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The Association Between the Orphan Drug Tax Credit Reduction and the Orphan Drug Pipeline

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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By Nova Yang

Rare diseases have significant consequences for patients and caregivers in the United States. One of the original financial incentives in Orphan Drug Act (ODA) to encourage investments, the orphan drug tax credit, was reduced by the Tax Cuts and Jobs Act in 2017 from 50% to 25%. This study examines the orphan drug pipeline and quantify the tax credit reduction policy impact. After using a differences in differences method, the results suggest that the orphan drug tax credit reduction is negatively associated with the number of drug candidates in the pipeline, although this association was statistically nonsignificant. Based on the limited sample size and study period, the study yields conservative estimates. This study sets the foundation for future work to better understand the impact of orphan drug tax credits on the orphan drug development.

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Table of Contents

LIST OF TABLES AND FIGURES

Chapter 1 Introduction

Rare diseases have significant consequences for patients and caregivers. In the United States, rare disease or orphan disease is defined by the Orphan Drug Act of 1983 as a disease or condition that affects less than 200,000 people.[1] Currently there are over 7,000 rare diseases affecting more than 30 million people in the U.S., which means 1 out of every 10 Americans lives with a rare condition.[2] Most rare diseases are serious and life-threatening. 50% of rare diseases affect children, 30% of whom will die before 5 years old. Rare diseases are also responsible for 35% of deaths in the first year of life.[3] Examples of rare diseases include rare cancers, Huntington's disease, Duchenne Muscular Dystrophy, and other disease categories. Many of these conditions have genetic causes, but the exact cause of many rare diseases is still understudied. Because of the relatively small number of people affected with any particular rare disease and the large number of rare diseases in total, the development of treatment for rare diseases is challenging. These challenges include difficulty in attracting funding for drug research and development (R&D) and recruiting enough research participants for clinical trials.[4]

The definition of orphan drug varies across different institutions and regulatory authorities. The U.S. National Cancer Institute defines orphan drug as a drug used to treat, prevent, or diagnose an orphan disease.[5] The U.S. Food and Drug Administration (FDA) defines orphan drug as one that meets one of the following two conditions: the number of people affected by the disease or condition for which the drug is to be developed is fewer than 200,000 persons, or there is no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug for the U.S. market and the costs of making the drug available in the United States.[7] In addition, the concept of "orphan drug" includes drugs, biological products, medical devices and dietary or diet products.[8] Based on

different definitions, orphan drugs aim at providing treatments for rare diseases with various types of interventions.

The Orphan Drug Act of 1983 (ODA) is the first act signed into law that aims at increasing investment in orphan drugs.[1] The ODA grants multiple financial incentives to orphan drug R&D and has boosted the orphan drug pipeline ever since.[9] The cumulative count of orphan drug designations and approvals has been increasing since 1983. One of the original financial incentives in ODA to encourage investments, the orphan drug tax credit, was changed by the Tax Cuts and Jobs Act in 2017.[10] This study will examine the impact of this new change on the orphan drug pipeline.

Chapter 2 Literature review

2.1 Overview of the Orphan Drug Act of 1983 (ODA)

The Orphan Drug Act was passed in 1983 to promote the development of products to treat rare diseases by providing financial incentives to the pharmaceutical industry. The ODA provides several rewards to orphan drug developers. Rewards include: (1) seven years of marketing exclusivity after FDA approval; (2) a 50% tax credit on R&D costs incurred in the U.S., as well as R&D grants for Phase I to Phase III clinical trials; (3) a fast-track procedure for the FDA to evaluate registration files; and (4) written recommendations provided by the FDA concerning clinical and preclinical studies to be completed in order to register the new drug. Because an orphan drug designation is different from a drug approval, written recommendations can be supporting evidence for the drug candidate's final approval as all drug candidates still have to submit a new drug application (NDA) through the Centre for Drug Evaluation and Research (CDER) in the FDA for final approval.[11,12] To obtain the rewards provided by the ODA, pharmaceutical companies need to submit the orphan drug

status application to the FDA. As long as a candidate meets the FDA orphan drug definition and has supporting evidence for verification criteria, it will receive an orphan drug status designation from the FDA Office of Orphan Products Development. Verification criteria includes disease prevalence, data on all costs of R&D and other requirements specified by the FDA. [6]

Currently, these rewards are included in the Orphan Drug Designation program by the FDA office of Orphan Products Development (OOPD).[6] The program provides orphan status to drugs or biological products that prevent, diagnose or treat a rare disease or condition. The ODA has catalysed the orphan drug pipeline from 10 medicines before 1983 to over 5800 treatments for rare diseases that had been approved by the FDA by 2021.[13]

2.1.1 Research and Development (R&D) Cost

The research and development cost for drugs is the full cost of bringing a new drug to market from drug discovery through clinical trials to approval. The total R&D cost include preclinical and clinical costs, which vary based on therapeutic areas, clinical trial success rates, preclinical expenditures, and cost of capital.[14] The estimate of R&D cost per drug varies across literature, with the highest at $2558 million (2013 dollars) for pre-approval cost per drug at a real discount rate of 10.5%.[15] A more recent study found that in 2018 the estimated median capitalized research and development cost per product was $985 million, counting expenditures on failed trials.[14] The R&D cost of orphan drugs are considered to be lower than non-orphan drugs because of smaller number of participants enrolled in trials and other financial incentives granted by the ODA. A study published in 2019 found the out-of-pocket clinical costs per approved orphan drug is about 60% the cost for approved non-orphan drugs, and the capitalized costs per approved orphan drug is about 70% of the cost for their non-orphan counterparts.[16]

2.1.2 Orphan Drug Tax Credit (ODTC)

The orphan drug tax credit (ODTC) is a federal tax credit that helps pharmaceutical companies lower their R&D costs for developing rare disease treatments. Until recently, the ODTC allowed orphan drug developers to claim a tax credit for up to 50 percent of qualified clinical testing expenses, providing a substantial financial incentive to drug developers to invest in trials for orphan conditions. Clinical testing costs are a subset of the total R&D cost. Qualified expenses for the ODTC include certain human clinical testing costs incurred between orphan designation and drug approval.[17]

Clinical trials that are conducted outside the United States are not eligible for orphan drug tax credits except for two special limitations: when there is insufficient clinical trial participants in the United States, and when clinical trials are conducted by a United States person or by any other person who is not related to the taxpayer to whom the designation under section 526 if the Federal Food, Drug, and Cosmetic Act applies.[1] In addition, clinical testing expenses that are funded by any grant, contract, or otherwise by another person or any government entity are not qualified for orphan drug tax credits. This makes clinical trials funded by the National Institutes of Health (NIH), other U.S. federal agencies or not-for-profit institutions ineligible for the ODTC, and clinical trials funded solely by pharmaceutical companies the biggest beneficiaries of the ODTC.

2.2 Overview of the Tax Cuts and Jobs Act (TCJA) in 2017

The Tax Cuts and Jobs Act (TCJA) was passed in 2017. TJCA was passed to reform both individual income tax and corporate income taxes. The TJCA is considered by its proponents as a pro-growth tax plan. Advocates of TJCA maintained that it would increase individual wages, create more jobs, and result in a larger economy.[18]

The TJCA reduced the top corporate income tax rate from 25% to 21%, a provision considered beneficial to some large multinational pharmaceutical companies. For corporations with more than $10 million in annual revenue, the Act lowered the maximum tax rate from 35% to 21%. It also allows repatriation of corporate foreign profits at markedly reduced rates of 14.5% for cash holdings and 7.5% for non-cash holdings.[18]

To generate revenue to offset some of these substantial tax cuts, the TJCA also cut the orphan drug tax credits in half — from 50% to 25%. This policy change applied to R&D expenses incurred beginning January 1, 2018.[10] The reason why orphan drug tax credits were specifically targeted for reduction has not been answered, but the change raised debate among advocates and critics. Rare disease patients are concerned that this policy change will stop their life-saving drugs from being developed because drug companies are less incentivized to invest in R&D for these types of diseases.

On the other hand, the skyrocketing price of orphan drugs has raised concerns among policy-makers and researchers.[19] A report suggests that manufacturers have significantly increased their use of the financial incentives and increased the orphan drug price by repurposing old, non-orphan drugs as new orphans, obtaining multiple orphan-designations, and splitting a disease into several sub-diseases in order for them to qualify as a rare diseases. Companies have the ability to command high prices, despite the relatively low cost of developing orphan drugs in certain therapeutic areas. A study found the capitalized clinical cost per approved orphan drug was half that of a non-orphan drug in 2013.[16] Researchers have also argued that the ODA has been outdated, misused, and subject to gaming, and the ODTC has limited significance as a credit.[9]

Companies are not required to disclose the amount of tax credits they receive, which has reduced transparency and raised concern about the misuse of the incentive.[22] Kesselheim et al. suggest that making certain manufacturers repay the tax credit and research grants by

requiring them to report annual revenues for orphan-designated drugs to the government would help control the price.[22] [22]Some researchers argue that the orphan drug tax credit is a flawed incentive with limited impact because companies are not required to disclose the amounts of the tax credits they receive. A Congressional Research Service (CRS) report using data from 1990 to 1994 suggests that the ODTC amounted to 0.3% of R&D expenditures. Although it is considered as a conservative estimate for large pharmaceutical companies, their conclusion indicates biotechnology and small pharmaceutical firms may obtain a disproportionate share of the tax credits. Researchers also argue that the share of R&D expenditures for which the orphan drug credit was applicable for traditional large multinational pharmaceutical firms is quite low because it is not available for foreign clinical trial costs unless it can be demonstrated that it is necessary to go outside the United States to find patients.[21] According to the United States Government Accountability Office(GAO) report on orphan drugs in 2018, some pharmaceutical companies' drug development decisions are based on their targeted disease areas and not due to ODA incentives. Therefore, they suggest the orphan drug tax credits should be replaced by direct government subsidies.[22] However, there is no direct studies that have examined the actual impact of the recent orphan drug tax credit reduction on the orphan drug pipeline.

2.3 Overview of oncology drugs and rare cancers

The National Cancer Institute at the NIH defines rare cancers as those that affect fewer than 40,000 people per year in the United States. Rare cancers represent 27% of all cancers, accounting for 25% of all deaths due to cancer.[25] Diagnosis of rare cancers can be challenging for patients, caregivers, clinicians, and researchers. Scientific understanding of rare cancers is usually gained from case reports, anecdotal evidence, single-institution case

series, and/or small multicentre series. Hence, there is lack of confidence in clinical decision-making and proper treatment for rare cancers.[26]

The current knowledge of rare cancers varies by age groups and gender. All pediatric cancers are considered rare, with about 15,000 individuals younger than 20 years diagnosed with pediatric cancer in a given year in the United States.[27] In adults age 20 and older, nearly 13% (1 in 8) of all cancer diagnoses are considered rare based on the NIH definition, equivalent to approximately 208,000 new cases in 2017.[28] Rare cancers were proportionally (and absolutely) more common than non-rare cancers among young adults ages 20–29 years. A study found the rates of rare cancers vary by gender. Cancers of the oral cavity/pharynx, respiratory, and urinary system sites were considerably less common among women than among men, while peritoneal, gallbladder, and anal cancers were more common among women. Overall males have a higher rare cancer incidence than females, some with a male-to-female incidence rate ratio (IRR) of at least 3:1.[29]

Oncology sits as the top-selling therapeutic area on the orphan drug market. In 2016, for example, 6 of the top 10 orphan drugs by revenue were designated as orphan drugs for oncology diagnoses, with annual sales ranging from $1.1 billion to $4.4 billion. About 40% to 45% of all orphan drug designations are requested for rare cancers.[30] Since 2017, oncology drugs continue to dominate the sector with more than 60% of the top 20 orphan products indicated within this therapeutic category. EvaluatePharma predicts oncology sales on the orphan drug market will continue to rise in the coming years.[33]

2.4 The Evidence Gap & Current Study

A study conducted in 2015 estimated that without the orphan drug tax credit 67 orphan drugs, or 33% of all orphan drugs, would likely not have been developed over the past 30 years. If the orphan drug tax credits were eliminated entirely, 57, or 33% fewer new

orphan drugs would be approved over the next decade. It is estimated that in 2016, the reduction in tax credit from 50% to 25% will translate into about $30 billion less given to pharmaceutical companies over 10 years. Despite the many arguments on both sides, no study has been done yet to explore the extent of the impact of the 50% tax credit reduction on orphan drug development.[31] As market interest in oncology drugs increases and cancer treatments takes up more than half of the orphan drug market share, the orphan drug tax credit reduction may have a potential impact on this therapeutic area.

This study will examine the impact of the reduction of orphan drug tax credits on the orphan drug R&D pipeline by focusing on cancers. This study will estimate the overall changes in number of clinical trials for oncology drugs and changes stratified by different funders, age groups, gender groups, and study types. The results of this study will inform policymakers whether the rewards for orphan drugs need to be re-evaluated in the current environment to prevent the ODA incentives from discouraging orphan drug R&D, as well as avoid any federal spending waste in unnecessary benefits.

Chapter 3 Methodology

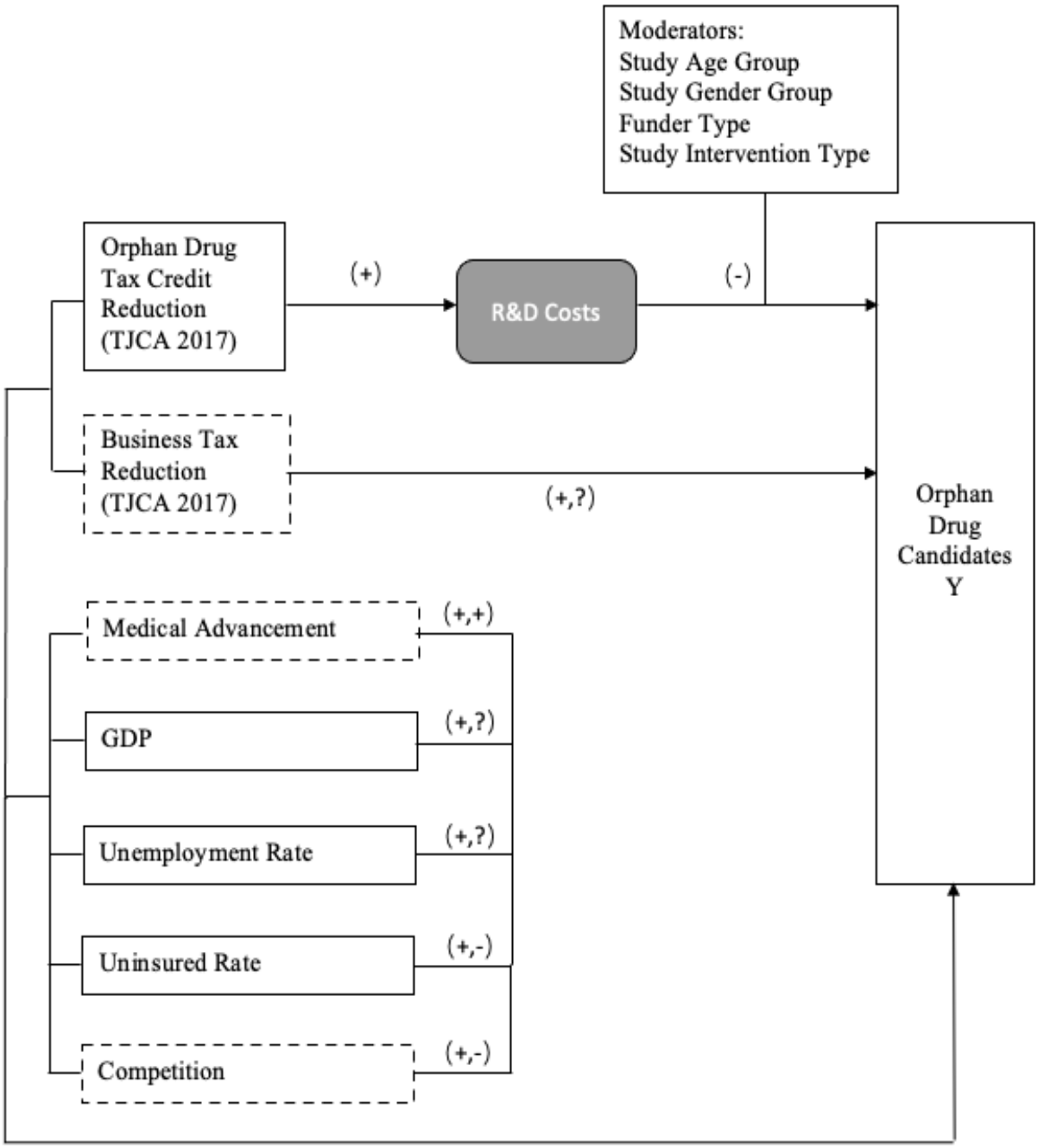
3.1 Theoretical Framework

To study the influence of the reduction of orphan drug tax credits on the number of orphan drug candidates, I will base my theoretical framework on the Giaccotto, Santerre, and Vernon's Drug R&D Investment Behaviour Model of drug prices.[32] This model hypothesizes that a direct relationship exists between drug prices and pharmaceutical R&D spending. The rationale behind this model is the microeconomic theory that the marginal revenues from successive increments of R&D spending decline with use of the product because of diminishing returns. Their model suggests that the optimal amount of pharmaceutical R&D spending depends on its future stream of expected marginal revenues(X) and costs(Z).

$$\mathbf{R\&D} = f(\mathbf{X}, \mathbf{Z})$$

Holding constant other determinants of R&D, increased marginal costs will slow down the growth of R&D and lead to increases in drug prices. For this study, I will draw on the portion of this model that suggests the negative correlation between costs and growth of R&D. The reduction of orphan drug tax credits has the potential to change the R&D costs for drug companies, and subsequently impact the number of orphan drug candidates in the pipeline.

Figure 1. Conceptual model for the relationship between the reduction of orphan drug tax credits and orphan drug candidates



Focal Relationship

The focal relationship that I studied is the reduction of orphan drug tax credits (ODTC) and its impact on orphan drug candidates. The 25% reduction of orphan drug tax credits as part of the Tax Cuts and Jobs Act of 2017 (TJCA) is a policy change that may impact on the pipeline. The orphan drug tax credit is one of the Orphan Drug Act (ODA)'s key provisions.[1] It is a financial incentive that the federal government gives to pharmaceutical

companies to encourage development of treatments for rare disease patients. Before the ODA of 1983, pharmaceutical companies were often unable and unwilling to invest in treatments for rare diseases because of the high cost and low probability to gain profits. The ODTC remained 50% between 1983 and 2017.

Orphan drug candidates are drugs or biological products that have received or may receive orphan drug designations granted by the FDA. An orphan drug designation is a status that means the sponsor qualifies for benefits provided by the ODA. However, obtaining an orphan drug designation does not guarantee the final market authorization by the FDA. All the orphan drug candidates form the orphan drug pipeline. By studying the total number of orphan drug candidates in the pipeline, it is possible to examine the impact of the reduction of orphan drug tax credits. The reduction of orphan drug tax credits will influence the number of orphan drug candidates by changing the R&D costs for pharmaceutical companies.

3.2 Hypothesis

The 25 percentage point orphan drug tax credit reduction has the potential to raise pharmaceutical firms' R&D costs by increasing their tax liability in proportion to the amount they invest in clinical trials for orphan drugs. Drug companies would be less incentivized to invest in orphan drug clinical trials, and subsequently reduce the number of orphan drug candidates in the pipeline.

Q1: What is the effect of reduction of orphan drug tax credits on the number of clinical trials for orphan drug candidates in the pipeline in the United States between 2010-2019?

H1: Since 2017, the reduction of orphan drug tax credits has a negative impact on the number of clinical trials for orphan drug candidates in the pipeline in the United States.

3.3 Data Sources

The outcome of interest in this study is the number of clinical trials initiated per orphan drug candidate. The key independent variables include prevalence of rare diseases and macroeconomic indicators including GDP, inflation, and country-level unemployment rate. The study uses clinical trials data from 2010 to 2019. My study period coincides with an upward trend in the number of orphan designations.[39] The count of the U.S. Food and Drug Administration (FDA) orphan drug designations have been generally increasing, with a cyclical trend since the launch of the Orphan Drug Act in 1983. These increases lead to the growth of the absolute number of orphan designations, as well as new orphan drug approvals.[13] Due to the COVID-19 pandemic recorded in early 2020, this study will focus on the period through 2019.[49]

Data used in this study were abstracted from Clinicaltrials.gov, which is a database maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH).[35] It collects data on privately and publicly funded clinical studies conducted around the world. For each clinical trial record, Clinicaltrials.gov includes study type, recruiting status, study phase, diseases and conditions targeted by the drug, funder type, and study protocol. Study status included in Clinicaltrials.gov does not contain information about all the clinical studies conducted in the United States because not all types of clinical studies are required to be registered. However, the focus of this study is on orphan drug trials and all interested candidates for such trials are required to register, as per the Final Rule by the FDA.[36] Therefore, the database provides inclusive and comprehensive information for the study.

Data from four additional databases were merged with data from Clinicaltrials.gov. First, the FDA Orphan Drug Product designation database is maintained by the FDA. This database records information on the process of designating a drug as an orphan drug prior to

its clinical trial. The database provides information on designation names, dates, status, and generic names for all FDA-approved orphan designations.[13] Disease prevalence information can be obtained from Orphanet. Orphanet collects disease prevalence data all over the world. It provides reference for the control group selection in this study.[43] Additional information for disease prevalence and rare disease status can be obtained from the National Organizations for Rare Disorders (NORD) database. NORD provides all registered rare diseases in the U.S. It is funded by the Anthem Foundation. NORD is a patient advocacy organization with more than 300 patient organization members. The NORD database collects information on diagnosis, therapies, and patient organizations for rare diseases. [44]

3.4 Analytic Sample

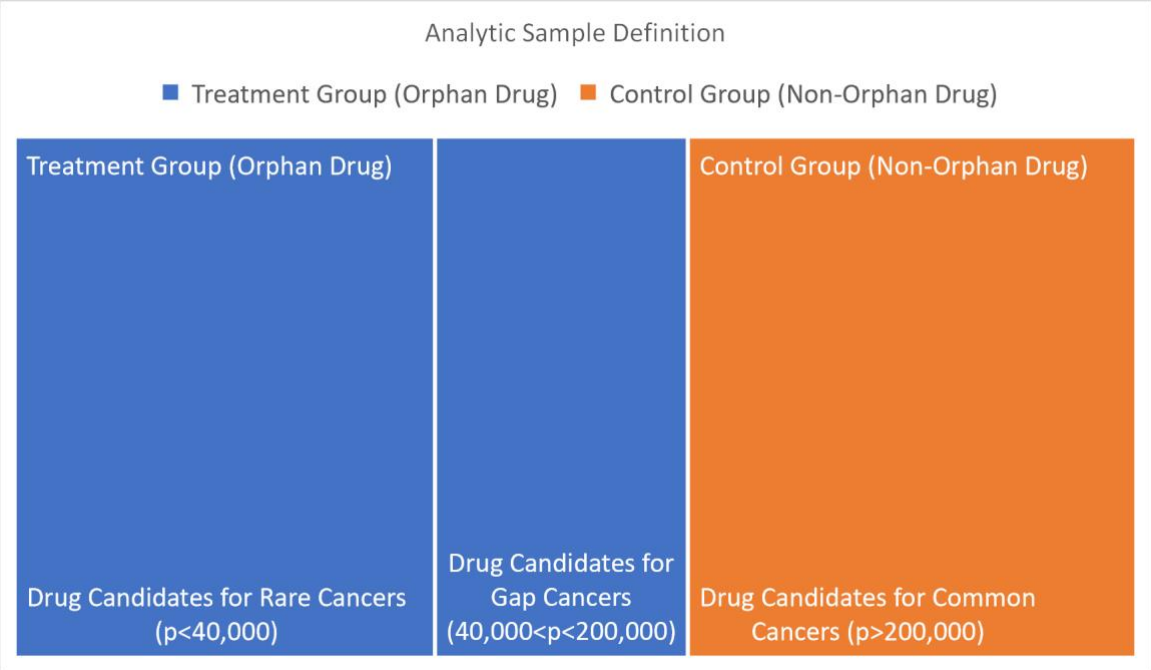
Analytic Sample Definition

The study is based on the assumption that any drug candidate for a disease with a prevalence of fewer than 200,000 patients would receive an orphan drug designation and therefore be eligible for orphan drug tax credits. To make a better comparison, I chose to focus the study on clinical trials for treatments of rare cancers because drugs being developed for oncology indications dominate the orphan drug pipeline landscape.[45] About half of the FDA-approved treatments were in the field of oncology in 2018.[46] I defined the treatment group as drug candidates that targeted rare cancer (i.e., those affecting fewer than 200,000 patients in the U.S.)and the control group as drug candidates targeting common cancers (i.e., those affecting more than 200,000 patients).

The NIH defines rare cancers as cancers that affect fewer than 40,000 people per year in the U.S..[47] In this study, the definition of rare cancer is different from the NIH definition because the study is interested in the overall policy impact on drug candidates that may receive potential orphan drug status designations. As long as the disease prevalence meets the

definition of rare disease in the U.S., the drug candidates for that particular disease are assumed to be eligible for an orphan drug status designation. Therefore, the definition of rare cancer in this study is expanded to the same definition as rare disease. There are some cancers that does not meet the NIH definition of rare cancers (<40,000 patients), but meet the definition of rare diseases (<200,000 patients), which means they would be eligible for orphan drug designations. They are recognized at 'Gap Cancers' in this study (Figure 2). Drug candidates for gap cancers are included in the treatment group along with drug candidates for rare cancers. Drug candidates for cancers that do not meet the definition of rare diseases are classified as control group. A complete list of rare cancers and common cancers used in this study is included in the appendix.

Figure 2. Analytic sample definition



Analytic Sample Derivation

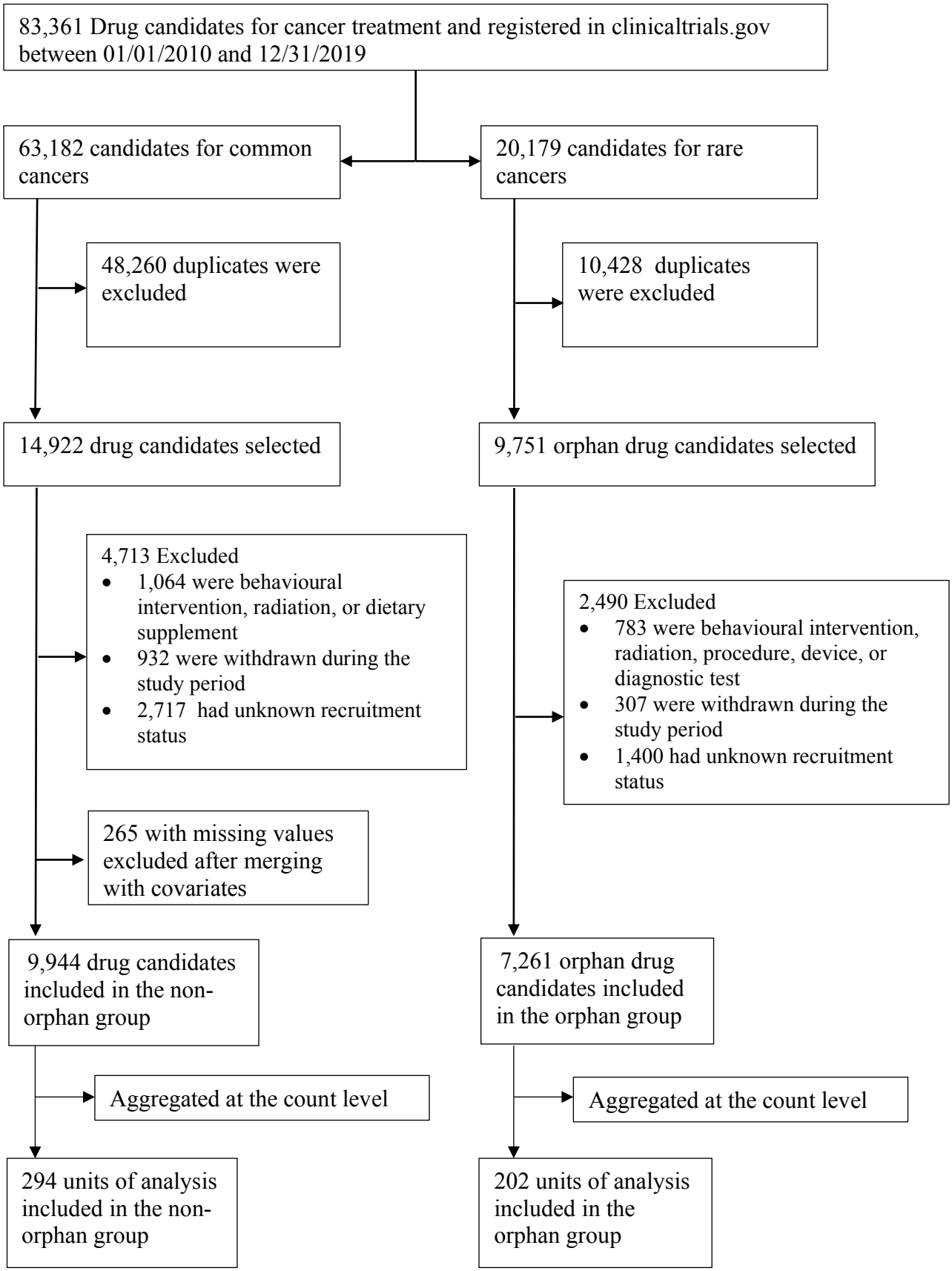
I first identified all drug candidates under clinical trials for cancer treatment in the United States (US) and registered in *clinicaltrials.gov* between January 1, 2010 and December 31, 2019. Data were pulled out from clinicaltrials.gov at the drug level. Because

the study focused on a US policy, I restricted the sample to the clinical trials exclusively conducted in the US.

Based on the FDA definition of an orphan product (FDA, 2021), I included drugs, biologics, and medical devices as interventions for drug candidates. I excluded non-interventional studies that contained observational studies, patient registry studies, expanded access studies, as well as other unqualified interventions including behaviour, radiation, and dietary supplement. I further excluded observations with unknown and withdrawn status to ensure a representative sample of drug candidates in active clinical trials because of their lack of verification and validation. Lastly, I excluded drug candidates with missing information on any of the model covariates. These exclusion criteria yielded 7,261 drug candidates in the treatment group (orphan drug group) and 9,944 in the control group (non-orphan drug group).

I further aggregated the drug level data to count level data by calculating the count of clinical trials by drug candidate after controlling for study type, funder type, study age group, and study gender group and by calendar year. My final analytic sample for statistical analysis included 496 units of analysis, including 294 units in the non-orphan group and 202 in the orphan group.

Figure 3. Analytic sample derivation flowchart


83,361 Drug candidates for cancer treatment and registered in clinicaltrials.gov between 01/01/2010 and 12/31/2019
63,182 candidates for common cancers
20,179 candidates for rare cancers
48,260 duplicates were excluded
10,428 duplicates were excluded
14,922 drug candidates selected
9,751 orphan drug candidates selected
4,713 Excluded
• 1,064 were behavioural intervention, radiation, or dietary supplement
• 932 were withdrawn during the study period
• 2,717 had unknown recruitment status
2,490 Excluded
• 783 were behavioural intervention, radiation, procedure, device, or diagnostic test
• 307 were withdrawn during the study period
• 1,400 had unknown recruitment status
265 with missing values excluded after merging with covariates
9,944 drug candidates included in the non-orphan group
7,261 orphan drug candidates included in the orphan group
Aggregated at the count level
Aggregated at the count level
294 units of analysis included in the non-orphan group
202 units of analysis included in the orphan group

3.5 Constructs

Macroeconomic Conditions

Macroeconomic variants including Gross Domestic Product (GDP), unemployment rate, and uninsured rate were captured in year fixed effects of the differences in differences model.

Competition(+,-)

Competition might negatively affect the number of drug candidates. Competition is an important factor for drug companies to consider when making investments and financial decisions. If there have already been approved drugs for a specific disease, drug companies may be less willing to develop a drug that treats the same disease because they can expect to capture less market share. Data has shown that there is a discontinuous trend of growths in new orphan designations in the U.S. from 2004 to 2018. The competition in the orphan drug pipeline will be different before and after the TJCA in 2017. However, the lack of disclosure of decision making in the pharmaceutical industry makes this factor an unmeasured confounder. This construct will be captured by the fixed effect in the model.

Medical Advancement (+,+)

Medical advancements might stimulate the orphan drug pipeline in many ways. One of the greatest barriers to the development of orphan drugs is patient recruitment. As a prerequisite for any successful clinical trials, the recruitment process is difficult given the rarity of rare disease patients. In addition to that, most rare conditions are caused by genetic abnormalities, which means that patients are unlikely to be clustered in specific geographic locations. These challenges make the participant outreach process both time-consuming and laborious. Because of the genomic signature and other advances in genomic technologies,

researchers are now able to conduct patient-specific treatment selection using the genetic makeup of the disease and the genotype of the patient.[42] This advance will shorten pre-clinical trial research time and reduce R&D costs, compared with traditional drug target R&D approach. Another medical advancement related to orphan drug development is the real-world data (RWD) that has gained widespread use in recent years.[43] RWD are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. They are collected from patient registries, healthcare databases, pharmacy and health insurance databases, social media and patient-powered research networks. RWD can be utilised in rare disease patient registries for patient stratification, and even replace the traditional clinical trial when the targeted population is too low to run a randomised trial. Therefore, medical advancements have paved the way for orphan drug R&D. Medical advances are happening over time, therefore over the study period more technologies are available and more mature in their use. Although we were unable to measure medical advancement, it was largely captured in the year fixed effects in the differences in differences model.

Business Tax Reduction(+,?)

The business tax reduction will be an unmeasured confounder of the focal relationship. Another component of the TJCA that might positively affect the number of orphan drug candidates is the business tax reduction. TJCA cut the corporate tax rate from 35% to 21% and repealed the corporate alternative minimum tax[10]. Pharmaceutical companies are likely to have increased cash flow and more freedom to invest in promising candidates, such as orphan drugs. However, pharmaceutical companies may use the money saved by the business tax reduction for other purposes, including paying dividends to shareholders. **Error! Reference source not found.** Larger pharmaceutical companies that are interested

in multiple projects may use the money to invest in other more established therapeutic areas including cardiovascular diseases, diabetes or vaccines, while pharmaceutical companies that only focus on rare diseases may use the money to invest in more orphan drug candidates. Therefore the business tax reduction affects pharmaceutical companies differentially. Choosing a drug portfolio is an internal decision-making process within each company. It is influenced by the size, level of expertise, finance situation, and other characteristics. For reasons of market competition and intellectual property protection, pharmaceutical companies generally do not disclose their internal decisions to the public. Therefore, the business tax reduction remains a confounder in this study.

Funders

Funders are organizations that provide funding or support for a clinical study.[44] Organizations listed as sponsors and collaborators for a study are considered as funders of the study in clinicaltrials.gov. Clinicaltrials.gov classifies funders into four types: U.S. National Institutes of Health, other U.S. Federal agencies, industry, and others. Other U.S. federal agencies include the U.S. Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and U.S. Department of Veterans Affairs (DVA). Industry consists of pharmaceutical companies and medical device companies. Others include individuals, universities, and community-based organizations.

Phase

Phase is the stage of a clinical trial studying a drug or biological product, based on definitions developed by the FDA. There are four phases of a complete clinical trial: Phase 1, Phase 2, Phase 3, and Phase 4. In clinilcaltrials.gov there are more defined phases including early phase 1, phase1/2, and phase2/3, but not all are a required part of testing a new drug. A

drug candidate will move to the next phase when it succeeds in the previous clinical phase. If a drug candidate continues to survive phase 3, it will be authorized with marketing approval by the FDA. It will then go through phase 4. Drug candidates have different pass rate for each clinical trial phase. The time and monetary costs for drug candidates that have passed different phases vary cross therapeutic areas.

Early Phase 1

Early phase 1(previously called as Phase 0) usually have fewer than 15 participants and use a few small doses of a new treatment in a short time. They are used to describe exploratory trials conducted before traditional phase 1 trials to investigate how or whether a drug affects the body. They involve very limited human exposure to the drug and have no therapeutic or diagnostic goals. Early phase 1 clinical trials are not required for testing a new drug.

Phase 1

For Phase I clinical trials, participants include 20 to 100 healthy volunteers or people with the disease. The study will take several months. The purpose of the study is to study the intervention to learn about its safety, dosage, and identify side effects. Approximately 70% of the candidates move to the next phase.[45]

Phase 1/2

Phase 1/2 clinical trial is the combination of traditional phase 1 and phase 2 clinical trials.[5] It tests the safety, side effects, and best dose of a new treatment. It also test how well a disease responds to a new treatment. Phase 1/2 clinical trials may allow research questions to be answered more quickly or with fewer patients, which is more efficient for rare disease treatments compared with separate phase 1 and phase 2 clinical trials.

Phase 2

Phase 2 clinical trials usually have 100-300 participants with the disease or condition. The study takes several months to 2 years. The purpose of the study is to determine the intervention's effectiveness and to further study its side effects. Approximately 33% of the candidates move to the next phase.

Phase2/3

Phase 2/3 clinical trial is the combination of traditional phase 2 and phase 3 clinical trials. It examines how well a new treatment works for a disease and compares the new treatment with a standard treatment. Phase 2/3 clinical trials may also provide more information about the safety and side effects of the new treatment. Similar to phase 1/2 clinical trials, they may allow research questions to be answered more quickly or with fewer patients.

Phase 3

Phase 3 clinical trials usually have 300 to 3,000 participants with the disease or condition. The study will take 1 to 4 years. The purpose of the study is efficacy and monitoring adverse reactions. Approximately 25-30% of the candidates move to the next phase.

Phase 4

Phase 4 clinical trials are post-approval trials. Phase 4 clinical trials usually have several thousand volunteers with the disease or condition. The purpose is to continue to track the safety and efficacy of the drug in the general population after the candidate is approved by the FDA.

3.6 Statistical Analyses

The study uses a differences-in-differences framework to examine the impact of the implementation of the TJCA. My dependent variable is the count of clinical trials by drug candidate and by year, for rare cancer and common cancer respectively. More specifically, the study aggregates clinical trial data to the drug candidate level. The unit of analysis is the number of clinical trials per drug candidate per year. The study included an interaction term of the pre/post policy period and rare (vs. common) disease status. The pre-policy period includes clinical trials conducted from 2010 to 2017. The post policy period includes clinical trials conducted in 2018 and 2019. Poisson regression is used to model count data. For ease of interpretation, marginal effects were reported as the predicted difference in the count of clinical trials conducted for each orphan drug candidates associated with the change in the orphan drug tax credit reduction, holding all other predictors in the regression at their observed values.[46]

$$\textbf{Count(DV)} = \beta_0 + \beta_1\ \textbf{post*orphan} + \beta_2\ \textbf{age\_group} + \beta_3\ \textbf{funder\_type} + \beta_4\ \textbf{study\_type} + \beta_5\ \textbf{gender\_group} + \textbf{post} + \textbf{orphan} + \beta_6\textbf{Year}$$

The coefficient of interest is the interaction term, β_1. The regression model controlled for study age group (age_group), study funder type (funder_type), study intervention type (study_type), and study gender group (gender_group). I also included year fixed effects (Year), which control for any national conditions in a given year (e.g., gross domestic product). To test for the parallel trend, I first graphed the changes in number of clinical trials in both groups by year. (Figure 4). To prove the pre-intervention trends do not differ across two groups, I further calculated the differences in the estimates for the interaction term. In both the unadjusted model and adjusted model, there is no significant difference between the estimates for the interaction term ($p=0.75$ in the unadjusted model, $p=0.87$ in the adjusted

model). Therefore there is no significant difference in slope between the orphan and non-orphan groups after testing for the pre policy parallel trend assumption.

Chapter 4 Results

4.1 Descriptive Statistics

Table 1. Descriptive statistics for the analytic sample

(a) The table shows row percentage for total counts.

(b) The table shows column percentage for the orphan group and non-orphan group.

		Orphan							Non-orphan						
		Phase							Phase						
	Total	1	2	1/2	3	2/3	4	Total	1	2	1/2	3	2/3	4	Total
Number of trials, N(%)	17205	2538(34.95)	2811(38.71)	1148(15.81)	587(8.08)	81(1.12)	96(1.32)	7261	3202(32.20)	3978(40.00)	1402(14.10)	1041(10.47)	118(1.19)	203(2.04)	9944
Study Start															
2010	1597(9.28)	218(8.59)	286(10.17)	105(9.14)	60(10.22)	7(8.64)	12(12.5)	688(9.48)	266(8.31)	397(9.98)	128(9.13)	86(8.26)	8(6.78)	24(11.82)	909(9.14)
2011	1517(8.82)	194(7.64)	308(10.96)	88(7.67)	50(8.52)	5(6.17)	6(6.25)	651(8.97)	268(8.37)	401(8.97)	94(6.70)	83(7.97)	7(5.93)	13(6.40)	866(8.71)
2012	1479(8.60)	222(8.75)	254(9.04)	89(7.75)	44(7.50)	5(6.17)	15(15.63)	629(8.66)	278(8.68)	347(8.66)	118(8.42)	77(7.40)	8(6.78)	22(10.84)	850(8.55)
2013	1499(8.71)	216(8.51)	246(8.75)	100(8.71)	59(10.05)	4(4.94)	7(7.29)	632(8.70)	273(8.53)	369(8.70)	108(7.70)	91(8.74)	9(7.63)	17(8.37)	867(8.72)
2014	1607(9.34)	274(10.80)	207(7.36)	119(10.37)	54(9.20)	5(6.17)	7(7.29)	666(9.17)	334(10.43)	343(9.17)	126(8.99)	110(10.57)	11(9.32)	17(8.37)	941(9.46)
2015	1670(9.71)	246(9.69)	249(8.86)	113(9.84)	52(8.86)	7(8.64)	7(7.29)	674(9.28)	316(9.87)	384(9.87)	151(10.77)	115(11.05)	11(9.32)	19(9.36)	996(10.02)
2016	1769(10.28)	269(10.60)	290(10.32)	118(10.28)	55(9.37)	9(11.11)	5(5.21)	746(10.27)	369(11.52)	382(11.52)	150(10.70)	92(8.84)	13(11.02)	17(8.37)	1023(10.29)
2017	2070(12.03)	263(10.36)	378(13.45)	146(12.72)	66(11.24)	13(16.05)	12(12.50)	878(12.09)	349(10.90)	485(10.90)	183(13.05)	127(12.20)	15(12.71)	33(16.26)	1192(11.99)
2018	2033(11.82)	308(12.14)	307(10.92)	146(12.72)	74(12.61)	11(13.58)	10(10.42)	856(11.79)	381(11.90)	464(11.90)	166(11.84)	134(12.87)	14(11.86)	18(8.87)	1177(11.84)
2019	1964(11.42)	328(12.92)	286(10.17)	124(10.80)	73(12.44)	15(18.52)	15(15.63)	841(11.58)	368(11.49)	406(11.49)	178(12.70)	126(12.10)	22(18.64)	23(11.33)	1123(11.29)
Study Type, N(%)															
Drug	13689(79.56)	1915(75.45)	2263(80.51)	852(74.22)	480(81.77)	58(71.60)	93(96.88)	5661(77.96)	2531(79.04)	3276(79.04)	1090(77.75)	846(81.27)	97(82.20)	188(92.61)	8028(80.73)
Biological	1338(7.78)	259(10.20)	168(5.98)	92(8.01)	22(3.75)	3(3.70)	3(3.13)	547(7.53)	331(10.34)	269(10.34)	109(7.77)	63(6.05)	6(5.08)	13(6.40)	791(7.95)
Genetic	27(0.16)	8(0.32)	3(0.11)	1(0.09)	0	0	0	12(0.17)	9(0.28)	3(0.28)	2(0.14)	1(0.10)	0	0	15(0.15)
Combination Product	41(0.24)	7(0.28)	2(0.07)	2(0.17)	0	1(1.23)	0	12(0.17)	15(0.47)	8(0.47)	2(0.14)	3(0.29)	0	1(0.49)	29(0.29)
Mixed	2110(12.26)	349(13.75)	375(13.34)	201(17.51)	85(14.48)	19(23.46)	0	1029(14.17)	316(9.87)	422(9.87)	199(14.17)	128(12.30)	15(12.71)	1(0.49)	1081(10.87)
Funder Type, N(%)															
Industry only	6242(36.28)	821(32.35)	677(24.08)	478(41.64)	415(70.70)	34(41.98)	30(31.25)	2455(33.81)	1169(36.51)	1126(36.51)	620(44.22)	778(74.74)	45(38.14)	49(24.14)	3787(38.08)
Industry with other institutions	3891(22.62)	542(21.36)	747(26.57)	243(21.17)	44(7.50)	8(9.88)	22(22.92)	1606(22.12)	667(20.83)	1142(20.83)	333(23.75)	84(8.07)	11(9.32)	48(23.65)	2285(22.98)
Other Institutions only	7072(41.10)	1175(46.30)	1387(49.34)	427(37.20)	128(21.81)	39(48.15)	44(45.83)	3200(44.07)	1366(42.66)	1710(42.66)	449(32.03)	179(17.20)	62(52.54)	106(52.22)	3872(38.94)
Study Gender Group															
Female Only	998(5.80)	88(3.47)	159(5.66)	27(2.35)	40(6.81)	5(6.17)	4(4.17)	323(4.45)	177(5.53)	316(5.53)	55(3.92)	92(8.84)	12(10.17)	23(11.33)	675(6.79)
Male Only	719(4.18)	3(0.12)	4(0.14)	2(0.17)	2(0.34)	0	1(1.04)	12(0.17)	157(4.90)	361(4.90)	81(5.78)	83(7.97)	16(13.56)	9(4.43)	707(7.11)
All Genders	15488(90.02)	2447(96.41)	2648(94.20)	1119(97.47)	545(92.84)	76(93.83)	91(94.79)	6926(95.39)	2868(89.57)	3301(82.98)	1266(90.30)	866(83.19)	90(76.27)	171(84.24)	8562(86.10)
Study Age Group															
Children only	127(0.74)	12(0.47)	21(0.75)	6(0.52)	8(1.36)	2(2.47)	4(4.17)	53(0.73)	23(0.72)	21(0.53)	10(0.71)	13(1.25)	2(1.69)	5(2.46)	74(0.74)
All Ages	17078(99.26)	2526(99.53)	2790(99.25)	1142(99.48)	579(98.64)	79(97.53)	92(95.83)	7208(99.27)	3179(99.28)	3957(99.47)	1392(99.29)	1028(98.75)	116(98.31)	198(97.54)	9870(99.26)

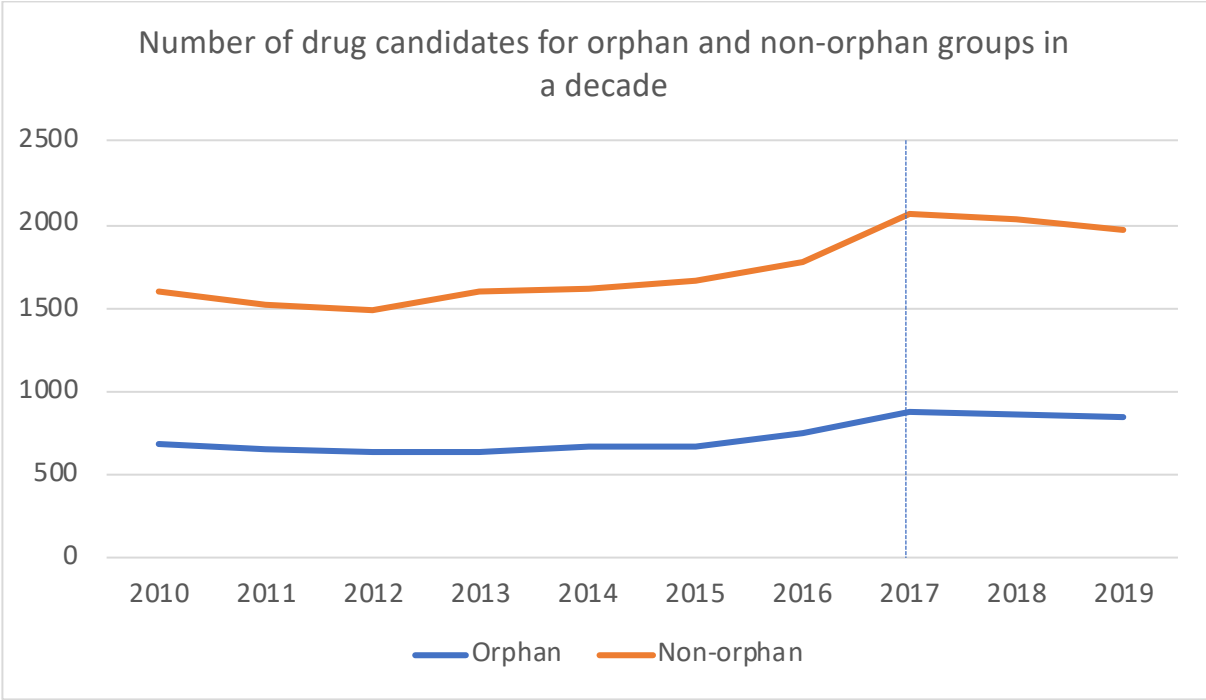


Figure 4. Number of drug candidates for rare cancer and common cancer during the study period

4.2 Descriptive Results

I identified a total of 17,205 clinical trials, including 7,261 trials in the orphan drug group and 9,944 trials in the non-orphan drug group (Table 1). The number of clinical trials in each year was increasing from 1,597 in 2010 to 1,964 in 2019. The number of clinical trials peaked at 2,070 in 2017 and started to decline after 2017 (Figure 2). The trend was similar across both the orphan drug group and the non-orphan drug group. The orphan group had the least number of trials (n=629) in 2012 and the largest number of trials in 2017 (n=878), while the non-orphan group had the least number of trials in 2012 (n=850) and the largest number of trials in 2017 (n=1,192).

The most common clinical intervention was drug for both groups (77.96% for orphan, 80.73% for non-orphan). When examining the type of study by counts, there were more clinical trials using genetic and mixed interventions in the orphan group than in the non-orphan group (0.17% using genetic intervention for orphan, vs. 0.15% for non-orphan; 14.17% using mixed interventions for orphan, vs. 10.87% for non-orphan), and fewer clinical trials using biological and combination product intervention in the orphan group than in the non-orphan group (7.53% using biological intervention for orphan, vs. 7.95% for non-orphan; 0.17% using combination product intervention for orphan, vs. 0.29% for non-orphan).

When examining the funder type, more than half of all clinical trials were funded solely or partially by industry (n=10,133, 58.9%), of which some were fully funded by industry(n=6,242, 36.28%) and the rest were co-funded by institutions and industry(n=3,891, 22.62%). 41.10% clinical trials (n=7,072) were funded by the NIH, other federal agencies, universities or organizations. The orphan group was more likely to receive funding from non-industry sponsors, compared with the non-orphan group (44.07% of other institutions only for orphan, 38.94% of other institutions only for non-orphan).

When examining the age group of study participants in clinical trials, most (99.26%) included participants of all ages. Overall, there were 0.74% trials that included only children participants. Trials in the orphan group were less likely to include child-aged participants than those in the non-orphan group (0.73% for orphan, 0.74% for non-orphan).

In addition, overall, over one-third of the trials were in Phase 2 (38.71% for orphan, 40.00% for non-orphan). Proportionally the orphan group had more trials in Phase 1 and Phase1/2 than the non-orphan group(34.95% in Phase 1 for orphan, 32.20% in Phase 1for non-orphan; 15.81% in Phase 1/2 for orphan, 14.10% in Phase 1/2 for non-orphan). The non-orphan group had more trials in Phase 3, Phase2/3, and Phase 4 than the orphan group(8.08% in Phase 3 for orphan, 10.47% in Phase 3 for non-orphan; 1.12% in Phase 2/3 for orphan, 1.19% in Phase 2/3 for non-orphan; 1.32% in Phase 4 for orphan, 2.04% in Phase 4 for non-orphan).

4.3 Results of regression analyses

Table 2. Differences-in-Differences estimates for the association between tax credit cut and the number of drug candidates

Overall and Stratified Regression Results		Orphan		Non-Orphan		Unadjusted DID estimate				Adjusted DID estimate[c]			
		2010-2017	2018-2020	2010-2017	2018-2020	Marginal Effects	CI	P value	SD	Marginal Effects	CI	P value	SD
Overall	**Count[a]**	696	849	956	1,150	-2.5	(-27.98,22.97)	0.85	13.00	-2.45	(-7.61,2.72)	0.35	2.64
By gender group	**Female Only**	31	38	65	77	-1.78	(-6.42,2.86)	0.45	2.37	-1.17	(-3.54,1.21)	0.34	1.21
	Male Only	1	2	67	86	-0.61	(-6.07,4.85)	0.83	2.79	-2.65	(-4.99,-0.32)	0.02*	1.19
	All genders	664	809	824	987	1.35	(-42.37,45.07)	0.95	22.31	-1.85	(-10.86,7.16)	0.67	4.60
By study age group	**Children**	5	5	8	7	0.68	(-1.61,2.98)	0.56	1.17	0.8	(-0.78,2.38)	0.32	0.81
	Adults	690	844	948	1,143	-4.78	(-32.62,23.06)	0.74	14.20	-2.9	(-8.78,2.97)	0.33	3.00
By funder type	**Industry**	228	314	362	447	-5.23	(-51.59,41.12)	0.82	23.65	-1.2	(-8.33,5.92)	0.74	3.63
	Industry and other institutions	151	199	215	281	-0.28	(-36.72,36.15)	0.99	18.59	-3.19	(-9.34,2.95)	0.31	3.14
	Other Institutions	316	336	379	422	-0.36	(-48.13,47.90)	0.99	23.33	-2.64	(-8.48,3.20)	0.37	2.98
By study type	**Drug**	551	627	784	877	-4.31	(-62.64,54.03)	0.89	29.76	-3.67	(-12.09,4.76)	0.39	4.30
	Biological	49	76	72	107	-0.44	(-10.63,9.75)	0.93	5.20	-1.01	(-5.07,2.84)	0.58	2.02
	Generic	1	3	2	2	0.03	(-1.21,1.27)	0.96	0.63	0.08	(-1.10,1.28)	0.89	0.61
	Combination Product	0	5	1	10	-0.36	-	-	-	-0.68	(-1.89,0.52)	0.27	0.62
	Mixed	94	140	96	155	-1.38	(-18.66,15.89)	0.87	8.82	-2.23	(-8.40,3.94)	0.48	3.15

(a) Average yearly count for the pre/post policy period
(b) *p<0.05
(c)After controlling for age group, gender group, study type and funder style

Overall Association between Policy Change and the Number of Orphan Drug Candidate

Figure 1 shows the number of drug candidates for rare cancer and common cancer during the study period. Both groups showed an upward trend from 2010 to 2017, with decreases in numbers of drug candidates from 2017 to 2019.

Prior to the policy change in 2017, there was an average of 696 orphan drug candidates and 956 non-orphan drug candidates entering the pipeline each year (Table 2). After the policy change, there was an average of 849 and 1,150 new candidates per year for the orphan and non-orphan groups respectively, accounting for a 22% relative increase in the number of orphan drug candidates and an 20.3% relative increase in the number of non-orphan drug candidates. Overall, the number of new drug candidates has increased by 21% after 2017.

In adjusted differences-in-differences regression models, overall, there was a decrease of 2.45 (95% CI = -7.61 to 2.72, p=0.35) in the number of clinical trials per orphan drug candidate after orphan drug tax credit was cut in 2017, compared with non-orphan drug candidates; however, the decrease was not statistically significant (Table 2).

Association between Policy Change and the Number of Orphan Drug Candidate in Subgroups

When stratifying the sample by study age groups, the adult group (adjusted DiD = -2.9; 95% CI = -8.78 to 2.97, p=0.33) had a larger reduction in magnitude associated with the policy change. The children group had an increase of 0.8 in the number of trials per orphan drug (95% CI = -0.78 to 2.38) but the estimate was not statistically significant.

Across different funder types, drug candidates that received funding from the industry and other institutions had the largest reduction in magnitude in the number of trials after the policy change (adjusted DiD = -3.19; 95% CI = -9.34 to 2.95), followed by clinical trials funded by other institutions (adjusted DiD = -2.64; 95% CI = -8.48 to 3.20). Drug candidates

that funded by the industry only had the least reduction in magnitude compared with drug candidates funded by other sources (adjusted DiD = -1.2; 95% CI = -8.33 to 5.92).

When examining different study types, drug candidates that use drugs as the intervention had the largest reduction in magnitude after the policy change (adjusted DiD = -3.67; 95% CI = -12.09 to 4.76), followed by drug candidates that used mixed intervention (adjusted DiD = -2.23; 95% CI = -8.40 to 3.94), combination product (adjusted DiD = -0.68; 95% CI = -1.89 to 0.52), biological (adjusted DiD = -1.01; 95% CI = -5.07 to 2.84). Drug candidates that used generic interventions had an increase of 0.08 in magnitude after the policy change (adjusted DiD =0.08; 95% CI = -1.10 to 1.28). Notably, all estimates above were statistically nonsignificant.

Across different study gender groups, drug candidates that study only males had the largest reduction (adjusted DiD = -2.65; 95% CI = -4.99 to -0.32), followed by drug candidates that study all genders (adjusted DiD = -1.85; 95% CI = -10.86 to 7.16), and drug candidates that study only females (adjusted DiD = -1. 17; 95% CI = -3.54 to 1.21).

Chapter 5 Discussion

5.1 Key Findings

Overall, there were 2.45 fewer clinical trials per orphan drug candidate in the pipeline following the orphan drug tax credit reduction. The DiD estimate is in the same direction as expected, but it was not statistically significant.

Findings by Funder type and Potential Reasons

The reduction in the number of clinical trials following the 2017 tax credit reduction was larger in magnitude for trials with multiple funders (industry and other institutions) than those funded by industry alone or other institutions alone; yet, these reductions were

statistically nonsignificant. In a competitive environment, it is likely that drug development in rare cancers relies on various funding revenues in comparison to solely industry-led trials studying non-orphan drugs. It is also likely that the NIH, other U.S. federal agencies, and not-for-profit institutions are funding certain extremely rare cancers in which pharmaceutical companies are not incentivized to invest even with tax benefits.

Findings by Study Age Group and Potential Reasons

Changes in the number of clinical trials following the tax credit reduction was smaller in magnitude for clinical trials that only study the pediatric population, compared with clinical trials for participants of all ages. Rare diseases affect children disproportionally less than adults, and the number of pediatric participants are usually smaller than the number of adult participants, resulting in inadequate recruitment. Thus, pharmaceutical companies may be less incentivised to invest in treatments for children with rare diseases. It is likely that most clinical trials that involve children are funded by non-industry funders who are exempt from the ODTC and are less affected by the policy change.

Findings by Study Gender Group and Potential Reasons

The number of clinical trials reduced more for trials only studying male participants than those studying female participants or participants of all genders, following the implementation of the 2017 tax credit cut.

Potential reasons of non-significant results

Tax benefits may not be the primary driver for drug companies to invest in orphan drugs. Developing orphan drugs or oncology drugs can still be profitable even without the tax credits. Therefore, the policy change may not have had a meaningful impact on drug

companies' decisions. The tax credit can be valuable to make the financial case work better for smaller orphan drugs where the ability to recover the investment is hurt by the usually low revenues expected from a small population of patients. Clinical trials funded by the NIH and other U.S. federal agencies or instructions are exempt from orphan drug tax credits.[41]

Descriptive results showed the orphan group had a higher proportion of Phase 1 and Phase1/2 trials while the non-orphan group had higher proportion of trials in Phase 2, Phase 3, Phase 2/3, and Phase 4. This implies that Phase 1 and Phase 1/2 trials are used as pivotal trials for orphan drugs and some orphan drugs may not even be tested in a phase 3 setting.

Omitted variable bias may also contribute to the insignificant estimate. Statistically insignificant results may derive from the small sample size, limited study time after the policy change, and the existence of a potential wash-out period. A wash-out period is a clinical research term often used to describe the phase built into the study design to separate two treatment periods to eliminate "carry-over" effects.[42] In the case of policy changes, implementing policies needs time and the pipeline is impacted by previous ODA incentives. Therefore, the true impact of the orphan drug tax credit reduction on the pipeline may take some time to emerge. The business tax reduction as part of TJCA may potentially bias the estimates. The direction of bias is unknown as is discussed in chapter 3. However, to the extent that the business tax reduction equally affects drugs for rare cancers and common cancers, its impact on this study is limited in a DiD framework.

5.3 Policy Implications

The orphan drug tax credit reduction is negatively associated with the number of clinical trials for drug candidates in the pipeline, although this association was statistically nonsignificant. One explanation is the orphan drug tax credit reduction is disincentivizing pharmaceutical companies from more investment in orphan drug R&D.

Granting tax credits for orphan drug development can be a huge cost of the federal budget in lost tax revenue. When the benefits of tax credits is limited for drug companies and the orphan drug pipeline is not significantly spurred by tax credits, there is weak rationale to provide firms with tax credits. However, these findings in isolation should not compel policy makers to rush to repeal the tax credits in order to generate more tax revenue because lack of statistical support. Future research is needed to further examine the impact of repealing orphan drug tax credits.

Despite the negative association between the tax credit cut and the orphan drug pipeline, the number of orphan drug candidates continued to grow in the past decade. The ODA tax credit may not be fully responsible for the increased focus in orphan drugs. An important factor in orphan drug development is the willingness of insurers to reimburse drug companies with higher prices for orphan drugs, especially for oncology drugs. As long as payers are willing to reimburse the high price tags of cancer drugs, the orphan tax credits may have minimal influence on drug developers' R&D investment decisions.

5.4 Strengths and Limitations

This is the first study that examines the orphan drug pipeline and quantify the tax credit reduction policy impact. Findings of this study help bridge the gap in the understanding of orphan drug financial incentives. However, this study has a number of limitations that should be considered.

First, there is limited study time after the policy change while the result remains negative, indicating the overall trend of orphan drug R&D and a conservative estimate of the policy impact. The study period includes seven years before the policy change and two years after the policy change. After 2017 there can be a wash out period with the implementation of the policy. Thus, it takes time for policy effects to emerge. The study has a relatively small

sample size. The sample only focuses on cancer, while rare diseases usually have a broader range, including non-oncology drugs for blood, musculoskeletal, cardiovascular, central nervous system, and immunomodulators diseases, an area that merit future research. This study did not track a drug candidate across different phases of clinical trials because of data restrictions. Tracing the same drug candidate from the beginning can bring more information on the barrier to entering each clinical phase and if the barrier stems from the focal policy change. Future research ma consider a more detailed examination of the pipeline by phase.

5.5 Recommendations for Future Research

Future research may look into the cost offsets of the repeal of orphan drug tax credits on the federal budget by including more rare disease categories. With the development of precision medicine, more rare diseases are identified and registered. The orphan drug market involves an increasing number of therapeutic areas which needs more thorough examination. Future research could focus on a longer study period with more rare disease categories in order to make the results more generalizable. By quantifying the budget impact, the cost of developing orphan drugs can be more transparent to the public and patients with rare diseases.

Future studies should also consider the overall impact of financial incentives on the orphan drug pipeline in the context of COVID-19. The pandemic has increased the exposure of orphan drug policies to the public with the withdrawn orphan drug designation of Remdesivir from Gilead Sciences.[49] There is an increasing concern about pharmaceutical companies taking advantage of orphan drug policy loopholes. On the other hand, some pharmaceutical companies have made adjustments to 2020 revenue projection which may affect key drugs in the pipeline. It is reported that many companies are reducing new starts and shifting investment to home care. The orphan drug pipeline is likely to be disrupted by

changes and shifts in investment. While the benefits of orphan drug financial incentives to pharmaceutical companies have come under close scrutiny, the real impact of COVID-19 on the pipeline remains undisclosed.[50]

Chapter 6 Conclusion

The orphan drug tax credit reduction is negatively associated with the number of clinical trials per orphan drug candidate in the pipeline, although this association was statistically nonsignificant. Based on the limited sample size and study period, the study yields conservative estimates. This study sets the foundation for future work to better understand the impact of orphan drug tax credits on the orphan drug development.

References

1. The Orphan Drug Act, H.R. 5238, 97th Cong. (1983). https://www.fda.gov/media/99546/download
2. Genetic and Rare Diseases Information Center (GARD). (2021). *FAQs About Rare Diseases | Genetic and Rare Diseases Information Center (GARD) – an NCATS Program*. FAQs About Rare Diseases. https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases
3. World Health Organization. (2009). *GLOBAL HEALTH RISKS GLOBAL HEALTH RISKS WHO Mortality and burden of disease attributable to selected major risks*. https://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf
4. Field, M. J., Boat, T. F., Committee on Accelerating Rare Diseases Research and Orphan Product Development, & Institute of Medicine. (2007). *Rare Diseases and Orphan Products: Accelerating Research and Development*. National Academy of Sciences.
5. *NCI Dictionary of Cancer Terms*. (2022). National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/orphan-drug
6. *Developing Products for Rare Diseases & Conditions*. (2018, December 20). U.S. Food and Drug Administration. https://www.fda.gov/industry/developing-products-rare-diseases-conditions
7. Orphan Drug Amendments of 1985, S.1147. 99th Cong.(1985). https://www.congress.gov/99/statute/STATUTE-99/STATUTE-99-Pg387.pdf
8. Orphan Drug Amendments of 1990, H.R.4638, 101st Cong. (1990) https://www.congress.gov/bill/101st-congress/house-bill/4638

9. Kesselheim AS. An empirical review of major legislation affecting drug development: past experiences, effects, and unintended consequences. Milbank Q. 2011;89(3):450-502. doi: 10.1111/j.1468-0009.2011.00636.x.
10. Tax Cuts and Jobs Act, H.R.1, 115th Cong. (2017). https://www.congress.gov/115/bills/hr1/BILLS-115hr1enr.pdf
11. Center for Drug Evaluation and Research. (2020, February 5). *Frequently Asked Questions on Patents and Exclusivity*. U.S. Food and Drug Administration. https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity
12. Center for Drug Evaluation and Research. (2019, June 10). *New Drug Application (NDA)*. U.S. Food and Drug Administration. https://www.fda.gov/drugs/types-applications/new-drug-application-nda
13. U.S. Food and Drug Administration. (2021). *Search Orphan Drug Designations and Approvals*. Developing Products for Rare Diseases & Conditions. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm
14. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. JAMA. 2020;323(9):844–853. doi:10.1001/jama.2020.1166
15. DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, 47, 20–33. doi:10.1016/j.jhealeco.2016.01
16. Jayasundara, K., Hollis, A., Krahn, M. et al. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J Rare Dis 14, 12 (2019). https://doi.org/10.1186/s13023-018-0990-4

17. “Form 8820 General Instructions” IRS website, accessed 5 January 2015, http://www.irs.gov/uac/Form-8820,- Orphan-Drug-Credit.
18. Tax Foundation. (2018). *Preliminary Details and Analysis of the Tax Cuts and Jobs Act*. https://files.taxfoundation.org/20171220113959/TaxFoundation-SR241-TCJA-3.pdf
19. Waxman, H., Corr, B., Martin, K., & Duong, S. (2017, July). *Getting to the Root of High Prescription Drug Prices: Drivers and Potential Solutions*. https://www.commonwealthfund.org/sites/default/files/documents/___media_files_publications_fund_report_2017_jul_waxman_high_drug_prices_drivers_solutions_report.pdf
20. Guenther, G., 1999. Federal taxation of the drug industry from 1990 to 1996. Memorandum to Joint Economic Committee, US Congress, Congressional Research Service, 13 December 1999.
21. DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: new estimates of drug development costs. Journal of Health Economics, 22(2), 151–185. doi:10.1016/s0167-6296(02)00126-1
22. Simoens S. *Pricing and reimbursement of orphan drugs: the need for more transparency*. Orphanet J Rare Dis. 2011 Jun 17;6:42. doi: 10.1186/1750-1172-6-42.
23. Sarpatwari A, Kesselheim AS. *Reforming the Orphan Drug Act for the 21st Century*. N Engl J Med. 2019 Jul 11;381(2):106-108. doi: 10.1056/NEJMp1902943.
24. United States Government Accountability Office. (2018). *FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue*. https://www.gao.gov/assets/gao-19-83.pdf
25. *About Rare Cancers*. (2019b, February 27). National Cancer Institute. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/about-rare-

cancers#:%7E:text=Rare%20cancers%20are%20those%20that,are%20due%20to%20rare%20cancers.

26. Pillai, R. K., & Jayasree, K. (2017). Rare cancers: Challenges & issues. The Indian journal of medical research, 145(1), 17–27. https://doi.org/10.4103/ijmr.IJMR_915_14
27. Ward E, DeSantis C, Robbins A, et al.: Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 64 (2): 83-103.
28. American Cancer Society, Inc., Surveillance Research. (2017). *Cancer Facts & Figures 2017 - Special Section: Rare Cancers in Adults*. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017-special-section-rare-cancers-in-adults.pdf
29. Greenlee, R. T., Goodman, M. T., Lynch, C. F., Platz, C. E., Havener, L. A., & Howe, H. L. (2010). The occurrence of rare cancers in U.S. adults, 1995-2004. Public health reports (Washington, D.C. : 1974), 125(1), 28–43. https://doi.org/10.1177/003335491012500106
30. Nabhan, C., Phillips, E. G., & Feinberg, B. A. (2018). Orphan Cancer Drugs in the Era of Precision Medicine. JAMA Oncology, 4(11), 1481. doi:10.1001/jamaoncol.2018.349
31. Ernst & Young, National Organization for Rare Disorders(NORD), & Biotechnology Industry Organization(BIO). (2015, June). *Impact of the Orphan Drug Tax Credit on treatments for rare diseases*. Ernst & Young. https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf

32. Giaccotto, C., Santerre, R., & Vernon, J. (2005). Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry. *The Journal of Law & Economics, 48*(1), 195-214. doi:10.1086/426882

33. Evaluate Pharma. (2020). *Orphan Drug Report 2020*. https://www.evaluate.com/media/2741/download

34. *Archived: WHO Timeline - COVID-19*. (2020, April 28). World Health Organization. https://www.who.int/news/item/27-04-2020-who-timeline---covid-19

35. *Home - ClinicalTrials.gov*. (2021). U.S. National Library of Medicine. https://clinicaltrials.gov

36. Food and Drug Administration Amendments Act of 2007, H.R.3580, 110th Congress https://www.govinfo.gov/content/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf#page=82

37. Reserved, R. A. U. I.-. (2021). *Orphanet*. Orphanet. https://www.orpha.net/consor/cgi-bin/index.php

38. NORD - National Organization for Rare Disorders. (2019, January 31). *List of Rare Disease Information*. https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information/

39. Evaluate Pharma. (2019). *Orphan Drug Report 2019*. https://www.evaluate.com/media/2741/download

40. U.S. Food and Drug Administration. "Introduction to the Office of Orphan Products Development (OOPD)," Pages 10, 17, and 21. Accessed Feb. 3, 2022.

41. *About Rare Cancers*. (2019, February 27). National Cancer Institute. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/about-rare-cancers

42. PMGroup Worldwide Limited. (2020, May). *Biopharma and orphan drugs*. PMLive. http://www.pmlive.com/pharma_intelligence/Biopharma_and_orphan_drugs_1338644

43. Office of the Commissioner. (2020, November 30). *Real-World Evidence*. U.S. Food and Drug Administration. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

44. ClinicalTrials.gov. Glossary of common site terms. https://clinicaltrials.gov/ct2/about-studies/glossary.

45. Office of the Commissioner. (2018, January 4). Step 3: Clinical Research. U.S. Food and Drug Administration. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

46. Norton EC, Dowd BE, Maciejewski ML. Marginal effects— quantifying the effect of changes in risk factors in logistic regression models. JAMA. 2019;321:1304-1305.

47. *26 CFR § 1.28-1 - Credit for clinical testing expenses for certain drugs for rare diseases or conditions.* (2022). LII / Legal Information Institute. https://www.law.cornell.edu/cfr/text/26/1.28-1

48. Evans S. R. (2010). Clinical trial structures. Journal of experimental stroke & translational medicine, 3(1), 8–18. https://doi.org/10.6030/1939-067x-3.1.8

49. Mahase, E. (2020, March 26). *Covid-19: Gilead withdraws orphan drug designation from potential treatment after criticism*. The BMJ. https://www.bmj.com/content/368/bmj.m1259

50. Healthadvances. (2020, May 14). *COVID-19 Impact on Rare Disease Patients and Manufacturers*. Health Advances Blog. https://healthadvancesblog.com/2020/05/14/covid-19-impact-on-rare-disease-patients-and-manufacturers/

Appendix

NIH List of rare cancers

5q- syndrome
Acinic cell carcinoma
Acral lentiginous melanoma
Acromegaly
Acrospiroma
ACTH-secreting pituitary adenoma
Acute erythroid leukemia
Acute leukemia of ambiguous lineage
Acute lymphoblastic leukemia
Acute lymphoblastic leukemia congenital sporadic aniridia
Acute megakaryoblastic leukemia
Acute monoblastic leukemia
Acute myeloblastic leukemia with maturation
Acute myeloblastic leukemia without maturation
Acute myeloid leukemia with abnormal bone marrow eosinophils inv(16)(p13q22) or t(16;16)(p13;q22)
Acute myeloid leukemia with inv3(p21;q26.2) or t(3;3)(p21;q26.2)
Acute myelomonocytic leukemia
Acute non lymphoblastic leukemia
Acute panmyelosis with myelofibrosis
Acute promyelocytic leukemia
Adenocarcinoid tumor
Adenocarcinoma of the appendix
Adenoid cystic carcinoma
Adenosarcoma of the uterus
Adrenal cancer
Adrenal medulla cancer
Adrenocortical carcinoma
Aggressive NK cell leukemia
Benign multicystic peritoneal mesothelioma
Bile duct cancer
Biliary tract cancer
Birt-Hogg-Dube syndrome
Blastic plasmacytoid dendritic cell
Bloom syndrome
Blue rubber bleb nevus syndrome
Bowen's disease
Brain stem cancer
Brain tumor, adult
Brain tumor, childhood
Aicardi syndrome
Alveolar soft part sarcoma
Ameloblastic carcinoma
AML with myelodysplasia-related features
Anal cancer
Anaplastic astrocytoma
Anaplastic ependymoma
Anaplastic ganglioglioma
Anaplastic large cell lymphoma
Anaplastic oligoastrocytoma
Anaplastic oligodendroglioma
Anaplastic plasmacytoma
Anaplastic small cell lymphoma
Anaplastic thyroid cancer
Angioimmunoblastic T-cell lymphoma
Angioma hereditary neurocutaneous
Angioma serpiginosum
Angiosarcoma of the breast
Angiosarcoma of the liver
Angiosarcoma of the scalp
Astroblastoma
Ataxia telangiectasia
Atrial myxoma, familial
Autoimmune lymphoproliferative syndrome
B cell prolymphocytic leukemia
B-cell lymphoma
Bannayan-Riley-Ruvalcaba syndrome
Basal cell carcinoma, infundibulocystic
Basal cell carcinoma, multiple
Bazex-Dupre-Christol syndrome
Becker nevus syndrome
Bednar tumor
Benign metastasizing leiomyoma
BRCA1 hereditary breast and ovarian cancer syndrome
BRCA2 hereditary breast and ovarian cancer syndrome
Breast cancer, male
Brenner tumor of ovary
Brenner tumor of the vagina
Bronchial adenomas/carcinoids childhood
Burkitt lymphoma
Buschke-Lowenstein tumor
Carcinoid syndrome
Carcinoid tumor
Carcinoid tumor childhood

Carcinoma of the vocal tract
Carney complex
Carney triad
Carotid body tumor
Cartilaginous cancer
CDK4 linked melanoma
Central nervous system germinoma
Central neurocytoma
Cerebellar astrocytoma, childhood
Cerebellar liponeurocytoma
Cerebral astrocytoma, childhood
Cerebral sarcoma
Cerebral ventricle cancer
Cerebro-oculo-facio-skeletal syndrome
Cervical intraepithelial neoplasia
CHILD syndrome
Childhood acute lymphoblastic leukemia
Childhood brain stem glioma
Childhood hepatocellular carcinoma
Childhood Supratentorial Embryonal Tumor, Not Otherwise Specified
Chondrosarcoma
Chordoid glioma of the third ventricle
Chordoma
Choriocarcinoma
Choroid plexus carcinoma
Choroid plexus papilloma
Chromophil renal cell carcinoma
Chromophobe renal cell carcinoma
Chronic lymphocytic leukemia
Chronic myeloid leukemia
Chronic myelomonocytic leukemia
Chronic myeloproliferative disorders
Chronic neutrophilic leukemia
Clear cell renal cell carcinoma
CLOVES syndrome
Cockayne syndrome type I
Cockayne syndrome type II
Cockayne syndrome type III
Collecting duct carcinoma
Common variable immunodeficiency
Costello syndrome
Cowden syndrome
Craniopharyngioma
Cronkhite-Canada disease
Cutaneous mastocytoma
Cutaneous T-cell lymphoma
Deafness-lymphedema-leukemia syndrome
Dendritic cell tumor
Denys-Drash syndrome
Dermatofibrosarcoma protuberans
Desmoid tumor
Desmoplastic infantile astrocytoma
Desmoplastic infantile ganglioglioma
Desmoplastic small round cell tumor
Diamond-Blackfan anemia
Diaphyseal medullary stenosis with malignant fibrous histiocytoma
Diffuse astrocytoma
Diffuse cavernous hemangioma of the rectum
Diffuse gastric cancer
Diffuse Large B-Cell Lymphoma
Digestive System Melanoma
Disseminated peritoneal leiomyomatosis
Dysembryoplastic neuroepithelial tumor
Dyskeratosis congenita
Dyskeratosis congenita autosomal dominant
Dyskeratosis congenita autosomal recessive
Dyskeratosis congenita X-linked
Eccrine mucinous carcinoma
Eccrine porocarcinoma
Embryonal carcinoma
Embryonal sarcoma
Embryonal tumor with multilayered rosettes
Enchondroma
Endemic Kaposi sarcoma
Endometrial stromal sarcoma
Enteropathy-associated T-cell lymphoma
Ependymoma
Epithelial-myoepithelial carcinoma
Esophageal cancer
Essential thrombocythemia
Ewing sarcoma
Extragonadal germ cell tumor
Extramammary Paget disease
Fallopian tube cancer
Familial adenomatous polyposis
Familial colorectal cancer
Familial hyperaldosteronism type 2
Familial pancreatic cancer
Familial platelet disorder with associated myeloid malignancy
Familial prostate cancer
Familial Wilms tumor 2
Fanconi anemia

Fibrolamellar carcinoma
Fibrosarcoma
Follicular lymphoma
Frasier syndrome
Functioning pancreatic endocrine tumor
Gallbladder cancer
Gangliocytoma
Ganglioglioma
Gardner syndrome
Gastric lymphoma
Gastric Non-Hodgkin Lymphoma
Gastro-enteropancreatic neuroendocrine tumor
Gastrointestinal Stromal Tumors
Giant cell tumor of bone
Giant congenital nevus
Glassy cell carcinoma of the cervix
Glioblastoma
Glioma
Gliosarcoma
Glomus jugulare tumors
Glomus tympanicum tumor
Glomus vagale tumor
Glucagonoma
Goblet cell carcinoid
Granular cell tumor
Granulomatous slack skin disease
Granulosa cell tumor of the ovary
Gray zone lymphoma
Gynandroblastoma
Hairy cell leukemia
Heart tumor
Hemangioblastoma
Hemangioendothelioma
Hemangioma thrombocytopenia syndrome
Hemangiopericytoma
Hemi 3 syndrome
Hepatoblastoma
Hereditary diffuse gastric cancer
Hereditary leiomyomatosis and renal cell cancer
Hereditary melanoma
Hereditary multiple osteochondromas
Hereditary paraganglioma-pheochromocytoma
Hereditary renal cell carcinoma
Hidradenocarcinoma
Hodgkin lymphoma
Hurthle cell thyroid cancer
Hyaline fibromatosis syndrome
Hyperparathyroidism-jaw tumor syndrome
Hypopharyngeal cancer
Indolent B cell lymphoma
Infantile myofibromatosis
Inflammatory breast cancer
Inflammatory linear verrucous epidermal nevus
Inflammatory myofibroblastic tumor
Insulinoma
Intrahepatic cholangiocarcinoma
Intraneural perineurioma
Intraocular melanoma
Juvenile myelomonocytic leukemia
Juvenile polyposis syndrome
Kaposi sarcoma
Kaposiform Hemangioendothelioma
Klatskin tumor
Krukenberg carcinoma
Langerhans cell sarcoma
Laryngeal cancer
Ledderhose disease
Leiomyosarcoma
Lentigo maligna melanoma
LEOPARD syndrome
Leukemia subleukemic
Leukemia, T-cell, chronic
Lhermitte-Duclos disease
Li-Fraumeni syndrome
Linear nevus sebaceous syndrome
Lip and oral cavity cancer
Lipoblastoma
Liposarcoma
Lung adenocarcinoma
Lymph Node Neoplasm
Lymphoblastic lymphoma
Lymphoma AIDS related
Lymphoma, large-cell, immunoblastic
Lymphomatoid papulosis
Lymphosarcoma
Maffucci syndrome
Mahvash disease
Malignant cylindroma
Malignant eccrine spiradenoma
Malignant germ cell tumor
Malignant melanoma, childhood
Malignant mesenchymoma
Malignant mesothelioma
Malignant mixed Mullerian tumor
Malignant peripheral nerve sheath tumor
Malignant Teratocarcinosarcoma

Mantle cell lymphoma
McCune-Albright syndrome
Mediastinal endodermal sinus tumors
Medulloblastoma
Medulloblastoma, childhood
Megalencephaly-capillary malformation syndrome
Melanocytic lesions of CNS
Melanoma astrocytoma syndrome
Meningioma
Merkel cell carcinoma
Metaplastic carcinoma of the breast
Metastatic insulinoma
Metastatic squamous neck cancer with occult primary
Microcystic adnexal carcinoma
Microcystic lymphatic malformation
Mosaic variegated aneuploidy syndrome
Mucoepidermoid carcinoma
Muir-Torre syndrome
Multicentric Castleman Disease
Multiple endocrine neoplasia type 1
Multiple endocrine neoplasia type 2A
Multiple endocrine neoplasia type 2B
Multiple fibrofolliculoma familial
Multiple myeloma
Multiple self healing squamous epithelioma
Mycosis fungoides
Myelocytic leukemia-like syndrome, familial, chronic
Myelodysplastic syndromes
Myeloid leukemia
Myeloid sarcoma
Myoepithelial carcinoma
Myxoid liposarcoma
N syndrome
Nasopharyngeal carcinoma
Neural crest tumor
Neuroblastoma
Neurocutaneous melanosis
Neuroendocrine carcinoma of the cervix
Neuroepithelioma
Neurofibromatosis type 2
Neurofibromatosis-Noonan syndrome
Neurofibrosarcoma
Nevoid basal cell carcinoma syndrome
Nevus comedonicus syndrome
Nevus of Ito
Nijmegen breakage syndrome
Nodular melanoma
Non functioning pancreatic endocrine tumor
Non-involuting congenital hemangioma
Nonseminomatous germ cell tumor
Noonan syndrome
Noonan syndrome 1 - See Noonan syndrome
Noonan syndrome 2 - See Noonan syndrome
Noonan syndrome 3 - See Noonan syndrome
Noonan syndrome 4 - See Noonan syndrome
Noonan syndrome 5 - See Noonan syndrome
Noonan syndrome 6 - See Noonan syndrome
Ocular melanoma
Olfactory neuroblastoma
Oligoastrocytoma
Oligodendroglioma
Ollier disease
Onychocytic matricoma
Optic pathway glioma
Oral cancer
Oral squamous cell carcinoma
Orbital lymphangioma
Orbital lymphoma
Oropharyngeal cancer, adult
Oslam syndrome
Osteofibrous dysplasia
Osteosarcoma
Ovarian cancer
Ovarian carcinosarcoma
Ovarian epithelial cancer
Ovarian germ cell tumor
Ovarian low malignant potential tumor
Ovarian small cell carcinoma
Paget disease of the breast
Painful orbital and systemic neurofibromas-marfanoid habitus syndrome
Pancreatic adenoma
Pancreatic cancer
Pancreatoblastoma
Papillary cystadenocarcinoma
Papillary renal cell carcinoma
Papillary thyroid carcinoma

Paraganglioma and gastric stromal sarcoma
Paranasal sinus cancer, adult
Paraneoplastic cerebellar degeneration
Parathyroid carcinoma
Pediatric T-cell leukemia
Penile cancer
Peripheral T-cell lymphoma
Perlman syndrome
Peutz-Jeghers syndrome
PHACE syndrome
Pheochromocytoma
Philadelphia-negative chronic myeloid leukemia
Phyllodes tumor of the breast
Phyllodes tumor of the prostate
Pilocytic astrocytoma
Pilomatrixoma
Pineal parenchymal tumors of intermediate differentiation
Pineoblastoma
Pituitary cancer
Plasma cell leukemia
Plasmablastic lymphoma
Pleomorphic xanthoastrocytoma
Pleuropulmonary blastoma
Plexosarcoma
POEMS syndrome
Polycythemia vera
Polyembryoma
Polymorphous low-grade adenocarcinoma
Primary central nervous system lymphoma
Primary effusion lymphoma
Primary liver cancer
Primary malignant melanoma of the cervix
Primary malignant melanoma of the conjunctiva
Primary melanoma of the central nervous system
Primary myelofibrosis
Proliferating trichilemmal cyst
Proteus syndrome
Proteus-like syndrome
Pseudomyxoma peritonei
Radiation induced angiosarcoma of the breast
Radiation induced cancer
Radiation induced meningioma
Rare adenocarcinoma of the breast
Renal cell carcinoma 4
Retinoblastoma
Retroperitoneal liposarcoma
Rhabdoid tumor
Rhabdomyosarcoma alveolar
Rhabdomyosarcoma embryonal
Richter syndrome
Ring dermoid of cornea
Rombo syndrome
Sacrococcygeal Teratoma
Saethre-Chotzen syndrome
Salivary gland cancer, adult
Sarcoma botryoides
Schinzel Giedion syndrome
Schwannomatosis
Secretory breast carcinoma
Sertoli-leydig cell tumors
Severe congenital neutropenia autosomal recessive 3
Sezary syndrome
Shwachman-Diamond syndrome
Sideroblastic anemia pyridoxine-refractory autosomal recessive
Simpson-Golabi-Behmel syndrome
Sinonasal undifferentiated carcinoma
Sinus cancer
Small cell carcinoma of the bladder
Small cell lung cancer
Small intestine cancer
Soft tissue sarcoma
Somatostatinoma
Sotos syndrome
Splenic neoplasm
Stomach cancer
Subcutaneous panniculitis-like T-cell lymphoma
Subependymal giant cell astrocytoma
Subependymoma
Superficial spreading melanoma
Supraglottic laryngeal cancer
Supratentorial primitive neuroectodermal tumor
Supraumbilical midabdominal raphe and facial cavernous hemangiomas
Synovial sarcoma
T-cell large granular lymphocyte leukemia
T-cell lymphoma 1A
T-cell/histiocyte rich large B cell lymphoma
Teratoma with malignant transformation
Testicular seminoma

Testicular yolk sac tumor
Thoracolaryngopelvic dysplasia
Thymic epithelial tumor
Thyroid cancer, follicular
Thyroid cancer, medullary
Tongue cancer
Transient myeloproliferative syndrome
Transitional cell cancer of the renal pelvis and ureter
Transitional cell carcinoma
Trichofolliculoma
Trophoblastic tumor placental site
Tuberous sclerosis complex
Tufted angioma
Turcot syndrome
Tylosis with esophageal cancer
Tyrosinemia type 1
Undifferentiated pleomorphic sarcoma
Unicentric Castleman disease
Urachal adenocarcinoma
Urachal cancer
Urethral cancer
Uterine Carcinosarcoma
Uterine sarcoma
Vaginal cancer
Verrucous nevus acanthokeratolytic
VIPoma
Visual pathway and hypothalamic glioma, childhood
Von Hippel-Lindau disease
Vulvar cancer
WAGR syndrome
Waldenstrom macroglobulinemia
Werner syndrome
White sponge nevus of cannon
Wilms tumor and radial bilateral aplasia
Wilms' tumor
Wiskott Aldrich syndrome
WT limb blood syndrome
X-linked lymphoproliferative disease due to SH2D1A deficiency
X-linked lymphoproliferative syndrome
Xeroderma pigmentosum
Zollinger-Ellison syndrome
Zuska's disease

List of rare cancers defined in this study

Abdominal Neoplasms
ACTH-Secreting Pituitary Adenoma
Adenocarcinoma
Adenoma, Islet Cell
Adenosarcoma
Adrenal Cortex Neoplasms
Adrenal Gland Neoplasms
Anus Neoplasms
Barrett Esophagus
Biliary Tract Neoplasms
Bowen's Disease
Brain Neoplasms
Brain Stem Neoplasms
Breast Neoplasms, Male
Brenner Tumor
Burkitt Lymphoma
Carcinoma, Adenoid Cystic
Carcinoma, Embryonal
Carcinoma, Ovarian Epithelial
Carcinoma, Renal Cell
Carcinoma, Squamous Cell
Carney Complex
Carotid Body Tumor
Central Nervous System Neoplasms
Chondrosarcoma
Chordoma
Choriocarcinoma
Choroid Plexus Neoplasms
Craniopharyngioma
Dendritic Cell Sarcoma, Follicular
Dendritic Cell Sarcoma, Interdigitating
Dermatofibrosarcoma
Eccrine Porocarcinoma
Endodermal Sinus Tumor
Esophageal Neoplasms
Esophageal Squamous Cell Carcinoma
Fallopian Tube Neoplasms
Fibrosarcoma
Gallbladder Neoplasms
Ganglioglioma
Gastrointestinal Stromal Tumors
Giant Cell Tumor of Bone
Glioblastoma
Glioma
Glioma, Subependymal
Gliosarcoma
Glucagonoma
Granular Cell Tumor
Heart Neoplasms
Hemangioblastoma
Hemangioendothelioma
Hemangioma
Hemangiopericytoma
Hepatoblastoma
Hodgkin Disease
Hypopharyngeal Neoplasms
Inflammatory Breast Neoplasms
Insulinoma
Kasabach-Merritt Syndrome
Klatskin Tumor
Laryngeal Neoplasms
Leiomyosarcoma
Leukemia, Hairy Cell
Leukemia, Large Granular Lymphocytic
Leukemia, Lymphocytic, Chronic, B-Cell
Leukemia, Megakaryoblastic, Acute
Leukemia, Monocytic, Acute
Leukemia, Myeloid
Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative
Leukemia, Myeloid, Chronic-Phase
Leukemia, Myelomonocytic, Acute
Leukemia, Myelomonocytic, Chronic
Leukemia, Myelomonocytic, Juvenile
Leukemia, Plasma Cell
Leukemia, Prolymphocytic, B-Cell
Leukemia, Promyelocytic, Acute
Leukemia, T-Cell
Li-Fraumeni Syndrome
Liposarcoma
Liposarcoma, Myxoid
Liver Neoplasms
Liver Neoplasms, Experimental
Lymphangioleiomyomatosis
Lymphoma, AIDS-Related
Lymphoma, Large-Cell, Anaplastic
Lymphoma, Large-Cell, Immunoblastic
Lymphoma, T-Cell
Lymphoma, T-Cell, Cutaneous
Lymphoma, T-Cell, Peripheral
Lymphomatoid Papulosis
Malignant Carcinoid Syndrome
Medulloblastoma
Melanoma
Meningioma
Muir-Torre Syndrome

Multiple Endocrine Neoplasia Type 1
Multiple Myeloma
Mycosis Fungoides
Nasopharyngeal Carcinoma
Neuroblastoma
Neurofibromatosis 1
Neurofibromatosis 2
Neurofibrosarcoma
Oligodendroglioma
Optic Nerve Glioma
Oropharyngeal Neoplasms
Osteosarcoma
Paget's Disease, Mammary
Pancreatic Cyst
Pancreatic Intraductal Neoplasms
Pancreatic Neoplasms
Pancreatic Pseudocyst
Parathyroid Neoplasms
Penile Neoplasms
Peutz-Jeghers Syndrome
Pheochromocytoma
Pituitary Neoplasms
Proteus Syndrome
Pseudomyxoma Peritonei
Retinoblastoma
Rhabdoid Tumor
Rhabdomyosarcoma
Rhabdomyosarcoma, Alveolar
Rhabdomyosarcoma, Embryonal
Salivary Gland Neoplasms
Sarcoma
Sarcoma, Alveolar Soft Part
Sarcoma, Kaposi
Sarcoma, Myeloid
Sarcoma, Synovial
Sezary Syndrome
Small Cell Lung Carcinoma
Soft Tissue Neoplasms
Somatostatinoma
Squamous Cell Carcinoma of Head and Neck
Stomach Neoplasms
Supratentorial Neoplasms
Synovial Cyst
Teratoma
Testicular Neoplasms
Thoracic Neoplasms
Thymoma
Thymus Neoplasms
Thyroid Cancer, Papillary
Thyroid Carcinoma, Anaplastic
Thyroid Neoplasms
Thyroid Nodule
Tongue Neoplasms
Trophoblastic Tumor, Placental Site
Tuberous Sclerosis
Ureteral Neoplasms
Urethral Neoplasms
Urinary Bladder Neoplasms
Uterine Cervical Dysplasia
Uterine Neoplasms
Uveal Neoplasms
Vaginal Neoplasms
Vascular Neoplasms
Vipoma
Vulvar Neoplasms
Waldenstrom Macroglobulinemia
Wilms Tumor
Xeroderma Pigmentosum
Zollinger-Ellison Syndrome

List of Common Cancers

Abdominal Neoplasms
ACTH Syndrome, Ectopic
Adamantinoma
Adenocarcinoma in Situ
Adenocarcinoma of Lung
Adenocarcinoma, Bronchiolo-Alveolar
Adenocarcinoma, Clear Cell
Adenocarcinoma, Follicular
Adenocarcinoma, Mucinous
Adenocarcinoma, Papillary
Adenocarcinoma, Sebaceous
Adenoma
Adenoma, Acidophil
Adenoma, Basophil
Adenoma, Chromophobe
Adenoma, Liver Cell
Adenoma, Oxyphilic
Adenoma, Pleomorphic
Adenomatous Polyposis Coli
Adenomatous Polyps
Adenomyoepithelioma
Adrenocortical Adenoma
Adrenocortical Carcinoma
Ameloblastoma
Angiofibroma
Angiomyolipoma
Appendiceal Neoplasms
Apudoma
Astrocytoma
Atypical Squamous Cells of the Cervix
Basal Cell Nevus Syndrome
Bile Duct Neoplasms
Birt-Hogg-Dube Syndrome
Blast Crisis
Bone Cysts
Bone Marrow Neoplasms
Bone Neoplasms
Breast Carcinoma In Situ
Breast Neoplasms
Bronchial Neoplasms
Carcinogenesis
Carcinoid Tumor
Carcinoma
Carcinoma in Situ
Carcinoma, Acinar Cell
Carcinoma, Adenosquamous
Carcinoma, Basal Cell
Carcinoma, Basosquamous
Carcinoma, Bronchogenic
Carcinoma, Ductal
Carcinoma, Ductal, Breast
Carcinoma, Endometrioid
Carcinoma, Giant Cell
Carcinoma, Hepatocellular
Carcinoma, Intraductal, Noninfiltrating
Carcinoma, Islet Cell
Carcinoma, Large Cell
Carcinoma, Lobular
Carcinoma, Medullary
Carcinoma, Merkel Cell
Carcinoma, Mucoepidermoid
Carcinoma, Neuroendocrine
Carcinoma, Non-Small-Cell Lung
Carcinoma, Pancreatic Ductal
Carcinoma, Papillary
Carcinoma, Signet Ring Cell
Carcinoma, Skin Appendage
Carcinoma, Small Cell
Carcinoma, Transitional Cell
Carcinoma, Verrucous
Carcinosarcoma
Cell Transformation, Neoplastic
Cerebellar Neoplasms
Cervical Intraepithelial Neoplasia
Chalazion
Cholangiocarcinoma
Chondrosarcoma, Mesenchymal
Choroid Neoplasms
Colonic Neoplasms
Colorectal Neoplasms
Colorectal Neoplasms, Hereditary Nonpolyposis
Common Bile Duct Neoplasms
Composite Lymphoma
Cystadenocarcinoma
Cystadenocarcinoma, Mucinous
Cystadenocarcinoma, Serous
Cystadenoma
Cysts
Digestive System Neoplasms
Duodenal Neoplasms
Dupuytren Contracture
Dysgerminoma
Dysplastic Nevus Syndrome
Endocrine Gland Neoplasms
Endometrial Neoplasms

Endometrial Stromal Tumors
Enteropathy-Associated T-Cell Lymphoma
Ependymoma
Epidermal Cyst
Erythroplasia
Esthesioneuroblastoma, Olfactory
Exostoses, Multiple Hereditary
Eye Neoplasms
Fibroadenoma
Fibroma
Fibromatosis, Abdominal
Fibromatosis, Aggressive
Ganglion Cysts
Ganglioneuroblastoma
Ganglioneuroma
Gastrinoma
Gastrointestinal Neoplasms
Genital Neoplasms, Female
Genital Neoplasms, Male
Germinoma
Gestational Trophoblastic Disease
Giant Cell Tumor of Tendon Sheath
Giant Cell Tumors
Glomus Tumor
Granulosa Cell Tumor
Hamartoma
Hamartoma Syndrome, Multiple
Head and Neck Neoplasms
Hemangioendothelioma, Epithelioid
Hemangioma, Capillary
Hemangioma, Cavernous
Hemangioma, Cavernous, Central Nervous System
Hemangiosarcoma
Hematologic Neoplasms
Hereditary Breast and Ovarian Cancer Syndrome
Histiocytic Disorders, Malignant
Histiocytic Sarcoma
Histiocytoma
Histiocytoma, Benign Fibrous
Histiocytoma, Malignant Fibrous
Hutchinson's Melanotic Freckle
Hydatidiform Mole
Hypothalamic Neoplasms
Immunoglobulin Light-chain Amyloidosis
Infratentorial Neoplasms
Intestinal Neoplasms
Intraocular Lymphoma
Keratosis, Actinic
Kidney Neoplasms
Lambert-Eaton Myasthenic Syndrome
Leiomyoma
Leiomyomatosis
Leukemia
Leukemia, B-Cell
Leukemia, Basophilic, Acute
Leukemia, Biphenotypic, Acute
Leukemia, Eosinophilic, Acute
Leukemia, Erythroblastic, Acute
Leukemia, Lymphoid
Leukemia, Mast-Cell
Leukemia, Myelogenous, Chronic, BCR-ABL Positive
Leukemia, Myeloid, Accelerated Phase
Leukemia, Myeloid, Acute
Leukemia, Prolymphocytic
Leukemia, Prolymphocytic, T-Cell
Leukemia-Lymphoma, Adult T-Cell
Leukoplakia
Leukoplakia, Oral
Leydig Cell Tumor
Limbic Encephalitis
Lip Neoplasms
Lipoma
Lung Neoplasms
Lymphangioma
Lymphangiomyoma
Lymphoma
Lymphoma, B-Cell
Lymphoma, B-Cell, Marginal Zone
Lymphoma, Extranodal NK-T-Cell
Lymphoma, Follicular
Lymphoma, Large B-Cell, Diffuse
Lymphoma, Mantle-Cell
Lymphoma, Non-Hodgkin
Lymphoma, Primary Cutaneous Anaplastic Large Cell
Lymphoma, Primary Effusion
Lymphomatoid Granulomatosis
Mammary Neoplasms, Animal
Mast-Cell Sarcoma
Mastocytosis
Mastocytosis, Systemic
Mediastinal Neoplasms
Meningeal Carcinomatosis
Meningeal Neoplasms
Mesenchymoma
Mixed Tumor, Malignant
Mixed Tumor, Mesodermal

Mixed Tumor, Mullerian
Mouth Neoplasms
Mucocele
Multiple Endocrine Neoplasia
Multiple Pulmonary Nodules
Muscle Neoplasms
Myelitis, Transverse
Myoepithelioma
Myofibroma
Myofibromatosis
Myoma
Myosarcoma
Nasopharyngeal Neoplasms
Neoplasm Metastasis
Neoplasm Micrometastasis
Neoplasm Recurrence, Local
Neoplasm Regression, Spontaneous
Neoplasm, Residual
Neoplasms by Histologic Type
Neoplasms, Adipose Tissue
Neoplasms, Adnexal and Skin Appendage
Neoplasms, Basal Cell
Neoplasms, Bone Tissue
Neoplasms, Connective and Soft Tissue
Neoplasms, Connective Tissue
Neoplasms, Cystic, Mucinous, and Serous
Neoplasms, Experimental
Neoplasms, Fibrous Tissue
Neoplasms, Germ Cell and Embryonal
Neoplasms, Glandular and Epithelial
Neoplasms, Hormone-Dependent
Neoplasms, Mesothelial
Neoplasms, Multiple Primary
Neoplasms, Nerve Tissue
Neoplasms, Neuroepithelial
Neoplasms, Plasma Cell
Neoplasms, Second Primary
Neoplasms, Squamous Cell
Neoplasms, Unknown Primary
Neoplasms, Vascular Tissue
Neoplastic Cells, Circulating
Neoplastic Processes
Neoplastic Syndromes, Hereditary
Nephroma, Mesoblastic
Nerve Sheath Neoplasms
Nervous System Neoplasms
Neurilemmoma
Neurocytoma
Neuroectodermal Tumors
Neuroectodermal Tumors, Primitive, Peripheral
Neuroendocrine Tumors
Neurofibroma
Neurofibroma, Plexiform
Neurofibromatoses
Neuroma
Neuroma, Acoustic
Nevi and Melanomas
Nevus
Nevus, Pigmented
Nevus, Sebaceous of Jadassohn
Nose Neoplasms
Odontogenic Tumors
Optic Nerve Neoplasms
Osteochondroma
Osteochondromatosis
Osteoma
Otorhinolaryngologic Neoplasms
Ovarian Cysts
Ovarian Neoplasms
Paget Disease, Extramammary
Papilloma
Papilloma, Intraductal
Papilloma, Inverted
Paraganglioma
Paraganglioma, Extra-Adrenal
Paranasal Sinus Neoplasms
Paraneoplastic Polyneuropathy
Paraneoplastic Syndromes
Paraneoplastic Syndromes, Nervous System
Parotid Neoplasms
Pelvic Neoplasms
Peripheral Nervous System Neoplasms
Peritoneal Neoplasms
Perivascular Epithelioid Cell Neoplasms
Pharyngeal Neoplasms
Phyllodes Tumor
Pinealoma
Plasmablastic Lymphoma
Plasmacytoma
Pleural Effusion, Malignant
Pleural Neoplasms
Polycystic Ovary Syndrome
Polycythemia Vera
Popliteal Cyst
Precancerous Conditions
Precursor B-Cell Lymphoblastic Leukemia-Lymphoma

Precursor Cell Lymphoblastic Leukemia-Lymphoma
Precursor T-Cell Lymphoblastic Leukemia-Lymphoma
Pregnancy Complications, Neoplastic
Preleukemia
Prolactinoma
Prostatic Neoplasms
Prostatic Neoplasms, Castration-Resistant
Pulmonary Blastoma
Rectal Neoplasms
Respiratory Tract Neoplasms
Retinal Neoplasms
Retroperitoneal Neoplasms
Sarcoma, Clear Cell
Sarcoma, Endometrial Stromal
Sarcoma, Ewing
Seminoma
Sertoli Cell Tumor
Sertoli-Leydig Cell Tumor
Sex Cord-Gonadal Stromal Tumors
Skin Neoplasms
Skull Base Neoplasms
Skull Neoplasms
Smoldering Multiple Myeloma
Smooth Muscle Tumor
Spinal Cord Neoplasms
Spinal Neoplasms
Squamous Intraepithelial Lesions of the Cervix
Sturge-Weber Syndrome
Submandibular Gland Neoplasms
Sweat Gland Neoplasms
Synovitis, Pigmented Villonodular
Syringoma
Tonsillar Neoplasms
Triple Negative Breast Neoplasms
Trophoblastic Neoplasms
Unilateral Breast Neoplasms
Urogenital Neoplasms
Urologic Neoplasms
Uterine Cervical Neoplasms