NORD®
National Organization for Rare Disorders

Impact of the Rare Pediatric Disease Priority Review Voucher Program on Drug Development 2012 - 2024

rarediseases.org

NORD® POLICY REPORT
JULY 23, 2024

NORD®
National Organization for Rare Disorders

Impact of the Rare Pediatric Disease Priority Review Voucher Program on Drug Development

Table of Contents

Introduction

As many as half of all people living with a rare disease are children, and the Rare Pediatric Disease Priority Review Voucher (RPD PRV) program offers a crucial incentive for companies to develop therapies for these particularly challenging to study patient populations. New data within this paper demonstrates its tangible impact on the rare disease patient community and reinforces the need to reauthorize the RPD PRV program before the September 30, 2024 deadline.

Purpose

This report assesses the impact of the RPD PRV program on rare disease drug development.

Key Findings

Since the last Government Accountability Office study of PRV data ended in 2019, the number of RPD PRVs that have been granted has more than doubled, emphasizing the need for an updated analysis. NORD's research and analysis found between the program's inception in 2012 and April 30, 2024:

53 PRVs have been awarded **across 39 rare pediatric diseases.**[1] Of these diseases, many typically lead to death before the children reach adulthood (see Table 2).

Prior to the creation of the RPD PRV program, **only three of these 39 rare pediatric diseases** had any FDA-approved treatments (see Table 1 and Table 2).

23 RPD PRVs have been redeemed for priority review of 21 different drugs for a variety of diseases, including six drugs to treat rare diseases (see Table 1).

Only three of the drugs for which vouchers were redeemed were among the top 50 drugs by Medicare Part B or D drug spend in 2022, and **fewer than half** were among the top 100 in Medicare Part B or D drug spend (see Table 1).

The RPD PRV program's impact has dramatically increased over time. **More than half** of all RPD PRV designations, awards and redemptions **occurred in the last four years** (see Figures 1 & 2, Table 2).

Based on these findings, the RPD PRV program is benefiting the rare disease community and must be reauthorized for at least another five years as included in H.R. 7384/S. 4583, the Creating Hope Reauthorization Act.

Impact of Rare Diseases on Children & Challenges in Rare Pediatric Disease Drug Development

FDA defines a rare pediatric disease as "a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents."[1] As many as half of the individuals living with a rare disease are children, and their conditions are often devastating and life-threatening.[2] In fact, approximately 30% of children diagnosed with a rare disease will not reach their fifth birthday.[3] Only about 5% of the more than 10,000 known rare diseases have an FDA-approved treatment.[4]

Developing therapies for rare diseases is uniquely challenging, especially for pediatric patient populations, as it can be significantly more complex to plan and implement clinical trials for these conditions compared to other diseases.

History and Reauthorization of the Rare Pediatric Disease Priority Review Voucher Program

The first PRV program began in 2007 to support the development of drugs for neglected tropical diseases and was expanded in 2012 to include rare pediatric diseases and again in 2016 to include medical countermeasures.[5]

To help address the dire circumstances for many children with rare diseases, the RPD PRV program established a valuable incentive for companies to develop therapies for hard-to-study rare pediatric diseases.[6] This program's success has resulted in more children living with rare diseases having a chance at a fuller, healthier life and gives hope to communities still waiting for a treatment option for their condition.

The current authorization for the RPD PRV program is set to expire September 30, 2024, and without reauthorization by Congress, this valuable incentive program will end.

NORD® National Organization for Rare Disorders

THE PATIENT PERSPECTIVE

MDA® Muscular Dystrophy Association

"The Rare Pediatric Disease Priority Review Voucher (RPD PRV) program has been instrumental in encouraging therapeutic development in challenging pediatric neuromuscular diseases that otherwise may not receive biopharmaceutical commercial attention. Already, several FDA-approved rare neuromuscular disease treatments have received a PRV upon approval, including seven treatments for Duchenne muscular dystrophy (DMD), three treatments for spinal muscular atrophy (SMA), and one treatment for Friedreich's Ataxia.

All three of these diseases had zero FDA-approved treatments prior to the creation of the RPD PRV program. Today, collectively, there are twelve approved treatments across these three diseases.

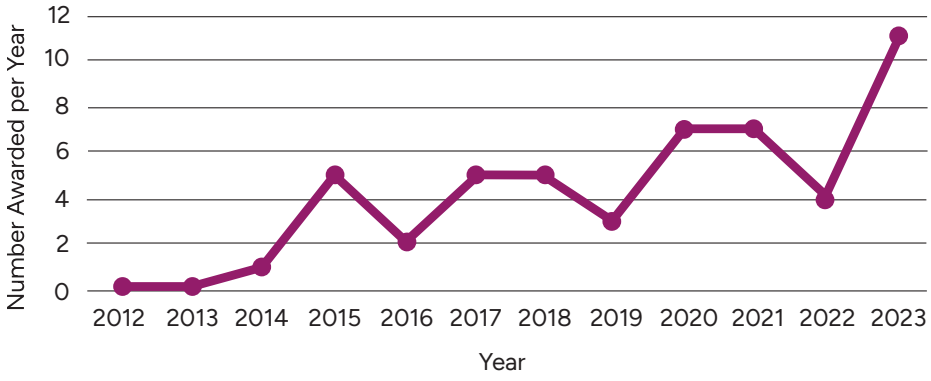
Most notably, all of the products are innovative and unique, and some may not have come to market without the voucher's incentive. For example, of the approved DMD treatments, several are exon-skipping treatments that target ultra-rare subpopulations of the Duchenne community, thus not exactly offering a financially lucrative opportunity for the sponsors bringing them to market. The voucher has also encouraged innovation in corticosteroid treatments for DMD as not only has a more advanced version of Prednisone been tested and approved for DMD (deflazacort), but a dissociative steroid without the problematic side effects (Vamoralone) has been approved, as has an innovative nonsteroidal treatment that preserves muscle function (Duvystat). Perhaps most notably, the very first gene therapy for a muscular dystrophy, Elevydis, was approved for Duchenne last summer and received a voucher.

In SMA, each of the three FDA-approved treatments that have received vouchers are incredibly innovative and unique in their own ways. These three treatments have transformed the experience of people living with SMA: while previously infants with

How the RPD PRV Program Works

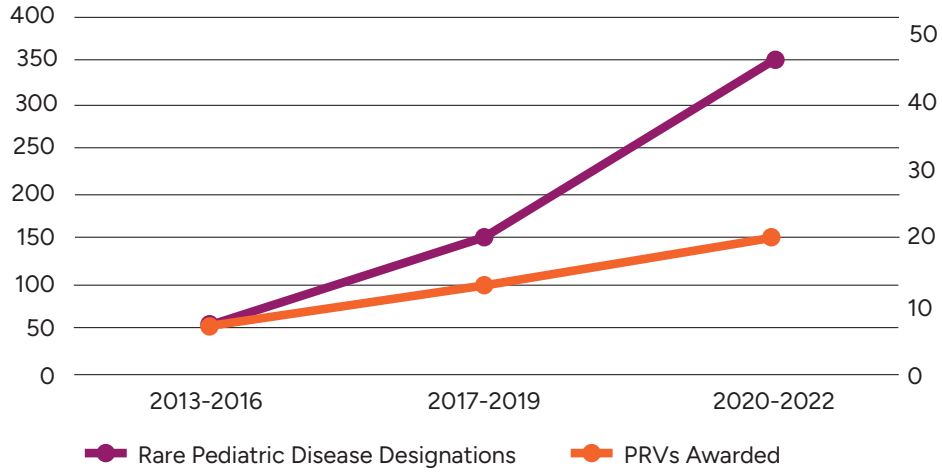
Under the RPD PRV program, companies that develop safe and effective novel therapies for rare pediatric diseases can be awarded a RPD PRV, which allows a sponsor to obtain priority review for a New Drug Application (NDA) or Biologic License Application (BLA) that would otherwise not qualify for priority review.[8,9]

Figure 1:
Rare Pediatric Disease Priority Review Vouchers Awarded Per Year[7]



Sponsors studying rare pediatric diseases are strongly encouraged to obtain a RPD designation, which typically occurs very early in the drug development process. RPD PRVs are only granted once a New Drug Application or Biologics License Application receives FDA approval following extensive clinical studies proving its safety and efficacy, and after FDA determines that all other relevant requirements linked to the PRV program are met.[10,11]

Figure 2: Trends in RPD PRVs and Rare Pediatric Disease Designations



SMA might die before their first birthday, children with SMA are living full childhoods, almost visibly unaffected by the SMA. Within Friedreich's Ataxia (FA), Skyclarys was the first and only FDA-approved therapy for the FA disease population, a community that has fought for FDA-approved treatments for decades.

While the RPD PRV program has contributed to the success of therapeutic development in these three disease areas, countless other rare pediatric disease populations are counting on the voucher to remain in place to continue to incentivize development in their disease area. The limb-girdle muscular dystrophy, congenital muscular dystrophy, mitochondrial myopathy and many more communities are counting on the voucher to create similar success stories to those already written for Duchenne, SMA and FA.

MDA has also heard from several small biotechnology companies developing treatments for ultra-rare pediatric neuromuscular diseases that the presence of the voucher upon approval, which they can then sell, is a major incentive for the continued activity in the space."

Paul Melmeyer, MPP
Executive Vice President, Public Policy and Advocacy, Muscular Dystrophy Association

Joel Cartner, Esq.
Director, Access Policy, Muscular Dystrophy Association

The RPD PRV Program Supports Rare Pediatric Disease Drug Development

A total of 53 RPD PRVs have been awarded as of April 30, 2024, reflecting a steady upward trend in rare pediatric disease drug development since the program was first authorized in 2012. Among the 39 rare pediatric diseases for which vouchers to treat those conditions have been awarded, only three of those rare pediatric diseases had any FDA-approved products on the market before the program's enactment (see Table 1).

Looking deeper into the drug development pipeline, the trend is even more encouraging. From 2012 to 2022, as many as 569 drug candidates were designated by FDA as rare pediatric disease drugs, with the vast majority designated since 2019 (see Figure 2).[12,13] This promises a further increase in RPD PRV awards in coming years.

Importantly, more than half of all RPD PRVs have been awarded since 2019 — the year the last program assessment by the Government Accountability Office ended.[14,15,16] It is also important to note that at the time of the Government Accountability Office's analysis, the program had only been in place for seven years, so the program's impact was not nearly as pronounced as today. This is hardly surprising given that, on average, it takes more than 10 years to bring a new rare disease therapy to market and many drug candidates that would have been incentivized by the RPD PRV program had not yet received FDA approval in 2019.[17] The significant uptick in rare pediatric disease drug approvals in recent years demonstrates the benefit of this incentive to the rare disease patient community.[18]

RPD PRVs Are Typically Sold Quickly, and Rarely Redeemed for "Blockbuster" Drugs

An integral component of the RPD PRV program is that companies can utilize the RPD PRV for a priority review of one of their own drug candidates, or sell or transfer RPD PRVs to another company, creating important additional assets for biopharmaceutical companies.[19] To date, 29 of the 53 awarded RPD PRVs have been sold, and others have transferred ownership as part of company mergers or acquisitions.[a] Almost all of the RPD PRV sales to date occurred within a year of award (mostly within six months or less), and about half of the sold RPD PRVs have been redeemed to date.[20]

THE PATIENT PERSPECTIVE

"Individuals with spinal muscular atrophy (SMA) have greatly benefitted from the [RPD] Priority Review Voucher (PRV) program and other policies that have spurred research and development into rare pediatric diseases such as SMA. Before 2012, when PRV was authorized, SMA was considered the leading genetic cause of infant death. Babies born with SMA Type 1, the most common form of the disease, often died before reaching their second birthday. There were no SMA treatments and few candidates in the SMA research pipeline. Fast forward to today and there are now three effective FDA-approved SMA treatments and more drug candidates in the various stages of development than at any time in Cure SMA's 40-year history. SMA is no longer the leading genetic cause of infant death. The mortality rate of SMA has decreased from 2.36 per 100 individuals in 2012 to less than 0.75 per 100 individuals with SMA today. There is no doubt that PRV and similar federal policies contributed to the research and development success we've experienced in SMA, which may have been overlooked otherwise given the extremely small SMA population, which affects only 1 in 15,000 births in the United States. Cure SMA and the individuals with SMA we represent fully support the reauthorization of [RPD] PRV."

Maynard Friesz
Vice President of Policy & Advocacy, Cure SMA

a. Data available upon request; of note, companies have to notify FDA within 30 days when a PRV is sold or transferred; although this information is often made public there is no centralized, publicly available repository at FDA to track these changes in ownership. Moreover, although FDA requires PRVs to be identified by the BLA or NDA number for which they were awarded, that information is not always publicly disclosed, making it nearly impossible to trace each PRV from award to sale or redemption.

b. Additional data available upon request; See: https://www.federalregister.gov/documents/search?conditions%5Bagencies%5D%5B%5D=food-and-drug-administration&conditions%5Bterm%5D=+Notice+of+Approval+of+Product+Under+Voucher

In total, 23 of the 53 awarded RPD PRVs have been redeemed[b] (see Table 2). In most years, between one and three RPD PRVs are redeemed, with the most (five) RPD PRVs redeemed in 2022. Among the RPD PRVs that have been redeemed, most have been redeemed within four years of being awarded, and in many cases RPD PRVs were redeemed within a year or two of being awarded.[21]

Because RPD PRVs can be redeemed to receive priority review for a drug that otherwise would not qualify for priority review, it is important to consider for which drugs RPD PRVs were redeemed. As shown in Table 2, the 23 redeemed RPD PRVs resulted in FDA approvals across 20 different drugs. For two drugs, sponsors redeemed more than one RPD PRV. In each of these cases, PRVs were redeemed to speed up the FDA review for two different indications of use. One drug received a Complete Response Letter and is not currently FDA approved.

RPD PRVs were redeemed for drugs that treat a variety of diseases and conditions, in many cases representing areas of public health importance and unmet medical need, including six different drugs for rare diseases. Moreover, in several instances, the drugs for which RPD PRVs were redeemed were the only available therapies for their indication in their given drug class, often representing important innovation in their therapeutic area.

Only three of the drugs for which RPD PRVs were redeemed were among the top 50 drugs by Medicare Part B or D drug spending in 2022, and only about half are among the top 100. Notably, Medicare drug spending is compiled across all FDA-approved indications of use, which in many cases includes additional indications beyond those for which the RPD PRVs were redeemed. Therefore, the actual Medicare drug spending linked to the redeemed PRV is often a fraction of that total drug spending.

Conclusion

The RPD PRV program has been successful in helping to spur 53 new and innovative treatment options for children living with one of 39 different rare diseases. Unfortunately, the FDA's authority to grant RPD designations is set to expire on September 30, 2024, and the authority to grant RPD PRVs upon approval of an NDA or BLA will expire two years later.[26]

For the children who still lack treatment options for their rare condition, letting this program lapse would be a devastating step backward. Given the vast unmet medical needs that remain, Congress should act swiftly to reauthorize it to help resolve the treatment challenges faced by millions of children living with rare diseases.

Thank You

NORD would like to thank Senators Bob Casey (D-PA), Markwayne Mullin (R-OK), Sherrod Brown (D-OH), Susan Collins (R-ME), as well as Representatives Mike McCaul (R-TX), Anna Eshoo (D-CA), Gus Bilirakis (R-FL), Nanette Barragán (D-CA), Lori Trahan (D-MA), and Michael Burgess (R-TX) for introducing **H.R. 7384/ S.4583, the Creating Hope Reauthorization Act,** which would reauthorize the critical RPD PRV program for at least five more years.

NORD also thanks the nearly 200 patient organizations that have signed on to **letters of support** to Congress, urging swift consideration of the Creating Hope Reauthorization Act.

NORD®
National Organization for Rare Disorders

THE PATIENT PERSPECTIVE

Dreamsickle Kids Foundation

"The PRV program, designed to stimulate investment in the development of treatments for rare diseases, has been a beacon of hope for the Sickle Cell Disease (SCD) community.

Historically, SCD, which primarily affects individuals of African descent, has not seen the same level of medical innovation as other diseases. This discrepancy stems, in part, from a lack of incentive for pharmaceutical companies to invest in diseases that are perceived as less profitable. The PRVs program has shifted this landscape by making the development of drugs for rare diseases more attractive.

The impact of this incentive is tangible. In 2023, the SCD community saw the FDA approval of two groundbreaking gene therapies, one of which received a PRV, noting the spur in innovation for SCD. These therapies represent not just medical advancements but hope for a better quality of life for those affected by SCD. Prior to the establishment of the PRV program, progress toward such innovative treatments was painstakingly slow, hampered by economic and logistical hurdles that dissuaded investment in necessary research.

Furthermore, the PRV program has catalyzed research into SCD that extends beyond gene therapies. It has spurred interest in a range of potential treatments, each tailored to address the unique complexities of SCD. The program's success in encouraging research and development provides a model that, if continued, promises to yield even more advances.

In conclusion, the PRD PRV program has not only validated the needs of those living with rare diseases but has also provided them with the most essential resource: hope. Hope for effective treatments, hope for relief, and hope for a future where SCD can be managed or even cured. I strongly advocate for the continuation and expansion of this vital program, which has proven its worth by transforming potential into progress."

Georgene Glass
Executive Director,
Dreamsickle Kids Foundation, Inc.

A Final Note on Methodology

This analysis was based on an assessment of publicly available data in the Federal Registrar, relevant Security and Exchange Commission (SEC) filings, the FDA's regulatory summaries, relevant Centers for Medicare and Medicaid Services data, news and trade press reports, and relevant peer-reviewed and non-peer-reviewed publications. Every datapoint was independently validated by at least two NORD staff members, and extensively cross-referenced with other relevant data sets and publications. However, two factors significantly complicated the analysis. First, although data on PRV designations are vitally important and leading indicators of future drug approvals for rare pediatric diseases, this information is not publicly disclosed. We referenced the data available through the peer-reviewed literature, but this data was only available in aggregate form, which severely limited our ability to analyze trends in RPD designations. Second, although the FDA requires sponsors to identify RPD PRVs by their voucher number (i.e., the unique BLA or NDA number for which the RPD PRV was awarded) in all relevant FDA correspondence (e.g., notifications of the transfer or redemption of PRVs), this number is not consistently disclosed in relevant FDA or SEC filings, and not all transfers of RPD PRV ownership are consistently disclosed to the public (e.g., changes due to mergers and acquisitions); this makes it very difficult to trace each individual RPD PRV from award to sale and redemption.

About NORD®

With a more than 40-year history of advancing care, treatments, and policy, the National Organization for Rare Disorders (NORD) is the leading and longest-standing patient advocacy group for the 30 million Americans living with a rare disease. An independent 501(c)(3) nonprofit, NORD is dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 340 patient organization members, is committed to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. For more information, visit rarediseases.org.

NORD®
National Organization for Rare Disorders

THE PATIENT PERSPECTIVE

LGS FOUNDATION
LENNOX GASTAUT SYNDROME

"As the Executive Director of the Lennox-Gastaut Syndrome (LGS) Foundation and mother to a 31-year-old daughter with LGS, I am honored to provide testimony on the profound impact of the Priority Review Voucher (PRV) program for my family and for our rare disease community.

LGS is a catastrophic form of childhood-onset epilepsy that causes frequent seizures, developmental delays, and a severely diminished quality of life. For decades, treatment options were limited and families faced immense challenges caring for their children with uncontrollable seizures, severe behaviors and profound intellectual disability.

The PRV program has been transformative, incentivizing pharmaceutical companies to invest in developing novel therapies for LGS and other rare pediatric epilepsies that have given our families new hope.

Without the PRV incentive, it is unlikely companies would have prioritized developing treatments for the relatively small, but profoundly impacted LGS population. The PRV program has been vital in driving innovation and providing new therapeutic options that have improved lives for LGS families. Its reauthorization is crucial to sustaining progress for our community and many others impacted by rare pediatric diseases."

Tracy Dixon-Salazar
Executive Director,
LGS Foundation

Table 1: Products for Which RPD PRVs Have Been Redeemed

PRV Redeemed For	Year	Therapeutic Area	Rare Disease	Only Therapy In This Class[22]	Top 50 Medicare Spend[23] in 2022	Top 100 Medicare Spend[24] in 2022
Ajovy	2018	Migraine	-	-	-	-
Beovu	2019	Macular degeneration	-	-	-	-
Cosentyx	2020	Ankylosing spondylitis	-	-	yes	yes
Descovy	2019	HIV pre-exposure prophylaxis	-	yes	-	yes
Filgotinib[25]	2018	Rheumatoid arthritis	-	n/a	n/a	n/a
Imjudo	2022	Liver cancer	yes	yes	-	-
Juluca	2017	HIV treatment	-	yes	-	-
Mayzent	2019	Multiple Sclerosis	-	yes	-	-
Rimegepant Zydis ODT	2018	Migraine	-	-	-	-
Praluent	2015	Cholesterol lowering treatment	-	-	-	-
Rinvoq[c]	2019; 2022	Rheumatoid Arthritis; Ulcerative Colitis	-	-	-	yes
Skyrizi	2022	Crohn's Disease	yes	-	-	yes
Soliqua	2016	Type II Diabetes	-	-	-	-
Tyvaso DPI	2022	Pulmonary Arterial Hypertension	yes	-	yes	yes
Ultomiris[c]	2018; 2022	Paroxysmal Nocturnal Hemoglobinuria; Myasthenia gravis	yes	yes	yes	yes
Vabysmo	2022	Macular degeneration	-	-	-	yes
Vafseo	2020	Chronic Kidney Disease	-	-	-	-
Veozah	2023	Vasomotor symptoms due to menopause	-	yes	-	-
Vyvgart Hytrulo	2024	Myasthenia Gravis	yes	yes	-	yes
Xywav	2020	Narcolepsy	yes	-	-	-
Zeposia	2021	Ulcerative Colitis	-	-	-	-

c. two different PRVs were redeemed to support different supplemental applications for this product

Table 2: Rare Pediatric Diseases That Have Benefitted From a RPD PRV

Disease	Disease Characteristics and Common Manifestations	Disease Prevalence	Number of RPD PRVs Awarded	Years Awarded	FDA-Approved Therapies Before 2012
Duchenne muscular dystrophy	Genetic disorder characterized by progressive muscle degeneration and weakness. **Until relatively recently, boys with DMD usually did not survive much beyond their teen years.** Thanks to advances in cardiac and respiratory care, life expectancy is increasing and many young adults with DMD attend college, have careers, get married, and have children. Survival into the early 30s is becoming more common than before.[27]	20,000 children diagnosed globally each year	7	2016; 2017; 2020; 2020; 2021; 2023: 2024	none
Neuroblastoma/ neurofibromatosis type 1	Neuroblastoma is the most common pediatric solid tumor outside the brain, and the most common cancer in infants. For the **most severe cases the five-year survival rate is 36%.**[63]	700 to 800 children diagnosed in the US per year	3	2015; 2020; 2020	none
Spinal muscular atrophy	Spinal muscular dystrophy is a severe neuromuscular disease characterized by progressive muscular weakness. In general, an earlier disease onset is associated with more severe symptoms. **Patients less than six months of age at disease onset will likely die of respiratory failure before 2 years of age.** In contrast, those with adult-onset SMA may experience muscle weakness but will have a normal life expectancy.[28]	Impacts 1 out of every 10,000 births	3	2017; 2019; 2020	none
Hypophosphatasia	Rare genetic disorder that affects the development of bones and teeth. Patients with the perinatal or infantile form **often die in the first 5 years of life.**[29]	~ 1 in 100,000 people	2	2015; 2018	none
Cystic fibrosis	Genetic disease that damages lungs, digestive tract and other organs. **Median age of death before treatment was 34 years; thanks to treatments now predicted at 56 years.**[30]	30,000 individuals in the United States	2	2019; 2020	TOBI; Cayston; Pulomzyme
Epidermolysis bullosa	A rare condition that causes fragile, blistering skin in response to minor injury, even from heat, rubbing or scratching; in severe cases, the blisters may occur inside the body, such as the lining of the mouth or stomach; **morbidity can be significant, and patients with the most severe form are at major risk of death during the first few years of life.**[31]	500,000 people worldwide	2	2023, 2024	none
Morquio A syndrome	Rare congenital lysosomal storage disease, leading to problems with bone development, growth, and movement. **Left untreated, MPS IVA (Morquio A) patients do not generally survive beyond the 30 years;** with appropriate management, patients may survive beyond the age of 50 with some surviving over 70 years of age.[32]	Between 1 in 71,000 and 1 in 500,000 individuals	1	2014	none
Bile acid synthesis disorders	Inborn errors of bile acid synthesis, leading to a failure to produce normal bile acids. **Severe forms lead to death in the first 2 years of life.**[33]	1 in 50,000	1	2015	none

Disease	Disease Characteristics and Common Manifestations	Disease Prevalence	Number of RPD PRVs Awarded	Years Awarded	FDA-Approved Therapies Before 2012
Hereditary orotic aciduria	Rare inborn error of metabolism; generally causes anemia and/or other hematological issues, excessive urinary excretion of orotic acid, failure to thrive, and developmental delay and cognitive impairment. **If left untreated, it may result in refractory megaloblastic anemia, neurodevelopmental disabilities, and crystalluria.**[34]	Fewer than 30 known cases	1	2015	none
CLN2 disease (Batten disease)	Rare and rapidly progressing pediatric brain disorder; leading to progressive decline in language, cognitive, and motor skills, epileptic seizures, vision loss and **premature death, with the median age of 10 years old without treatment.**[35]	0.6 to 0.7 per million people	1	2017	none
Acute lymphoblastic leukemia	Cancer of the blood and bone marrow; survival rare has increased drastically thanks to therapies. Acute lymphoblastic leukemia is a cancer of the bone marrow and blood that progresses rapidly without treatment. **Without treatment, survival is only a few months.**[36] With current treatment regimens, about 80%–90% of people with ALL will reach a complete remission.[37]	Less than 10,000 per year	1	2017	Arranon; Clolar
Mucopoly-saccharidosis Type VII	Mucopolysaccharidosis type VII is an ultra-rare progressive inborn error of metabolism disease that affects many parts of the body and varies from mild to moderate or severe forms. **Severe forms lead to death during the first year of life.**[38]	1 in 250,000 live births	1	2017	none
Biallelic RPE65 mutation	Inherited retinal diseases due to RPE65 refers to a group of conditions that include retinitis pigmentosa, Leber congenital amaurosis and early-onset severe retinal dystrophy. **These forms differ in severity and may lead to complete blindness in children or young adults, if untreated.**[39]	1 in 50,000-100,000 cases	1	2018	none
Dravet Syndrome or Lennox-Gastaut Syndrome	Group of largely genetic epilepsies often leading to long-term seizures, cognitive decline, and mobility impairment; for **severe forms, seizures typically occur between the ages of 3 – 5, with 10-20 percent of Dravet syndrome patients passing away before adulthood.**[40]	1 in 15,700 and 0.1 to 0.28 per 100,000 people respectively	1	2018	Felbatol; Onfi; Lamictal; Topamax; Banzel
Adenosine Deaminase-Severe Combined Immunodeficiency	Inherited disorder that damages the immune system and causes severe combined immunodeficiency (SCID) and related frequent severe infections, behavioral and psychological problems, and occasionally deafness; **untreated it is typically fatal within the first 2 years of life.**[41]	1 in 500,000 live births	1	2018	none
Hemophagocytic/ lymphohistiocytosis	Aggressive and life-threatening syndrome of excessive immune activation leading to multi-organ failure; **most frequently affects infants from birth to 18 months of age; without treatment it is often fatal within 2 – 6 months of onset.**[42]	1.5 per million live births	1	2018	none

NORD® National Organization for Rare Disorders

Disease	Disease Characteristics and Common Manifestations	Disease Prevalence	Number of RPD PRVs Awarded	Years Awarded	FDA-Approved Therapies Before 2012
Lysosomal Acid Lipase deficiency	Inherited lysosomal storage disorder, which typically causes liver disease, developmental delays, and other health issues including cardiovascular issues and secondary blood disorders; left untreated, **children with the severe forms of the disease usually do not survive past their teenage years.**[43]	1 in 40,000 or more	1	2019	none
Pro-opiomelanocortin (POMC)	POMC deficiency affects the way the body stores and uses energy. The main symptoms include constant hunger and excessive feeding, known as hyperphagia. Hyperphagia leads to obesity by one year of age and **without treatment people with POMC deficiency remain obese throughout life.**[44]	approximately 50 cases reported	1	2020	none
Progeria	A rare, fatal, genetic condition of childhood with striking features resembling premature aging. At approximately nine to 24 months of age, affected children begin to experience profound growth delays, **and without treatment, children rarely survive past their 15th birthday. Treatment improves survival, but it is still not curative, and more research is ongoing.**[45]	approximately 400 children	1	2020	none
Primary hyperoxaluria type 1	Group of rare genetic and progressive metabolic disorders characterized by the accumulation oxalate in the kidneys and other organs, ultimately leading to end-stage renal disease and death from renal failure; **most cases manifest before age 10 and become progressively worse.**[46]	1 to 3 per million people	1	2021	none
Molybdenum Cofactor Deficiency	A rare condition characterized by progressive brain dysfunction. Babies with this condition appear normal at birth, but within a week they have difficulty feeding and develop intractable seizures; **median age at death is before 3 years of age.** Those who survive beyond the first few months without treatment often have severe developmental delays.[47]	1 in 100,000 to 200,000 births	1	2021	none
Hypopla-sminogenemia	A rare multi-system disease leading to thick growths on mucous membranes (e.g., in the eyes and mouth, ear, respiratory tract, kidneys etc.); **without adequate treatment it is associated with significant disability and can be life-threatening.**	1.6 people per million people	1	2021	none
Congenital athymia	Infants are born without a functioning thymus, **and without treatment, typically die by age two or three.**[48]	17 to 24 live births per year	1	2021	none
ß-thalassemia	Inherited blood disorder characterized by reduced levels of functional hemoglobin. **There are several forms and severity grades. People with beta thalassemia major live an average of 17 years and usually die by 30 years of age., mostly due to the cardiac complications of iron overload.**[49]	1 in 100,000 people	1	2022	none

NORD® National Organization for Rare Disorders

Disease	Disease Characteristics and Common Manifestations	Disease Prevalence	Number of RPD PRVs Awarded	Years Awarded	FDA-Approved Therapies Before 2012
Cyclin-dependent kinase-like 5	Rare developmental epileptic encephalopathy; onset of seizures usually at a very early age and **severe neurodevelopmental delay impacting cognitive, motor, speech, and visual function.** While this is not a life-threatening condition, treatment significantly reduced major motor seizure frequency.[50]	1 in 40,000 to 60,000 live births	1	2022	none
Achondroplasia	Achondroplasia is the most common skeletal dysplasia, characterized by disproportionately short stature (adult height about 4 feet) and an unusually large head (macrocephaly), short upper arms , leg bowing and craniocervical junction anomalies. Life expectancy is near normal but infants and children under 2 years of age have increased risk for death and without intervention, between 2% and 5% of children will die. **Mortality is increased compared to the general population.**[51]	1 in 20,000 to 30,000 people	1	2022	none
Familial intrahepatic cholestasis	Progressive liver disease, which typically leads to liver failure and an increased risk of hepatocellular carcinoma; **severe forms lead to liver failure in the first years of life.**	1 in 18,000 live births	1	2022	none
Cerebral adreno-leukodystrophy	Progressive peroxisomal disease, characterized by endocrine dysfunction (adrenal failure and sometimes testicular insufficiency), progressive myelopathy and peripheral neuropathy, and leukodystrophy; **age of onset is often in the first decade of life, and premature death typically occurs within 2-4 years of symptom onset.**[52]	1 in 5,000 to 17,000 live births	1	2022	none
Alpha-mannosidosis	Alpha-mannosidosis is a rare lysosomal storage disorder caused by a deficiency of the enzyme alpha-D-mannosidase. It is characterized by progressive mental and cognitive impairment, hearing loss, facial dysmorphism and skeletal abnormalities, behavioral problems, among other symptoms. **In the most severe cases, an affected fetus may die before birth while others may have milder symptoms that progress more slowly.** People with later-onset alpha-mannosidosis may survive into their fifties.[53]	1 in 300,000 to 1,000,000 live births	1	2023	none
Friedreich's ataxia	Friedreich's ataxia is a progressive, neurodegenerative movement disorder, leading to frequent falling, fatigue and progressive difficulty walking due to impaired ability to coordinate voluntary movements (ataxia); typical age of onset between 10 and 15 years. **Commonly, patients survive to 25-30 years of age, although some patients have survived into the sixth and seventh decades, especially if they are free of heart disease and diabetes.**[54]	1 in 40,000 people	1	2023	none

Disease	Disease Characteristics and Common Manifestations	Disease Prevalence	Number of RPD PRVs Awarded	Years Awarded	FDA-Approved Therapies Before 2012
Rett Syndrome	Rett syndrome is a progressive neurodevelopmental disorder that almost exclusively affects females. Infants with Rett syndrome usually develop normally until 7 to 18 months, and then they lose previously acquired skills (developmental regression). Due to its rarity, very little has been published about life expectancy. Data from a Natural History Study determined that there is a **90% chance of reaching age 20, a greater than 75% chance of reaching age 30, a greater than 65% chance of reaching age 40, and a greater than 50% chance of reaching age 50.** As improved nutrition and overall care are provided, these probabilities are expected to improve.[55]	1 in 23,000 live female births	1	2023	none
Activated PI3K delta syndrome	Activated PI3K is a rare inborn error of immunity characterized by frequent infections, autoimmune disease, and lymphoproliferation; **age of onset tends to be in early childhood (before 5 years).[56] Despite available treatments, survival appears to be shortened from the average lifespan and the most common cause of death was lymphoma, followed by complications from hematopoietic stem cell transplantation (HSCT).** New treatments are needed to decrease the risk of death from lymphoma and other cancers as well as infection.[57]	unknown	1	2023	none
fibrodysplasia ossificans progressiva	Rare genetic connective tissue disorder characterized by the abnormal development of bone in areas of the body where bone is not normally present (heterotopic ossification), such as the ligaments, tendons, and skeletal muscles; **leads to shortened life expectancy and most patients require help with walking by age 30.**	1 in 2,000,000 people	1	2023	none
CHAPLE Disease	Inherited immune disease leading to severe gastro-intestinal problems, severe lung infections, and severe blood clots, among other systems. **Severe thrombotic vascular occlusions (blockage of blood vessels) can occur which can be life-threatening.**	fewer than 100 worldwide	1	2023	none
Acid sphingomyelinase deficiency	Rare, progressive, and often fatal lysosomal storage disease often associated with developmental delays, regression, and learning disability; **the most severe infantile forms are typically fatal by 3 years of age.**	1 in 250,000 people	1	2023	none

Disease	Disease Characteristics and Common Manifestations	Disease Prevalence	Number of RPD PRVs Awarded	Years Awarded	FDA-Approved Therapies Before 2012
Congenital thrombotic thrombocytopenic purpura (cTTP)	Congenital thrombotic thrombocytopenic purpura is a rare blood disorder in which blood clots form in the small blood vessels throughout the body. Most people respond well to treatment, which can prevent long-term organ complications due to relapses. However, life expectancy largely depends on severity and whether other underlying conditions are present. **Without treatment, congenital TTP is fatal (mortality rate > 90%).** Therapeutic plasma exchange and plasma infusion has led to a decrease in the mortality rate to around 15% and prevents long term organ damage.[58]	Fewer than 1,000 people in the United States	1	2024	none
Sickle Cell Disease (SCD)	A rare blood disorder that is inherited in an autosomal recessive manner. It is characterized by the presence of sickle, or crescent-shaped, red blood cells (erythrocytes) in the bloodstream. **People with SCD have a reduced life expectancy of 20 years less than the general population.**[59]	70,000 to 100,000 people in the United States	1	2024	none
Metachromatic leukodystrophy (MLD)	Metachromatic leukodystrophy (MLD) is a rare hereditary disease characterized by accumulation of fats called sulfatides in the cells of the nervous system that produce myeline, the substance that surrounds the nerves, resulting in progressive destruction of white matter (leukodystrophy) throughout the nervous system. Symptoms include progressive deterioration of intellectual functions and motor skills, such as the ability to walk, loss of sensation in the extremities (peripheral neuropathy), incontinence, seizures, paralysis, an inability to speak, blindness, hearing loss, and, eventually, loss of awareness of the surroundings.[60] The prognosis for MLD is poor. Survival depends on the form of the disease. **Affected children with the infantile form die by age 5.** Research to find a cure is ongoing.[61]	Between 1 in 40,000 and 1 in 160,000	1	2024	none

Endnotes

1. Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), Office of Orphan Products Development (OOPD), & Office of Pediatric Therapeutics (OPT). (2019, July). Rare pediatric disease priority review vouchers. https://www.fda.gov/media/90014/download
2. Government Accountability Office. (2021, October). *RARE DISEASES Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial.* https://www.gao.gov/assets/gao-22-104235.pdf
3. Fleming, S. (2020, February 29). One in three children with a rare disease won't live to see their fifth birthday. ThePrint. https://theprint.in/science/one-in-three-children-with-a-rare-disease-wont-live-to-see-their-fifth-birthday/372994/
4. U.S. Department of Health and Human Services. (2023, March 21). Rare disease day at NIH 2023: Putting hope into action. National Center for Advancing Translational Sciences. https://ncats.nih.gov/pubs/features/rare-disease-day-at-NIH-2023-putting-hope-intoaction#:~:text=Of%20the%20more%20than%2010%2C000,(FDA)%E2%80%93approved%20treatments.
5. A third priority review voucher program was established for material threat medical countermeasures (MCMs) by the passage of the 2016 21st Century Cures Act. See: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/21st-century-cures-act-mcm-related-cures-provisions#MCMprovisions
6. Ridley, D. (n.d.). Home. Priority Review Vouchers. https://sites.fuqua.duke.edu/priorityreviewvoucher/
7. Data shown until December 31, 2023
8. Drug sponsors can sell the PRV an unlimited number of times (but must notify FDA each time they do so). Sponsors can redeem the PRV for adult or pediatric diseases including rare and non-rare diseases. Drug sponsors must notify FDA of their intent to redeem a PRV at least 90 days ahead of the NDA or BLA filing date and pay the increased user fees for priority compared to standard review ($1,314,206 for priority review in FY2024). Priority review shortens FDA's target review time from 10 to 6 months. Of note, FDA may determine that the application is deficient and either request additional information, in which case the 6-month timeline may not be met or issue a complete response letter (both cases have in fact occurred).
9. Center for Biologics Evaluation and Research. (2019, July). *Rare pediatric disease priority review vouchers*. US Food and Drug Administration. https://www.fda.gov/media/90014/download
10. Center for Biologics Evaluation and Research. (2019, July). *Rare pediatric disease priority review vouchers*. US Food and Drug Administration. https://www.fda.gov/media/90014/download
11. Center for Biologics Evaluation and Research. (2019, July). *Rare pediatric disease priority review vouchers.* US Food and Drug Administration. https://www.fda.gov/media/90014/download
12. Contrary to PRV awards and redemptions, or orphan drug designations, RPD designations are NOT made public; 2012 – 2022 is the only data available. See Mease et al. 2024 (full citation below).
13. Mease, C., Miller, K. L., Fermaglich, L. J., Best, J., Liu, G., & Torjusen, E. (2024). *Analysis of the first ten years of FDA's rare pediatric disease priority review voucher program: designations, diseases, and drug development.* Orphanet Journal of Rare Diseases. https://link.springer.com/epdf/10.1186/s13023-024-03097-x?sharing_token=tVsd-cxtCuGoLKGG18G02G_BpE1tBhCbnbw3BuzI2ROyCDnBKI_41BmSn3a_5qr-zjgrLXsufvRX0wtQEnALK9Za3v_5zjNTa3quYxLJ0LC4dnFV94TbHqovQ6Vq5sRWu7_u2v1C7h16jaeLChSswkyx4eSqy_KycTNie1qfGSM
14. U.S. Government Accountability Office. (2020, January 31). *Drug development: FDA's Priority Review Voucher Programs.* Drug Development: FDA's Priority Review Voucher Programs | U.S. GAO. https://www.gao.gov/products/gao-20-251
15. U.S. Government Accountability Office. (2020, January 31). Drug development: FDA's Priority Review Voucher Programs. Drug Development: FDA's Priority Review Voucher Programs | U.S. GAO. https://www.gao.gov/products/gao-20-251
16. U.S. Government Accountability Office. (2020, January 31). *Drug development: FDA's Priority Review Voucher Programs.* Drug Development: FDA's Priority Review Voucher Programs | U.S. GAO. https://www.gao.gov/products/gao-20-251
17. Orphanet: About orphan drugs. (n.d.). https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN
18. Center for Drug Evaluation and Research. (n.d.). *CDER continues to advance rare disease drug development.* U.S. Food and Drug Administration. https://www.fda.gov/drugs/our-perspective/cder-continues-advance-rare-disease-drug-development-new-efforts-including-accelerating-rare-disease#:~:text=New%20Drug%20Approvals%20for%20Rare,for%20patients%20with%20rare%20diseases.
19. Mezher, M., Brennan, Z., & Gaffney, A. (2020a, February 24). Regulatory explainer: Everything you need to know about FDA's priority review vouchers. RAPS. https://www.raps.org/news-and-articles/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know
20. Based on an analysis of SEC files and FDA regulatory summaries; data not shown, available upon request.
21. Additional data available upon request; See: https://www.federalregister.gov/documents/search?conditions%5Bagencies%5D%5B%5D=food-and-drug-administration&conditions%5Bterm%5D=+Notice+of+Approval+of+Product+Under+Voucher
22. In the same therapeutic area as defined by drug class on https://dailymed.nlm.nih.gov/dailymed/
23. Based on Medicare Part B or Part D spent, whichever is lower; see
24. Based on Medicare Part B or Part D spent, whichever is lower; see
25. Has not been approved for use by the FDA
26. Office of Orphan Products Development. (2024, March). Rare Pediatric Disease Designation and Priority Review Voucher Programs. US Food and Drug Administration. https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/rare-pediatric-disease-designation-and-priority-review-voucher-programs
27. https://www.mda.org/disease/duchenne-muscular-dystrophy
28. https://www.ncbi.nlm.nih.gov/books/NBK533981/
29. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7436954/
30. https://www.cff.org/managing-cf/understanding-changes-life-expectancy
31. https://www.niams.nih.gov/health-topics/epidermolysis-bullosa
32. https://www.orpha.net/en/disease/detail/582
33. https://rarediseases.org/rare-diseases/bile-acid-synthesis-disorders/
34. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10043439/
35. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10104757/
36. https://www.lls.org/leukemia/acute-lymphoblastic-leukemia
37. https://cancer.ca/en/cancer-information/cancer-types/acute-lymphoblastic-leukemia-all/prognosis-and-survival/survival-statistics
38. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893087/
39. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8268668/
40. https://dravetsyndromenews.com/dravet-syndrome-prognosis/
41. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4985714/
42. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9469671

NORD®
National Organization for Rare Disorders

43. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331358/
44. https://medlineplus.gov/genetics/condition/proopiomelanocortin-deficiency/
45. https://www.tandfonline.com/doi/full/10.1517/21678707.2014.970172
46. https://www.ncbi.nlm.nih.gov/books/NBK558987/
47. https://www.childneurologyfoundation.org/disorder/molybdenum-cofactor-deficiency-type-a/
48. https://primaryimmune.org/understanding-primary-immunodeficiency/types-of-pi/congenital-athymia#:~:text=Without%20a%20thymus%2C%20children%20with,by%20age%20two%20or%20three.
49. https://www.aafp.org/pubs/afp/issues/2009/0815/p339.html
50. https://www.cdkl5.com/about-cdkl5
51. https://www.sciencedirect.com/science/article/pii/S875632822100034X
52. https://www.childrenshospital.org/conditions/adrenoleukodystrophy-ald#:~:text=Cerebral%20adrenoleukodystrophy%2C%20also%20known%20as,highly%20unlikely%20to%20develop%20CALD.
53. https://medlineplus.gov/genetics/condition/alpha-mannosidosis/
54. https://emedicine.medscape.com/article/1150420-followup#
55. https://www.rettsyndrome.org/about-rett-syndrome/faqs/
56. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10432830/
57. https://pubmed.ncbi.nlm.nih.gov/38280023/
58. https://www.orpha.net/en/disease/detail/93583
59. https://ashpublications.org/bloodadvances/article/7/13/3276/494890/Long-term-survival-with-sickle-cell-disease-a
60. https://medlineplus.gov/genetics/condition/metachromatic-leukodystrophy/
61. https://www.ninds.nih.gov/health-information/disorders/metachromatic-leukodystrophy
62. https://www.medicalnewstoday.com/articles/neuroblastoma#:~:text=Neuroblastoma%20in%20adults%20is%20extremely,help%20treatment%20be%20more%20effective

Alone we are rare. Together we are strong.®

NORD®
National Organization for Rare Disorders