvals were precision medicine approvals. [45] Our findings suggest that precision medicine is driving new drug development but not helping improve the efficiency with which applications for old drugs are discovered. Post-approval research does not appear to redeem its value in the form of more efficient drug development through precision medicine approaches.

The inefficiency at which approvals are generated post-approval might be offset by the generation of impactful off-label recommendations in clinical practice guidelines. The use of off-label recommendations is widespread in cancer as 50% to 75% of all cancer treatments in the US are given off-label. [46,47] In the US, NCCN recommendations are often sufficient for reimbursement. [48] Therefore, off-label recommendations in NCCN guidelines may be the easiest way to make new applications available to patients. Should post-approval research generate off-

label recommendations supported by high-quality evidence, then the value of post-approval research might be redeemed. However, NCCN guidelines are known to make off-label recommendations based on low evidentiary standards than FDA. [49,50] In alignment with this tendency, none of the off-label recommendations generated from post-approval research in our study were supported by high-quality evidence. There are also many reasons why off-label recommendations are not the best outcome of public investment for patients. First, not all countries reimburse off-label use. [51,52] Second, off-label recommendations lack a mechanism of post-approval monitoring to collect further understanding of side effects and efficiency, leading to many drugs continuing to be used off-label despite a lack of efficiency. [53,54] Third, off-label recommendations do not ensure access for patients since drugs may be removed from formularies or manufacturers because they are replaced by others for their authorized indications. [53] Generating off-label recommendations likely provides insufficient value to patients to excuse the lack of official approvals generated from post-approval research. To justify patient participation in post-approval research, high-quality evidence should be produced to weed out ineffective recommendations and transform effective off-label recommendations into approvals.

We evaluated if approvals originating from post-approval research were responsive to the desires of patients despite not being more efficient than pre-approval research. According to our consultation with a leader of an influential cancer advocacy organization in the US, patients prefer to have approvals supported by high-quality clinical trials that include quality of life (QoL) as an endpoint. [55] Choice of endpoints in pivotal trials plays a critical role in the final evaluation and perceived value of a drug to patients [56], and payers [57], especially when there is a modest benefit without extending life. [58] Should post-approval research generate approval based on high-quality evidence, then investment in this avenue of research might be worthwhile for

patients. Our findings do not suggest that this is the case. Generating high-quality approvals proved to require a greater number of patients than generating approvals regardless of supportive evidence quality. The generation of approvals supported by low-quality evidence that is not responsive to the desires of patients is consistent with prior studies. Previous work shows that data supporting label extension is often heterogeneous and is based on decreasing evidentiary standards. [59] Another study showed that of 144 cases of repurposed drugs, only 4% improved convenience for patients in the US. [60] This suggests that repurposing often doesn't respond to the needs of most patients, as observed in our work. It should be noted that little QoL data might have been observed in our sample due to the high rate of accelerated approvals. [58] Almost two-thirds (57%) of the secondary approvals in our sample were approved through the accelerated approval pathway. This translates to reduced developmental timelines that don't allow for patient-reported outcome data collection. [58] As it stands, the merit of post-approval research can't be explained by its responsiveness to patients' wishes.

Why isn't Post-Approval Research Delivering Good Value? Implications of the Economic Incentives for Post-Approval Research

Our findings suggest diminished returns of investment in post-approval research, despite drug developers having prior knowledge about safety and efficacy. Post-approval research is not generating approvals anymore more efficiently than pre-approval research. The approvals generated are not attributed to any features that would make post-approval research stand out from pre-approval research. Is it the lack of clinical impact due to a dearth of promising clinical hypotheses or the absence of economic incentives for repurposing drugs? Is the economic incentive structure behind drug repurposing insufficient resulting in promising avenues of

research not fulfilling their therapeutic potential? To address this question, we must dive deeper into the policies that are designed to encourage post-approval research and their impact.

Many pharmaceutical companies used to not invest in post-approval drug repurposing due to the lack of economic incentives. In response, in 1984, Drug Price Competition and Patent Term Restoration Act was passed to encourage greater exploration of applications post-approval. [61] According to this policy, FDA offers a 3-year period of market exclusivity for a new use of a previously marketed drug. This extends to 7 years if the label extension involves a rare disease. [42] The temporary market exclusivity is for the newly approved indication and not the drug as a whole. [42] Companies face challenges when attempting to increase the price of their drug following label extension despite the market exclusivity. Payers are resistant to paying a higher price for new indications of an existing medical product. [62] As it stands, companies must recoup their investment in drug repurposing through the profit generated by selling their drug for the newly approved indication.

The current evidence suggests that market exclusivity is an ineffective incentive for post-approval research. Pharmaceutical companies generally discontinue pursuing post-approval applications after a drug has been approved for several years. In one analysis, the vast majority (92.5%) of extensions for new indications were authorized during the exclusivity period of the original product. [63] An upsurge in additional approvals is observed after the initial marketing authorization and peaks 3 years before the generic introduction. [63] Another study also observed that label extensions peak 1-2 years after a first FDA approval and then drop off. [42] Similarly, we observed that all secondary approvals occurred in less than 5.8 years since initial licensure. The evidence suggests that companies tend not to pursue post-approval research after their initial patent expires despite the offer of market exclusivity for label extensions.

One possible explanation as to why market exclusivity is not working as an incentive is a common practice called skinny labelling. Companies cannot recoup their investment in label extension research since market exclusivity for the label extension is not observed in practice. Once the initial patent of a drug expires, generic entry may begin. At this time, generics can be approved with a "skinny" version of the brand-name drug's label which only includes the non-patented indication. Skinny labelling allows generics to enter the market before the brand-name drug's patent for label extension expires. Once a skinny-labelled generic version is available, they are commonly dispensed for all indications regardless of what is included on the generic label. Generics are prescribed for patent-protected uses that have been technically excluded from the generic label. An example of this practice is provided by imatinib. [64] Imatinib was initially approved for chronic myeloid leukemia (CML). By 2015, it had 9 additional approvals on its label, including gastrointestinal stromal tumours (GIST). One year after generic imatinib became available for CML alone, 88% of patients with the patent-protected indication GIST received the generic version off-label. [64] Legally enforcing a secondary medical use patent against competitors is challenging even for large pharmaceutical companies. [65] Consequently, pharmaceutical companies face difficulties when trying to recoup their investment post-approval research. Skinny labelling deters companies from investing time and resources in label extension research. Not only does skinny labelling possibly impact the quantity of research conducted post-approval, but it could influence which avenues of research are pursued.

The private sector is conscious of the fact that skinny labelling diminishes its ability to profit from label extensions. In alignment with this knowledge, we observed that the indications pursued post-approval are generally for more common diseases that can maximize earnings. Companies are not incentivized to pursue narrow markets despite post-approval research being

discussed as a promising approach to uncovering therapy for smaller disease populations. [18] Rare diseases and precision medicine approvals are not profitable since they entail more research for reduced markets. [56] Consequently, we did not observe a trend toward rare disease approvals nor towards biomarker-selected approvals. However, twenty-four percent of trajectories were biomarker enriched. Illustrating that the research is being done for smaller disease populations, but they are not proceeding to approval. Marketing to larger populations instead of narrowing down to more granular indications allows companies to capitalize on the most profit before inevitable generic entry. The economic advantage of drug repurposing could be overshadowed by the threat of generic entry, potentially depriving patients of approvals for smaller disease populations from which they stand to benefit.

The current economic structure and outcomes observed in our project suggest that the deficiency of label extension might in part be due to the lack of strong incentives for repurposing approved cancer drugs.

Public Investment in Research

Eighteen percent of trajectories in this study were industry initiated. Of the 14 trajectories that resulted in a secondary approval, seven (50%) resulted from industry-initiated trajectories. This suggests that public or other non-industry sponsors are undertaking a substantial amount of the costs of discovering new applications for already approved drugs and that industrial funders are more effective at selecting indications that are likely to advance to a new approval.

Pharmaceutical companies are selective about the repurposing avenues they chose to pursue, leaving many clinical hypotheses to be explored by the public sector. That the public sector is underwriting much of the expenses associated with uncovering new applications makes sense. The public budget for research is smaller, so it is logical to invest in drug development

where the marginal cost is lower. [18] In addition, the public sector invests where pharmaceutical companies do not. This allows for the possibility of uncovering helpful applications for the public that would not have been discovered otherwise. However, the public sector doesn't recoup its investment in post-approval research in full. On the one hand, subsidizing drug repurposing results in pharmaceutical companies economically benefiting from additional approvals without reduced drug prices for the public. [56] On the other hand, skinny labelling allows patients to benefit from newly discovered applications off-label at a reduced cost compared to the brand-name competitor. Although the public sector isn't getting back all its investment in repurposing research, it is providing additional treatment options to the public. However, it isn't providing access to treatment options without hurdles. Currently, only marketing authorization holders can apply for marketing authorization extensions for a specific drug. [54] Patient access to treatments discovered by the public still depends on the willingness of pharmaceutical companies to register for new indications. Although investing in drug repurposing is justified by the public sector, the regulatory system doesn't allow the public to invest independently of pharmaceutical companies.

The public sector faces financial and regulatory hurdles that hinder its ability to obtain additional approvals. The current regulatory structure may frustrate the public's ability to utilize valuable patient participation to the fullest extent. If we are depending on the public sector to unwrite the costs associated with drug repurposing, then the regulatory process should be improved to support public efforts. The approval pathway should be restructured to give the public sector more agency independent of the private sector if we are to maximize the outcomes of public investment.

Implications for Policy and Recommendations

Our principal finding is that greater maturity of knowledge about a new drug does not appear to translate into a reduced number of patients needed to unlock a new clinical application. The number of patients needed to extend the label of an approved drug is no less than the number of patients needed to develop a new drug *de novo*.

When considering our work's policy implications, we must note that most post-approval drug repurposing trajectories (97%) did not result in a label extension. We have observed that the economic system underlying drug repurposing is such that pharmaceutical companies may not have sufficient incentives to see promising potential trajectories to fruition. The public sector faces sobering budgetary constraints and sparse returns for the public. As a consequence of hardships faced by both the private and public sectors, it is possible that the majority of trajectories were started but not finished post-approval. Some were picked up in NCCN guidelines supported based on low-level evidence. However, many of these drugs stand to be ineffective for the indications for which they are recommended off-label. This is due to the generally low success rates in advancing drugs from phase 2 through to positive phase 3 trials in cancer. [66] Ineffective recommendations and unfulfilled avenues of research divert patients from more effective avenues of treatment and research.

Patient advocates should, all else being equal, advise their patients to participate in trials testing new drugs, rather than repurposing approved drugs, if the patients value participating in the testing of a treatment that will receive regulatory approval and strong evidentiary support for clinical application. Patients may believe that the risk-benefit balance of post-approval drug repurposing efforts is more favourable than novel drug development since the drug they are taking is approved by a trusted regulatory body. They may assume that the risks are minimal and so they only stand to benefit – which is not the case we observed in our study. Our findings

suggest the diminished returns of post-approval research and that approvals generated have a limited impact on care. The probability for regulatory success of certain research avenues should be included in the informed consent process to allow patients to understand the probability that their contribution leads to the change they care about. Such information could aid patients in mitigating their expectations when choosing to participate in a clinical trial attempting to repurpose a drug.

If it turns out that drug developers do not exhaust the clinical possibilities of new compounds pre-approval, appropriate regulatory bodies might modify the incentive structure for drug repurposing given that strong incentives might be lacking. This would need to take two forms. First, policies should provide greater rewards for successfully completed trajectories testing approved drugs for new indications. Possible approaches could include greater upfront government funding to private companies, expedited FDA review of new indications for old drugs or tax breaks for repurposing. Some commentators have also suggested that the market exclusivity offered should extend to all patents and other exclusivities that exist for the same product – an incentive structure coined the "patent extension model". [42] In parallel, the FDA should make it easier for government research bodies to apply for extensions. Institutions such as the NIH should be granted the authority to apply for market extensions despite not being the marketing authorization holder on the brand-name product. Such policy changes may help post-approval repurposing research fulfill its potential for impactful clinical change. On the other hand, regulations should not encourage profligate conduct of small and ultimately inconclusive repurposing trials. As described elsewhere in this thesis, in an environment where off-label prescription is reimbursed, this practice may result in expensive and ineffective prescription of drugs. Accordingly, the above incentives should be dispensed sparingly, and only based on

compelling preclinical evidence of promise and a strong commitment to following up positive phase 2 trials with decisive phase 3 trials using clinical endpoints.

If we are trying to address the question of how to balance a research portfolio between drug repurposing and *de novo* drug development based on our metric of patient involvement compared to impact, then our findings suggest that public policy and research oversight should not favour post-approval research since whatever advantages are present regarding prior knowledge about safety and pharmacology do not translate to lower patient burden or high research efficiencies. Our findings do not suggest that drug repurposing is without merit. Rather our work on efficiency- combined with our work on the clinical impact of post-approval research [28] - suggests that the merit of repurposing is likely diminished compared with pre-approval research. Until policy changes can be implemented, researchers and regulatory bodies should evaluate drug repurposing with closer scrutiny- and a bit more skepticism- then is applied to current pre-approval research.

Limitations

Our findings have several limitations. First, our estimation between patient participation and impact is crude and does not quantify the levels of the burden associated with participation in specific clinical trials. It may be the case, for example, that due to safety being well established, adverse event rates in repurposing trials are lower than in new drug trials. If this is the case, similar patient volumes may not track similar patient burdens. Second, our cohort of cancer drugs is limited as we restricted our analysis to cancer drugs approved by the FDA between 2012 and 2015. Third, we strictly considered FDA and NCCN approvals within 6 years. However, it is important to note that FDA and EMA approval decisions align in more than 90% of new drugs [67] and are often based on the same pivotal trials. [68] Therefore, our results are likely

to apply in the European context. Fourth, we have not reached 5 years of follow-up for all accelerated approvals, so confirmatory trials of higher quality evidence may surface and change the clinical impact of some secondary approvals in our project.

Unresolved Questions Concerning Research Efficiencies in Cancer Drug Repurposing

We began with a hypothesis that repurposing efforts would have diminished marginal costs, in terms of patient volume, associated with medical advances. Our principal finding does not support this hypothesis. However, there are several other considerations that our findings are unable to address that are relevant to evaluating the value of drug repurposing in cancer.

Our work does not identify the factors that motivate the trends we observe in our study. The diminishing returns of post-approval research could be due to reduced prior probability of success at trajectory launch or it could be due to reduced company incentives. To address this limitation, we could uncover the extent to which repurposing efforts are terminated before high-quality evidence is produced. We could identify the last clinical trials in each research trajectory and pinpoint whether the trial results were positive or negative. If the last clinical trial in a trajectory is positive, and no approval or bigger confirmatory trial is followed, then it might suggest that research was stopped due to insufficient incentive or competing clinical efforts taking the forefront. If a trajectory ends due to negative results or a safety issue, then research is likely halted due to scientific rationale. Such a finding could help us distinguish between the exhaustion of a paradigm (in which case policies encouraging further off-label drug development are unlikely to bear fruit) from the extinction of productive research efforts due to financial disincentives (in which case promising research hypotheses are abandoned due to financial constraints post-approval).

Another is the level of clinical adoption of label extension. Label extension is not an end in itself. However, it does initiate a cascade of events that can include updating clinical practice guidelines, inclusion formularies and reimbursement by health providers. We could study the frequency drugs are prescribed for their label extension indications to uncover the extent to which label extension is incorporated in practice. Such a study could help put the real-life impact of label extensions into perspective. Despite the diminishing returns of post-approval drug repurposing observed in our project, if label extensions are frequently used in practice and benefit patients, then post-approval research might merit the further investment of public resources.

Other remaining questions include the burden borne on patients in pre-approval clinical trials versus post-approval. A study could be conducted to compare the rate of adverse events in post-approval vs pre-approval clinical trials. Our findings suggest that a comparable number of patients are needed to obtain licensure post-approval vs pre-approval. If post-approval research is less burdensome for individual patients, then it might propose a better risk-benefit analysis than pre-approval research. Understanding the risk-benefit analysis of both approaches could aid in prioritizing research accordingly.

Another question left unresolved by our study and ones prior to it concerns "peri-approval" research. The "peri-approval" period is the year before and after the initial licensure of a drug where many research trajectories begin. Previous work has shown that the majority of trajectories resulting in secondary approvals were initiated in this period. [28] Instead of evaluating research in terms of pre and post-approval, the in-between period could be a time where patients stand to benefit from participating in clinical trials. Using the same methods used in this study, we could evaluate the per-patient efficiency of generating approvals 1 year before and after

initial licensure. The results from this study compared to the previous work which evaluated pre and post-approval efficiency could help us identify at which instance patients stand to benefit the most from participating in clinical trials within a certain drug's development timeline. This information could help prioritize certain periods in drug development that are most likely to best utilize patient participation in clinical trials.

Conclusion

This thesis provides an estimate of the number of patients required to successfully repurpose a recently approved cancer drug, an overview of the outcome of post-approval research, as well as the ethical and policy implications of our findings.

Drug repurposing entails clinical efforts that are directed at finding new uses for existing drugs. Such an approach to research accounts for a third of clinical trials in cancer and requires human welfare expenditure. Patients bear the risks and burdens of clinical trials. Basic principles of research ethics entail that we should strive to minimize patient burden while maximizing therapeutic outcomes across all research efforts. Since more is understood about the safety, pharmacology, and targets of approved drugs, the marginal cost of drug repurposing should be lower than *de novo* drug development. Yet, the efficiency of this approach- measured on a per-patient basis- to research had yet to be compared to *de novo* drug development.

Our core findings report how many patients are needed to obtain a label extension for a cancer drug. We undertook a cohort analysis of all cancer drugs approved by the FDA between 2012 and 2015. We identified all unique drug-indication research trajectories that were initiated after the initial licensure of a drug. We found that 14 secondary approvals originated from these post-approval trajectories, four of which were deemed to present substantial clinical benefit by ESMO-MCBS. A total of 9253 patients were needed to attain a secondary FDA approval and 16,596 patients were needed to obtain an initial secondary approval, which is no more efficient than the 12,217 patients needed to obtain initial licensure in cancer.

De novo and drug repurposing efforts compete with each other for resources, personnel and patients. Research systems must balance different approaches to drug development to optimize social returns on the investment of sparse resources. If we must balance a research

portfolio between drug repurposing and *de novo* drug development, then our findings suggest that research oversight should generally prioritize pre-approval research, since the lower scientific uncertainties associated with drug repurposing do not appear to produce gains in efficiency.

Future work exploring the reasons for the diminishing returns of drug repurposing remains to be conducted. One possible explanation for these diminishing returns includes the exhaustion of promising clinical hypotheses by the time of initial approval. Work elsewhere in our laboratory (data not shown) provide evidence for this explanation. Another is that economic and regulatory incentives might be insufficient for motivating proper investments in cancer drug repurposing.

Cancer remains one of the leading causes of death in North America. The need for new therapeutic options for patients is pressing. Research systems must strive to invest in research that makes the greatest use of the human welfare invested in clinical trials. Our findings suggest that drug repurposing isn't the more efficient way to invest patient-participants as the current regulatory and financial structure stands.

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