The Impact of Medicaid Expansion on Investments into Orphan Drugs

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Abstract

In this study, I examine the effects of Medicaid expansion following the passing of the Affordable Care Act (ACA) on investments into treatment for orphan diseases. Orphan drugs received special classification in 1983 with the passing of the Orphan Drug Act to incentivize research and development into creating treatments for diseases that affect small populations. The ACA, which passed on March 23, 2010, and the subsequent Medicaid expansion occurred at the state-level, but many states have not opted to expand their Medicaid programs. To ascertain the impact that Medicaid expansion had on investments into orphan drugs, I combine state level incidence data for orphan diseases by therapeutic class from disease-specific patient registries with state-level Medicaid expansion status data from the Kaiser Family Foundation. This allowed me to create therapeutic class specific ratios representing the proportion of a given class' market that lies within Medicaid expanded states. This market ratio variable becomes the foundation for my analysis to determine whether or not therapeutic classes with more of their markets within expanded states have seen greater increases to their investment relative to therapeutic classes with less of their market in Medicaid-expanded states. Contrary to what was expected, the results of this study indicate that there is a detrimental effect to investments of having a higher Market Expansion Ratio.

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Introduction

In 1983, the Orphan Drug Act (ODA) was passed in the United States, paving the way for the development of treatments for diseases with affected populations too small for pharmaceutical developers to be able to develop a treatment with any expectation of profit. The ODA accomplished establishing a flourishing industry for drugs to treat diseases with small populations by reducing the costs associated with clinical trials. This reduction in cost stemmed from reducing the number of participants needed in the clinical trial, by giving greater leniency on the results of the clinical trials, giving firms extended periods of market exclusivity that allows for seven years of exclusivity, and providing tax incentives for the clinical trials themselves called the Orphan Drug Tax Credit (ODTC) which grants tax credits for costs associated with clinical trials for a given drug's U.S. orphan indication. (IQVIA, 2018). Since the passing of the ODA, drugs targeting a disease classified as orphan diseases by the FDA have become a massive multibillion-dollar industry with the rate of new products accelerating year after year, and this trend seems to be continuing into the foreseeable future. EvaluatePharma estimates that total worldwide orphan drug sales will hit $234 billion in 2024, and are projected to make up 21.4% of global prescription sales by 2022.

An orphan disease is formally defined as any condition that affects fewer than 200,000 people within the U.S., or that the affected population is not large enough for a firm to expect to be able to recoup development costs for a treatment (IQVIA, 2018). Due to the nature of orphan diseases afflicting small populations, the treatments for these conditions tend to be very expensive to the end user as the drug developers have only a small pool of potential clients from which they have to recoup their development costs. In the U.S., the average cost to a patient for a year of treatment for orphan drugs was $140,443 in 2016 (EvaluatePharma, 2017). Because of

the high cost for treatment, insurance payers bear the brunt of the financial burden of orphan drugs. As such, expansions in the number of individuals in the U.S. covered under some form of health insurance has the potential to expand the market for orphan drugs by granting more people access to them. Individuals previously lacking health insurance or the financial means to afford these expensive treatments who have recently become enrolled in a health insurance program could now have access to these incredibly cost prohibitive treatments. The recent Medicaid expansion that was initiated by the Affordable Care Act (ACA) combines the right components to test to see whether or not expansions to insured populations affects the orphan drug industry. The ACA, which was passed on March 23, 2010, paved the way for states to choose to expand their Medicaid programs to cover individuals earning up to 138% of the federal poverty level. This is ideal because the population targeted by the recent expansions to Medicaid are poorer individuals who previously were uninsured, and are the same individuals who would likely have been unable to access orphan medications without this kind of assistance. Furthermore, the decision on whether or not to expand Medicaid programs was made at the state level, resulting in a scenario were 36 U.S. states and the District of Columbia have implemented Medicaid expansions and 14 states have not.

With the importance of orphan drugs becoming more pronounced as the industry hits its stride, understanding which factors influence the progression and development of orphan drugs becomes increasingly important as well. There has been no prior research aiming to ascertain the impact that Medicaid expansion has had on investments into orphan pharmaceuticals. In this paper, I aim to fill this gap in the literature and research investigating orphan drugs. To accomplish this, I leverage the current patchwork state of Medicaid expansion implementation along with state-level differences in the incidence of diseases to see what the affect is on

investments into orphan drugs by therapeutic category if more or less of their target population falls within states that have implemented Medicaid expansion.

In answering the question: "*How has the recent Medicaid expansion impacted investments into rare and orphan pharmaceutical products?",* my hypothesis is that Medicaid expansion will increase the demand for orphan products in states which have implemented it, and so orphan therapeutic categories with larger proportions of their target populations in states that have implemented Medicaid expansion will see increases to investment as their markets grow.

Literature Review

Much of the research surrounding orphan drugs and the Orphan Drug Act analyzes shifting trends in drug development that have occurred since 1983. Since the inception of the Orphan Drug Act, the types of treatments being developed to target rare and orphan diseases has shifted. Kesselheim found that there is a trend in more and more orphan products taking the form of biologics, with biologics comprising 21% of orphan products from 1990 to 1999, and 29% of orphan products from 2000 to 2009 (Kesselheim, 2010). Kesselheim also notes that oncology treatments comprise the largest category by drug indication comprising 28% of orphan treatments. This is noteworthy as it is also the indication class that is the most concerning to pharmacy benefit management firms and managed care providers as evidenced by the survey later in this study.

Growth in consumption of rare products is also evolving rapidly, with the sales of orphan products increasing 12% from 2015 to 2016 alone (Pagliarulo, 2017). This rapid increase in consumption is due in part to orphan products becoming major components of many

pharmaceutical firms' development pipelines, with "nearly 40% of the New Molecular Entities [NMEs] approved over the past five years" having been initially indicated for orphan applications (Pagliarulo, 2017). Another major trend in the development of orphan products that Pagliarulo found is the rise in importance of gene-therapy and gene-editing which "could prove [to be] powerful tools for addressing rare diseases, especially those with genetic links (Pagliarulo, 2017). My analysis adds to the literature surrounding the development of orphan pharmaceuticals by investigating whether or not certain therapeutic categories of drugs are disproportionately advantaged by the recent Medicaid expansion.

A large portion of the research involving rare and orphan treatments investigates how investment trends have changed since the passing of the Orphan Drug Act. Due to the unique legal situation of orphan drugs, orphan drugs enjoy many benefits that do not apply to drugs with indications targeting more pervasive conditions. Kwon found that investors, due to large changes and variability in development costs, are shying away from backing drugs that are still under development, but the same trend has largely spared orphan drugs (Kwon, 2018). This is likely because the prices of orphan drugs, once they come to market, are held artificially high by design to recoup development costs from small populations. Furthermore, in the midst of rapidly rising drug development costs, growing from circa $802 million during the 1990s up to around $2.6 billion "between 2005 and 2013", drugs seeking an orphan designation with the FDA are allowed smaller and less rigorous clinical trials, and also receive tax incentives (Kwon, 2018). These advantages greatly reduce the development cost for orphan drugs, further removing them from the volatility that is inherent with more mainstream pharmaceutical products. Dr. Miller, in her research investigating investor responses to drugs receiving orphan designations from the FDA, found that the average abnormal return to stock values of a firm receiving an orphan

designation for one of their treatments is 3.36% over the entire time period since the ODA was passed for both oncology and non-oncology treatments (Miller, 2017). Miller also found that orphan oncology drugs outperformed non-oncology drugs in terms of positive shocks to stock prices (Miller, 2017). My research furthers the existing literature surrounding investments into orphan products by being the first to attempt to ascertain how expanding Medicaid programs affects a variety of therapeutic classes with the sphere of orphan products.

A less explored area within the literature on orphan drugs is the impact that these medications have on insurance payers. In a survey of leadership within 7 of the largest private insurance firms operating in the United States, Robert Handfield found that the majority were indeed concerned about orphan drugs and how they should be approached from the perspective of the insurance payer, but very few had actually "developed [any] meaningful strategy for addressing the cost of orphan drugs" (Handfield, 2013). With the growing cost and consumption of orphan products, their burden to insurance payers will only continue to climb, and for the majority of the firms, lack of suitable comparisons means that it is difficult, and or impossible, to conduct any sort of cost-effectiveness analysis to assess the price of a rare and orphan drug (Handfield, 2013). While my main analysis is less focused on the perspective of insurance payers themselves and more with how an expansion in insurance coverage impacts investments on the development side, the survey which I conducted to augment my empirical analysis provides additional perspective from the point of view of managed care providers and pharmacy benefit mangers on the consumption of orphan products and how it reacts to expansions of Medicaid eligible populations.

Data & Methodology

In order to answer the question, "*How has the recent Medicaid expansion impacted investments into rare and orphan pharmaceutical products?"* I compiled data from a variety of sources, and filtered it down to observe yearly investment in a given therapeutic class of drug.

EvaluatePharma was, with the permission and assistance of Casey Cormier at Blueprint Orphan, the source for data on both yearly investment totals by therapeutic class and average cost per patient per year by therapeutic class. The first dataset from EvaluatePharma provides details including dollar amounts in millions of dollars for each transaction, the date, and the therapeutic class of product acquisitions and in/out-licensing agreements for rare and orphan products. I collapsed this dataset to yearly investment totals into each therapeutic class by year over the period of 2000-2018. The second dataset from EvaluatePharma lists the cost to patient for a year of treatment for the top 50 orphan products in the U.S., cross-referencing the drugs listed with the therapeutic categories from the investment dataset, I created average cost estimates for each therapeutic class. This will be used as a control in the later regressions as the ACA at a federal level put strict limitations on the use of annual and lifetime insurance benefit limits, and this may advantage more expensive orphan therapeutic categories disproportionately as they would be the ones that are more likely to exceed an annual or lifetime limit rather quickly.

Data on patient distributions on a state level by therapeutic class was gathered from individual disease-specific patient registries and Invitae's Patient Insights Network Database (PIN). After gathering the data, diseases that are treated by a common therapeutic category are aggregated together, and then used to create therapeutic category level data on patient distributions. I chose to use patient registries, as there is no singular source of state-level data on

patient locations based on diagnoses or reported cases that is available. While a patient's participation in a patient registry is voluntary, I believe that it is safe to assume that the relative densities would be quite synonymous between the registries and any actual geographic trend that may exists on a disease level.

Data on the implementation status of Medicaid expansion at a state level are from the Kaiser Family Foundation. This data includes information on which states have adopted and implemented Medicaid expansion, and gives dates for when each state implemented Medicaid expansion. This information is then combined with the data on state-level patient distributions by therapeutic class to create a ratio that equals the proportion of a given therapeutic class' potential market that lies within Medicaid expanded states after the expansion takes place. This then becomes the Market Expansion Ratio, which is defined by:

$$Market\ expansion\ ratio_{\boldsymbol{i}} = \frac{\sum_{\boldsymbol{states}}(\#\ \boldsymbol{of\ cases})(\boldsymbol{Expantion\ Status_s})}{\sum_{\boldsymbol{states}}(\#\ \boldsymbol{of\ cases})}$$

My empirical analysis will take the form of a difference-in-difference regression, dividing the therapeutic classes into High and Low categories based on their Market Expansion Ratios. Therapeutic categories with a Market Expansion Ratio at or above .78 will be categorized as High, and those with a Market Expansion Ratio below .78 will be in the Low category. This level was chosen to split the observations relatively equally, and the overall range for Market Expansion Ratios is from .645 to .907.

The initial iteration of the regression model will be the simplest form of the difference-in-difference regression, including only a dummy variable for the passing of the Affordable Care Act, a dummy for the high Market Expansion Ratio category, and an interaction term between the two. All of the regression models will have Investment as the left-hand side variable.

$$Investment_{it} = \beta_0 + \beta_1 (High\ Market\ Expansion\ Ratio_i) ACA_t + \beta_2 (High\ Market\ Expansion\ Ratio_i) + \beta_3 (ACA_t) + \varepsilon_{it}$$

(1)

The second iteration will be the same basic model as the first, but with the addition of both year fixed effects to account for major time trends that fall within the years of observation, 2000-2018, and type fixed effects for therapeutic categories. The dummy variables for both the ACA and high expansion ratio are dropped from the model because they are captured and controlled for by the fixed effects, and so cannot be included because they would be collinear with those controls.

$$Investment_{it} = \beta_0 + \beta_1 (High\ Market\ Expansion\ Ratio_i) ACA_t + \delta_i + \gamma_t + \varepsilon_{it}$$

(2)

The third version of the regression model will by replacing the High Market Expansion Ratio interaction term with Market Expansion Ratio as a continuous variable interacted with the ACA dummy variable to measure the marginal effects of an addition percent of a given therapeutic category's population lying within Medicaid expanded states in that therapeutic category's investment after the passing of the ACA.

$$Investment_{it} = \beta_0 + \beta_1 (Market\ Expansion\ Ratio_i * ACA_t) + \delta_i + \gamma_t + \varepsilon_{it}$$

(3)

The final version of the regression model will add an interaction term for the average cost per patient per year for a given therapeutic class to the regression in model three. The new

interaction term itself will be an interaction between the average cost per patient per year and the ACA dummy variable:

$$CostACA = AverageCost * ACA$$

For the same collinearity issues as stated above, just the interaction term will be added as the average cost variable and the ACA dummy are already accounted for by the fixed effects.

$$Investment_{it} = \beta_0 + \beta_1(Market\ Expansion\ Ratio_i * ACA_t) + \beta_2(Cost_i * ACA_t) + \delta_i + \gamma_t + \varepsilon_{it} \quad (4)$$

Summary Statistics & Results

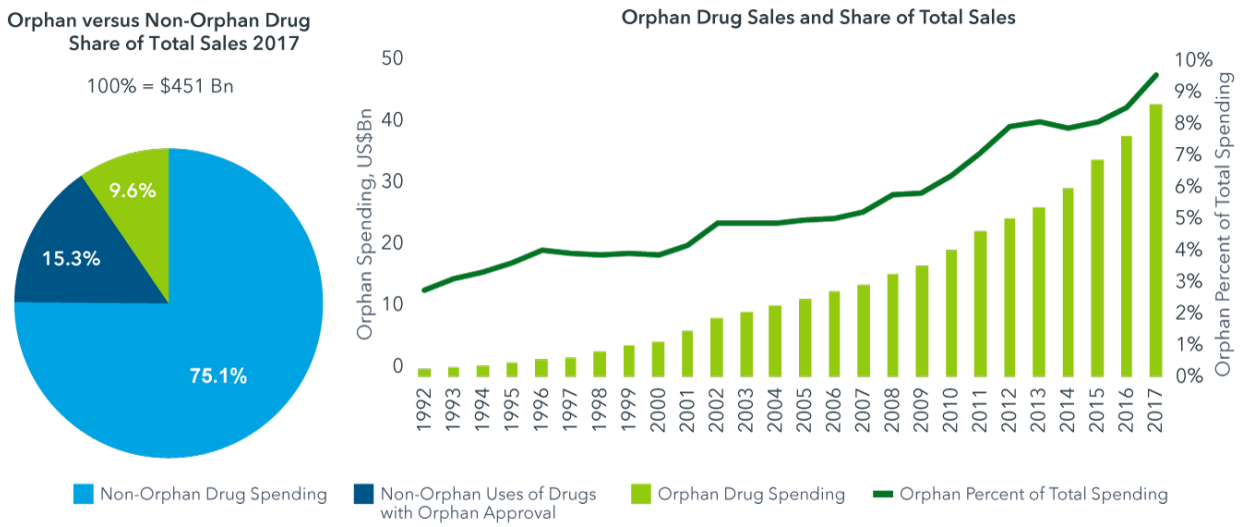
Since 2000, both the investment into and number of new orphan products has been rapidly expanding.

Table 1: Yearly Averages for Deal Values & Number of New Designations

Year	Mean total value of product acquisitions & in-licensing agreements	Number of new orphan designations
2001	$18m	77
2002	$391m	63
2006	$100m	142
2010	$208m	193
2014	$379m	288
2017	$607m	460
2018	$586m	312

Figure 1 provides additional context for the trends in product acquisition shown in Table 1 by showing the growth of the share of total pharmaceutical spending that is comprised by drugs with orphan indications. As illustrated, there has been a steady increase to the portion of pharmaceutical spending that pertains to orphan products. Not only is the industry for orphan pharmaceutical products expanding, but it is doing so faster than the pharmaceutical industry as a whole, becoming more and more important with each passing year.

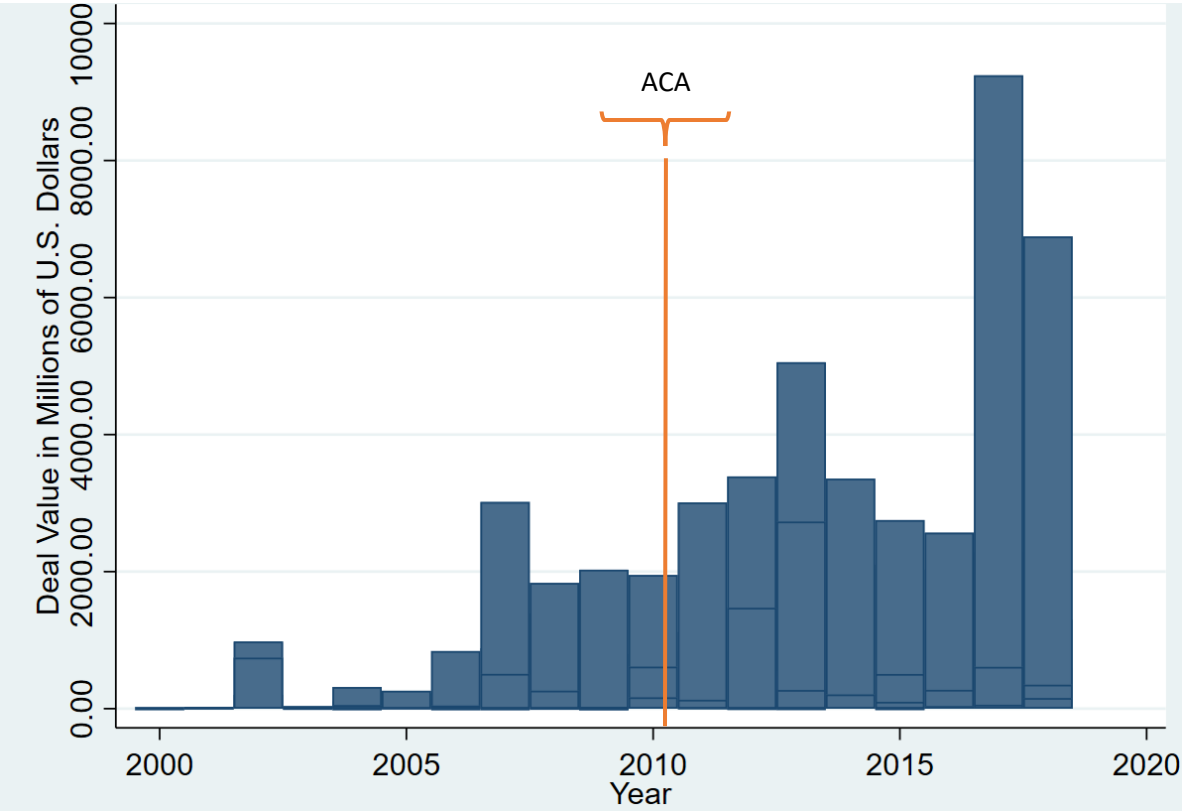
Figure 1: Growth of Spending and Sales for Orphan Drugs



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Accessed Sep 2018
Note: Volume is based on Extended Units. Orphan drug spending includes only orphan approved uses of drugs with orphan approvals.
Report: Orphan Drugs in the United States Growth Trends in Rare Disease Treatments. IQVIA Institute for Human Data Science, Oct 2018

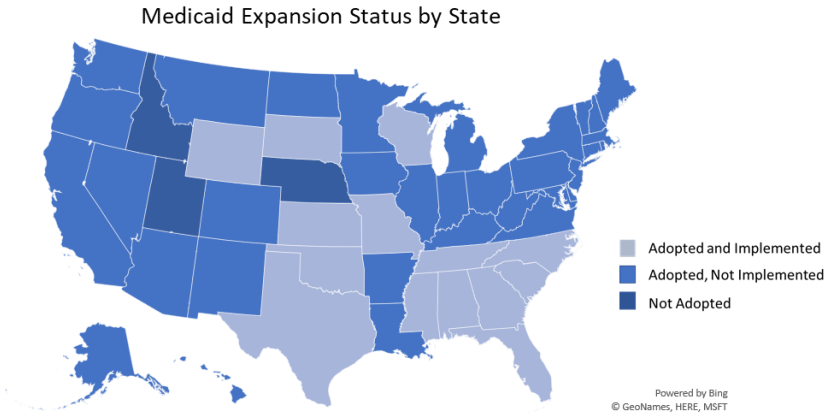
The graph below, figure 2, illustrates how the total value of product acquisitions and in/out-licensing agreements have developed over the past two decades. While investments were increasing before the implementation of the Affordable Care Act, represented here by the vertical orange line, it isn't until just after the implementation of the Affordable Care Act in 2010 that the yearly deal value totals really take off. Over the period of 2000 until the end of 2009, just before the ACA comes into effect, the average yearly investment total is $353 million across all therapeutic classes. In the post ACA period, the average yearly investment more than doubles to $885 million.

Figure 2: Yearly investment totals, 2000-2018

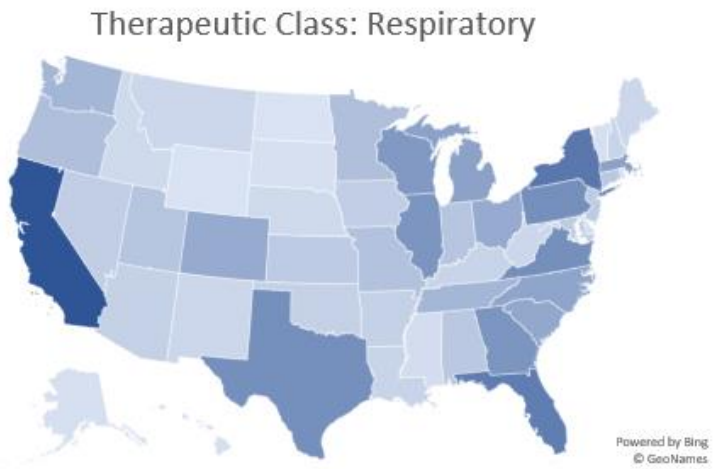


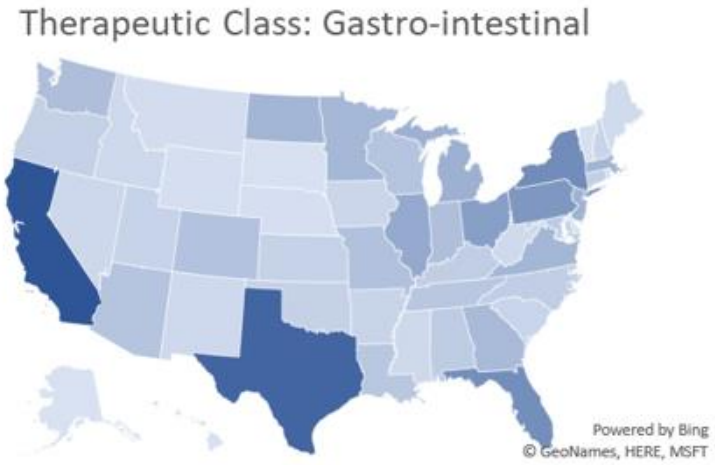
The focus of my analysis revolves around state-level differences in Medicaid expansion implementation, and combining this with state-level differences in disease incidence by therapeutic class. The maps below, Figures 3-6, show the state-level differences in Medicaid expansion status as well as, three sample maps of state level disease prevalence. A feature to note in Figure 3, the Medicaid Expansion Status map, is that three of the states have adopted Medicaid expansion, but have not actually implemented the changes yet, and as such they will be considered the same as state which have not implemented Medicaid expansion.

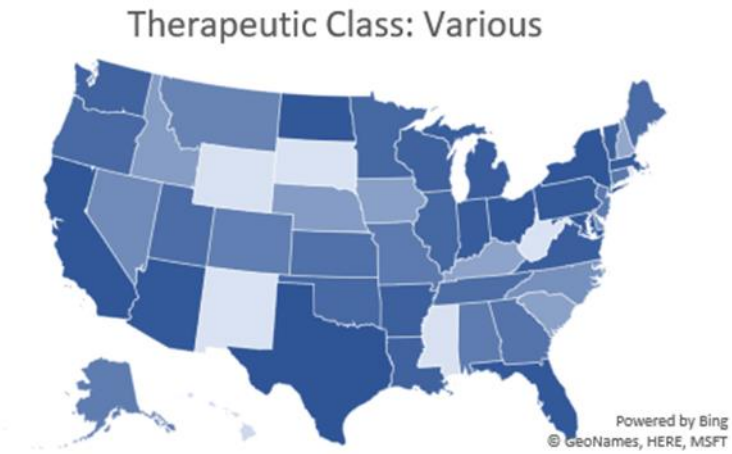
Figure 3: Medicaid Expansion Status by State



Figures 4, 5, & 6: Sample Therapeutic Categories State-level Incidence







*These maps are displaying relative densities for patient distributions

Table 2: Market Expansion Ratio by Therapeutic Category

Therapeutic Category	Market Expansion Ratio	Therapeutic Category	Market Expansion Ratio
Blood	.792	Immunomodulators	.898
Cardiovascular	.866	Musculoskeletal	.781
Central Nervous System	.778	Oncology	.737
Dermatology	.783	Respiratory	.811
Endocrine	.645	Sensory Organs	.823
Gastro-intestinal	.821	Various	.766
Genito-urinary	.907		

Table 2 lists the Market Expansion Ratios for all therapeutic classes used in my analysis. The Market Expansion Ratio gives the proportion of a therapeutic category's market that falls within states that have implemented Medicaid expansion, and the range of values spans from .645 with Endocrine on the low end, up to .907 for Genito-urinary on the high end. Something to note, is that due to scarcity of data on rare conditions, some therapeutic categories such as Various and Gastro-intestinal have better coverage in terms of observations than categories like Genito-urinary. The expectation is that the therapeutic categories with higher Market Expansion Ratios will see greater increases in their average investments post-ACA than therapeutic categories with lower Market Expansion Ratios.

Table 3: Average Cost per Patient per Year by Therapeutic Category

Therapeutic Category	Average Cost per Patient per Year
Blood	$446,944
Cardiovascular	$112,100
Central Nervous System	$70,863
Endocrine	$220,452
Immunomodulators	$113,927
Oncology	$130,756
Respiratory	$190,964

The ACA on a federal level mandated changes regarding insurance payers placing annual or lifetime benefits on health insurance plans. The changes allowed some limits to be grandfathered in, but new plans can not contain these kinds of restrictions. Because of this, I will be controlling for the average cost per patient for a year of treatment in my later regression as therapeutic categories with more expensive treatments may see greater benefit from this change in legislation as those are the products which would be more likely to exceed an annual or lifetime insurance benefit limit, when compared with less expensive therapeutic categories. Table 3 lists the average cost to a patient for a year of treatment for the therapeutic categories for which the data were available. The pricing information behind these numbers is pricing data for the top 50 orphan products in the U.S. from EvaluatePharma.

Table 4: Average Yearly Investment Pre and Post-ACA

Market Ratio	Pre ACA	Post ACA	Change
High	$250.537m	$360.252m	$109.715m
Low	$504.873m	$1999.081m	$1494.208m

The $1384.493 million gap between the high and low categories is represented by the High Market Expansion Interaction term's coefficient value.

Table 4 is useful for interpreting the difference-in-difference regression, as it shows how the average yearly investment changes for both the High, therapeutic categories with a Market Expansion Ratio at or above .78, and Low, therapeutic categories with a Market Expansion Ratio below .78, expansion ratio groups. Contrary to what was expected, the therapeutic categories within the Low Market Expansion Ratio group far surpassed those in the Market Expansion Ratio group, with investments increasing by $1.384 billion more than the investment increase for the High Market Expansion Ratio group.

Table 5: Regression Results

Variables	Model 1	Model 2	Model 3	Model 4
Market Expansion Ratio Interaction Term			-7186.857* (3471.596)	-8862.104* (4250.067)
Affordable Care Act (ACA)	1494.208*** (321.788)	Captured in time fixed effects	Captured in time fixed effects	Captured in time fixed effects
High Market Expansion Interaction Term	-1384.493*** (425.845)	-1325.449*** (399.431)		
High Market Expansion Ratio	-254.336 (321.788)	Captured in type fixed effects		
Average Cost ACA Interaction Term				-.0039342 (.0022758)
Observations:	122	122	122	84

$*$ p < 0.05, $**$ p < 0.01, $***$ p < 0.001

Market Expansion Ratio Interaction Term = Market Expansion Ratio * ACA dummy

High Market Expansion Interaction Term = High Market Expansion Ratio dummy * ACA dummy

Average Cost ACA Interaction Term = Average Cost per Patient per Year * ACA dummy

As represented in the regression results in Table 5, Model 1 represents the most basic form of the difference-in-difference analysis comparing the high expansion ratio group to the low expansion ratio group, and as such, includes no form of either time or type fixed effects for year or therapeutic class. The coefficient for the ACA dummy variable is showing the increase in average yearly investment for therapeutic classes which fall under the low expansion ratio category after the ACA was implemented. The value of 1494.208 indicates that the Low Market Expansion Ratio group experienced an increase of $1494.208 million, or almost $1.5 billion, in average yearly investments. The coefficient for the High Market Expansion interaction term

shows the difference in changes to average yearly investment for the High Market Expansion Ratio group relative to the Low Market Expansion Ratio group. Id est, the increase to average yearly investment for the High Market Expansion Ratio group, post-ACA, was $1384.493 million less than the increase for the Low Market Expansion Ratio group. Both variables, the ACA dummy and the High market expansion interaction term are significant at the 1% level. The High Market Expansion dummy variable's coefficient value of -254.336 indicates the difference in average yearly investment between the High and Low Market Expansion Ratio groups before the ACA was enacted. The results of this first difference-in-difference are contrary to my hypothesis as the therapeutic categories within the Low Market Expansion Ratio category experienced a far greater gain in average yearly investment than the therapeutic categories within the High Market Expansion category.

Model 2 is the same difference-in-difference analysis as before, but this time both type fixed effects for therapeutic category and time fixed effects for year have been included. Both the ACA dummy and High Market Expansion Ratio dummy are collinear with the time and type fixed effects respectively, and so, neither are included explicitly in the model as they are accounted for within the fixed effects. The coefficient for the High Market Expansion Ratio interaction term remains relatively unaffected, only becoming slightly less negative than in the base difference-in-difference model by 59.044, which equates to $59.044 million, as the investment data are in millions of dollars. The significance level is also relatively unaffected from Model 1, and is still significant at the .1% level.

Model 3 evolves Model 2 by incorporating a continuous variable for the interaction between the Market Expansion Ratio and the ACA dummy variable instead of the interaction term for the difference-in-difference. Because the Market Expansion Ratio only takes values

between 0 and 1, the value of the coefficient must be divided by 100 to be correctly interpreted. -7186.857 then becomes -71.86857, and the interpretation of this would be that the difference in effects to investment for a 1 percentage point increase in a therapeutic category's Market Expansion Ratio leads to $71.86 million dollars less investment on average after the passing of the Affordable Care Act. This result also goes against the idea behind my hypothesis that therapeutic classes with more their target populations within Medicaid expanded states would receive greater increases to their investment following Medicaid expansion and the ACA. This coefficient is also significant at the 5% level.

The final iteration of the regression in Model 4 adds a continuous variable for the interaction between the ACA dummy variable and average cost to patient per year of treatment to the regression in Model 3. The sign on the coefficient for average cost interaction term is not what I would have expected, as the parts of the ACA legislation which eliminated annual and lifetime insurance benefit limits, I would have assumed to be more significant for the therapeutic classes with very high average costs, as they are more likely to exceed those limits than the less expensive therapeutic classes. This term, however, suggests just the opposite, that an increase in the average cost to a patient for a year of treatment is detrimental to average investment. The coefficient of -.0039342 for the average cost interaction term implies that there is an additional loss to yearly investments of $3934.2 for every dollar increase to the average cost per patient per year for a given therapeutic class. The Market Expansion Interaction is still significant at the 5% level, but has become larger in magnitude, jumping from -7186.857 to -8862.104 after the average cost control is added in. This shift may be due in part to the loss in observations from 122 to 84 from the inclusion of the pricing variable, but is still showing a large and negative

relationship between an increase in a therapeutic category's Market Expansion Ratio and investment.

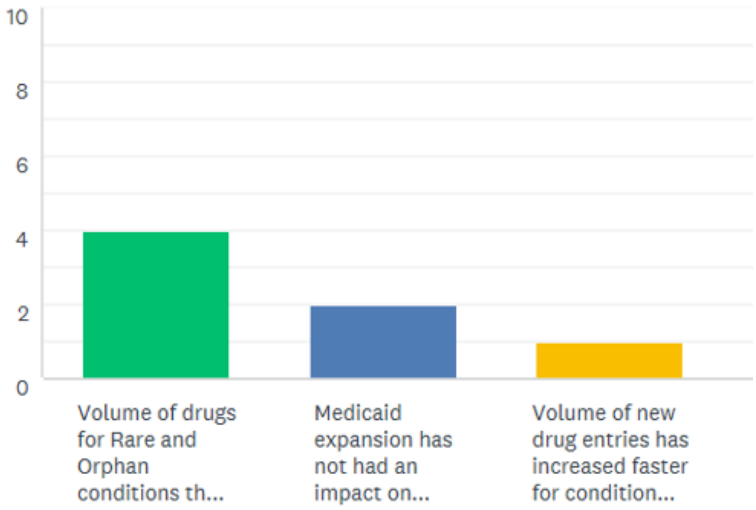
Survey Results

To augment the empirical analysis, I conducted a survey of ten Pharmacy and Medical Directors from a mix of national and regional Health Plans and Pharmacy Benefit Managers. Results were captured from six respondents, collectively representing management of a total of 93,460,000 lives. Each respondent is a voting member of the Pharmacy and Therapeutics committees in their respective organization, with lead responsibility for managing the evaluation of all therapeutic agents and establishing clinical and utilization management policies for each. While there is certainly variability in the responses I received, it appears to be the case for many of the firms that their perception is that utilization of orphan drugs has increased following the Affordable Care Act and Medicaid expansion. There is also rising concern regarding how access to orphan drugs, particularly oncologic treatments, will be governed, with many insurance payers moving to implement more strict criteria to be met for a patient to receive or continue with a treatment. The individuals surveyed represent the following organization types (blinded):

Table 6: Organization Information

Plan	Respondent	Commercial	Medicare	Medicaid
Pharmacy Benefit Manager - State Medicaid	Pharmacy Director	N/A	N/A	6,000,000
Pharmacy Benefit Manager	Pharmacy Director	65,000,000	5,000,000	3,000,000
Health Plan - Blues Affiliate	Pharmacy Director	5,500,000	130,000	500,000
Health Plan	Medical Director	3,000,000	30,000	-
Pharmacy Benefit Manager	Pharmacy Director	2,000,000	100,000	2,000,000
Health Management Organization	Pharmacy Director	1,100,000	100,000	-
		76,600,000	**5,360,000**	**11,500,000**

Q1: Select the option you feel best describes the trends in the volume of new drug entries for rare and orphan diseases since Medicaid Expansion in 2010?

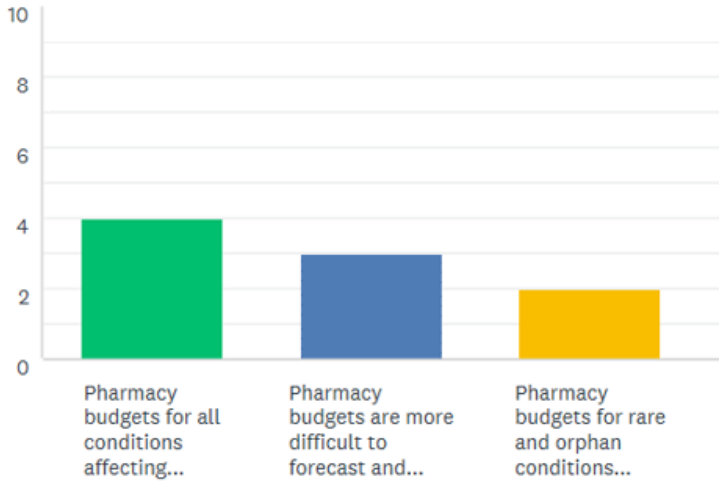


- Volume of drugs for Rare and Orphan conditions that effect all populations has increased
- Medicaid expansion has not had an impact on development of new drugs for rare and orphan conditions
- Volume of new drug entries has increased faster for conditions that disproportionately effect Medicaid populations than prior to Medicaid expansion

The feedback from question 1 is largely in-line with my hypothesis regarding how the Medicaid expansion and Affordable Care Act, in general, have impacted orphan pharmaceutical development. Five of the respondents reported that orphan product development increased across all classes of patient populations, not just those disproportionately represented in Medicaid populations. While it is not possible to tease out any causality from this result, it is not unreasonable to assume that this is due in part both to the expansions in individuals with access to health insurance via the Medicaid expansion, as well as, the changes in legislation governing

annual and lifetime benefit limits allowing for greater access to orphan products across the spectrum of insurance types. One thing to bear in mind is that, due to the very large lead-times involved with drug development, more time will likely need to pass before any reaction by drug developers manifests, let alone drawing any firm conclusions as to how this legislation has impacted drug development decisions.

Q2: Select the statement that best describes how these trends have affected your business



- Pharmacy budgets for all conditions affecting Medicaid populations have grown significantly
- Pharmacy budgets are more difficult to forecast and manage since Medicaid expansion
- Pharmacy budgets for rare and orphan conditions affecting Medicaid populations have grown disproportionately to all conditions

Only two of the respondents reported that their budgets for orphan conditions affecting Medicaid populations have grown disproportionately to all other conditions, but the general theme

remains, costs are rising to cover the medical expenses of Medicaid populations. Costs associated with orphan treatments will still be captured within the overall rising costs to cover Medicaid recipients, but by the experience of many of the firms surveyed, the difference in cost growth may not be as disproportionate as I anticipated.

Q3: Which therapeutic categories within the rare and orphan conditions have the greatest potential for impact on your organization? (i.e. oncology, respiratory, cardiovascular, etc.)

*The following are direct responses provided by the respondents to this survey

- Oncology as more and more drugs that are quite expensive enter this space
- Oncology, respiratory, hemophilia, enzyme deficiencies
- Oncology overall has had the greatest impact, both from a rare tumor types as well as from the standpoint of research in newly discovered metabolic pathways for which targeted medications are being researched and approved.
- Oncology, Multiple Sclerosis, Hemophilia

The fact that Oncology is a significant concern for all respondents to this question is telling. I reached out to Joseph Genco from Novartis Oncology for his input, and he outlined that a major trend occurring in oncology is that treatments are becoming far more effective at extending the life of patients on drug. This coupled with the fact that drug pricing in this space is largely tied to a drug's efficacy brings us to the current situation that exists within oncology where patients are surviving far longer on treatments that are very expensive. This is a boon to the oncologic drug developers but becomes problematic from the insurance side

of the equation as more and more individuals are surviving far longer than in previous decades on drugs that are very expensive.

Q4: Identify and provide examples for any rare and orphan conditions that disproportionately affect Medicaid populations which may drive investment into treatment options?

- Hemophilia (*This falls within the Blood therapeutic category in this study)
- DMD, Cystic Fibrosis, Oncology
- Any genetic rare disease because the genetic factor may have predisposed family previously to Medicaid
- Oncology, neurodegenerative conditions

Q5: How do you foresee evolving managed care policies influencing the development of drugs to treat rare and orphan diseases?

- On the medical benefit we have partnered with Magellan RX for all lines of business to better manage our infused specialty drugs which include drugs for rare and orphan conditions

- No effect on developmental pipeline.

- I really do not see policies changing. Currently today, the only ability that managed care has is to ensure that the patient in deed has the condition and is appropriate for the medication in question (meaning that other appropriate therapies have been tried). If the patient is appropriate for the medication, then the plan is obligated to provide coverage.

- Expansion of value-based contracting agreements to improve access and protect against treatment failures

- I believe that more MGD Care policies would either exclude certain orphan drugs (if there is minimal clinical evidence) or create criteria more restrictive than FDA label. Payors would look at inclusion and exclusion criteria before approving certain patients for orphan drug therapy.

- Benefit design - deductible, coinsurance, higher/elimination of caps, exclusions. Stricter PA beyond label. More targeted clinical programs - care management/case management, specialty programs.

- Tight control, requirement for long term data on safety and efficacy/durability, innovative contracting

While this question is not directly relevant to the impact of Medicaid expansion on the investments into treatments for rare and orphan diseases, I included this to capture the perspective of how insurance payers view this impact, and how they intend to evaluate and manage such therapies. It is clear that payers intend to implement tighter utilization restrictions that align to the structure of and to the clinical evidence demonstrated in the pivotal trials. Future analysis should evaluate the impact of such evolving controls on the development and introduction of treatments in these categories.

The following are response to a follow-up question: "*To what extent has Medicaid expansion affected the volume of rare and orphan treatments being consumed annually?"*

Pharmacy Director, Blues Plan

"As most rare and orphan disease drugs are covered, I am not aware of the State restricting any, I would guess we would see consumption increase in the Medicaid population as people under the age of 13 are one of our largest demographics and typically where rare and orphan diseases are diagnosed. If expansion gives people that do not have insurance access, then it will increase but I would wager the majority of people with rare and orphan disease are already on some form of assistance or insurance."

Medical Director; Pharmacy Benefit Manager

"Potential significant impact as some of the neuromuscular childhood conditions affect the Medicaid population disproportionately."

Pharmacy Director; Regional Health Plan

"With the expansion of the Medicaid market through Medicaid Expansion efforts, we have seen an increase in the utilization of treatments for rare and orphan diseases. We believe this is correlated to the greater ability of the patients to obtain these medications because they are more accessible to them through the Medicaid program. Under either no insurance, or an individual health benefit, the patient out-of-pocket would be significant, thus presenting as a barrier to treatment. This is a prime example of the

"Financial Toxicity" that patients experience when being [treated] with high cost medication, and subsequently go untreated. We believe Medicaid expansion provides greater access to medications treatments for rare and orphan conditions."

Pharmacy Director; Pharmacy Benefit Manager

"I really don't have the data to quantify the impact of expansion on utilization orphan treatments. That is all firewalled from our formulary and rebate team. Anecdotally, we did pick up lives from Medicaid expansion and our pharmacy budgets reflect that. We could do the work to analyze these trend and expenditures but have not done this. I do expect that we have incurred the costs associated with treating patients commensurate with the prevalence of orphan treatments."

Findings from this survey are anecdotal in nature, but reflect the perception of major managed care organizations, how they see the market behaving, and the impact this has on their business. The majority consensus of the respondents is in-line with a portion of my initial hypothesis, that the expansions to Medicaid has increased access and, by extension, sales of orphan products to Medicaid recipients. Whether or not this boost in sales has resulted in any concrete response from the drug development and pharmaceutical side, in direct response to larger potential markets, unfortunately remains unclear.

Discussion & Conclusion

While it is undeniable that the overall scope and scale of the industry for orphan drugs has grown significantly in the near decade following the passing of the Affordable Care Act, it is not clear that the Medicaid expansion itself is a major driving factor behind this. I was not able to detect any significant benefit to investment for a therapeutic category to have more of its patients located within Medicaid expanded states. Completely contrary to what I had anticipated, I actually found that those therapeutic categories that fell within my Low Market Expansion category received far more in investments on average than those in my High Market Expansion Ratio category. Furthermore, the marginal effect of the increase in a therapeutic category's Market Expansion Ratio led to lower levels of investments. I believe that this is likely because patient distributions relative to Medicaid expansion states is probably not something that ever enters the decision-making process for a firm looking to acquire an orphan drug or enter into a licensing agreement. In the grand scheme, what proportion of a given drug's patient population that lies with Texas or Washington, for example, just isn't a factor that is likely ever considered. If it were ever considered, it likely doesn't hold a candle to drug features such as efficacy, safety, patent life-span, etc. While it may indeed be the case that there is an impact on investments into orphan drugs caused by Medicaid expansion, higher resolution data would be needed to make observations at the disease level within a therapeutic category. This would eliminate any inconsistencies trying to compare across therapeutic categories that may be based on radically different technologies and have radically different patient outcomes. Comparing oncology drugs with gastro-intestinal treatments may be too large of a jump to isolate the effect of Medicaid expansion on changes in investments.

The outcome that the relationship between average cost and investment was negative was also a surprise, but it does make sense. While it may be the case that the Affordable Care Act did place restrictions on the use of annual and lifetime insurance benefit limits, and this would seem to favor the more expensive indications, high prices of orphan products are due, in large part, to the small populations of individuals afflicted with a given disease, and so, the orphan products with lower average costs may be less expensive because they are targeting diseases that have larger populations. From an investment standpoint, a large population of potential clients is certainly a beneficial characteristic. And from a more political standpoint, there is growing scrutiny in recent years of high drug prices, and this could potentially play a part in investment trends as well.

The feedback from the survey does highlight some opportunities for extensions to this topic which could be beneficial to explore. A common response was that costs associated with Medicaid populations is rising in the years after the Affordable Care Act, and the possible causes for this are numerous, from health complications of an expanding elderly population as Baby Boomers age, to increased access to more expensive pharmaceutical products. A detailed and nuanced understanding of how the costs associated with state-provided health insurance change and are affected by new legislation is imperative if we as a country insist on having sustainable state-provided health insurance. Another rabbit hole in the landscape of insurance and orphan drug relationships, is how insurance payers are adapting their coverage policies in the face of orphan drugs with higher and higher prices. Orphan drugs have enjoyed almost ubiquitous coverage, but as the market for orphan products expands, so too does insurance payers' incentive to reign in on how often they cover medications that can cost millions of dollars per year for a single patient. Payers indicate that, unless there is no evidence of efficacy, they must cover drugs

for rare and orphan conditions. They, however, do structure inclusion criteria for approving therapy to closely reflect those in the clinical trials for such medications. Additionally, they carefully structure criteria to determine the appropriateness of continuing therapy and set definitive timelines for evaluating each case against such criteria.

My work here has been the first foray delving into how a large and complicated piece of legislation has impacted an equally complex and dynamic industry. With access to more and higher resolution data, it is entirely possible that an affect could be uncovered that was missed in my study. The FDA recognizes over 7000 orphan diseases, and I was only able to collect data on just over 130 of these; A group with greater resources may be able to expand upon this, and look not at a therapeutic category level, but at an individual disease level. This kind of precision would be far better suited to try and explain what is going on in the incredibly intricate world that is specialty pharmaceutical products. It is my hope that my work here can act as a stepping stone or inspiration for continued research into a topic that is becoming more and more important with each passing year.

Appendix

Diseases used in this study:

Blood Related Conditions	Cardiovascular Diseases
At hereditary risk for CADASIL	(HMG) 3-hydroxy-3 -methylglutaryl-CoA
Eosinophilic Colitis	Cancer Genetic Testing Only (No Cance..
Epithelioid Hemangioendothelioma	Cardio-Facio-Cutaneous syndrome
GM1 Gangliosidosis Type 1 Infantile	Cardio-Facio-Cutaneous syndrome
GM1 Gangliosidosis Type 2 Juvenile	Cardio-Facio-Cutaneous syndrome (BRAF..
GM1 Gangliosidosis Type 2 Late Infant..	Cardio-Facio-Cutaneous syndrome (KRAS..
GM1 Gangliosidosis Type 3 Adult	Cardio-Facio-Cutaneous syndrome (MEK ..
GM2 Sandhoff (Infantile Onset)	Cardio-Facio-Cutaneous syndrome (Othe..
GM2 Sandhoff (Juvenile Onset)	Cardio-Facio-Cutaneous syndrome (Unkn..
GM2 Tay-Sachs (Adult Onset)	
GM2 Tay-Sachs (Infantile Onset)	**Genito-Urinary Diseases**
GM2 Tay-Sachs (Juvenile Onset)	5-oxoprolinemia
Hypertriglyceridemia	Eosinophilic Cystitis
LCHAD	
MCAD	**Respiratory Diseases**
SCAD	Eosinophilic Asthma
	Eosinophilic Esophagitis
Gastro-Intestinal Diseases	Eosinophilic Granulomatosis with Poly..
(2MBCD) 2-Methylbutyryl-CoA Dehydroge	Eosinophilic Pneumonia
(BKT) Mitochondrial Acetoacetyl CoA T	
(IVA) Isovaleryl CoA Dehydrogenase	**Dermatology Related Conditions**
(MGA) 3-Methylglutaconic acidemia or	Cholesteatoma
(MMA) Methlymalonic Acidemia	Eosinophilic Fasciitis
(PA) Propionyl CoA Carboxylase Defici..	Linear Scleroderma
2,4-Dienoyl-CoA Reductase Deficiency	Morgellons Disease
Eosinophilic Duodenitis	Parry Romberg Syndrome
Eosinophilic Gastritis	

Eosinophilic Gastroenteritis	**Musculoskeletal Diseases**
Food Protein Induced Enterocolitis Syndrome	CACT
GA 2/MADD	Costello Syndrome
Protein-losing Eosinophilic Enteropathy	Eosinophilic Myositis
TFP	Essential Tremor
VLCAD	MPS I Hurler-Scheie Syndrome
	MPS I Scheie Syndrome
Oncology	MPS II Hunter Syndrome
Diffuse Gastric Cancer	MPS IVA Morquio A Syndrome
Double hit lymphoma	MPS VI Maroteaux-Lamy Syndrome
Gastric (Stomach) Cancer	Superior Canal Dehiscence (SCD)
Gastric (Stomach) Cancer, Other	
Hereditary Diffuse Gastric Cancer (HD..	**Various**
Kidney Cancer	Confirmed CDG, Type Known
PROMPT Study	Confirmed CDG, Type Not Teste
Small Cell Carcinoma of the Ovary	Confirmed CDG, Type Tested but Unknow..
	EEF1A2 Gene Variant
Central Nervous Diseases	Eosinophilia Myalgia Syndrome
17q12 deletion	Idiopathic Intracranial Hypertension
(GA-I) Glutaryl CoA Dehydrogenase Deficiency	MPS I Hurler Syndrome
17q12 duplication	MPS III Sanfilippo Type Unknown
Agyria pachygyria polymicrogyria	MPS IIIA Sanfilippo A Syndrome
Bilateral Frontal Polymicrogyria	MPS IIIB Sanfilippo B Syndrome
Bilateral Frontoparietal Polymicrogyria	MPS IIIC Sanfilippo C Syndrome
Bilateral generalized polymicrogyria	MPS IIID Sanfilippo D Syndrome
Bilateral Perisylvian Polymicrogyria	Mucolipidosis II, II/III, III Alpha
BPPV (Benign Paroxysmal Positional Vertigo	Noonan syndrome
CADASIL	Noonan syndrome with multiple lentigi..
Canavan disease	Trisomy 13
Chronic Subjective Dizziness	Trisomy 18
Dandy-Walker Syndrome	
GNAO1 Variant	**Sensory Organs Diseases**

Guanidinoacetate Methyltransferase De..	Acoustic Neuroma
Hereditary Spastic Paraplegia	Autoimmune Inner Ear Disease (AIED)
KCNQ2 Encephalopathy	Bilateral Vestibular Hypofunction
Labyrinthitis (aka Vestibular Neuritis)	Circadian Rhythm Sleep Disorder
Mal de Debarquement	Coats disease
Megalencephaly, polymicrogyria, and h..	Hypereosinophilic Syndrome
Polymicrogyria (PMG)	Meniere's Disease
Primary Lateral Sclerosis	Otosclerosis
X-Linked Creatine Transporter Deficiency	Ototoxicity
	Perilymph Fistula
Conditions treated with Immunomodulators	Secondary Endolymphatic Hydrops (SEH)
Alagille Syndrome	Tinnitus
CPT 1&2	Vestibular Hyperacusis
	Vestibular Migraine
	Vestibular Schwannoma

Bibliography

"Data on Orphan Product Deals." EvaluatePharma, 2019.

"Data on Patient Locations by State and by Disease." Invitae Patient Insights Network (PIN), 2019.

"EvaluatePharma® Orphan Drug Report 2017." *EvaluateGroup*, EvaluatePharma, 2017, info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf.

Fete, Mary. "Data on Ectodermal Dysplasia." NFed, 2018.

Handfield, Robert, and Josh Feldstein. "Insurance Companies' Perspectives on the Orphan Drug Pipeline." *Current Neurology and Neuroscience Reports.*, U.S. National Library of Medicine, 2013, www.ncbi.nlm.nih.gov/pmc/articles/PMC4046481/.

IQVIA. "Orphan Drugs in the United States (Part One)." *IQVIA*, 2018, www.iqvia.com/institute/reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments.

Kesselheim, Aaron S. "Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs." *Current Neurology and Neuroscience Reports.*, U.S. National Library of Medicine, 1 Jan. 1970, www.ncbi.nlm.nih.gov/books/NBK56187/.

Kwon, Diana. "How Orphan Drugs Became a Highly Profitable Industry." *Recent Articles | Air Pollution | The Scientist Magazine®*, The Scientist Magazine, 2018, www.the-scientist.com/features/how-orphan-drugs-became-a-highly-profitable-industry-64278.

Miller, Kathleen L. "Do Investors Value the FDA Orphan Drug Designation?" *Current Neurology and Neuroscience Reports.*, U.S. National Library of Medicine, 2017, www.ncbi.nlm.nih.gov/pmc/articles/PMC5477091/.

Mulle, Jennifer. "Data on 3q29 Deletion and Duplication by State." Emory University School of Medicine, 2019.

Pagliarulo, Ned. "5 Trends Shaping Rare Disease Drug Development." *BioPharma Dive*, 10 Apr. 2017, www.biopharmadive.com/news/trends-rare-disease-orphan-drug-development/439866/.

"Pricing Data for Top 50 Orphan Products." EvaluatePharma, 2019.