Reauthorize the Rare Pediatric Disease Priority Review Voucher Program

Support H.R. 7384, the Creating Hope Reauthorization Act

As many as half of the individuals living with a rare disease are children. Rare pediatric disease (RPD) priority review vouchers (PRVs) offer a crucial incentive to develop therapies for children with devastating and often life-threatening rare conditions. Timely reauthorization of this vital program before the September 30, 2024, deadline is crucial to address the significant unmet medical needs in pediatric rare disease communities. We would like to thank Reps. 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, the Creating Hope Reauthorization Act, and all co-sponsors for supporting the bill. On behalf of the are disease community, NORD urges Congress to quickly pass this bill.

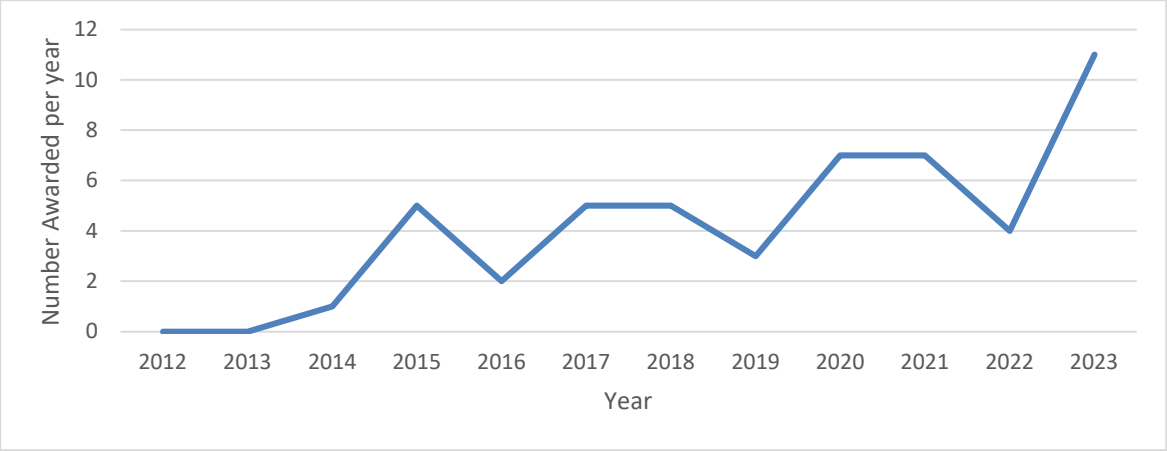
Key Facts about the Rare Pediatric Disease (RPD) Priority Review Voucher (PRV) Program

- Since the program's inception in 2012, **53 PRVs** have been awarded across **39 rare pediatric diseases.**[1] Of these diseases, many typically lead to death before the children reach adulthood and only three had any FDA-approved treatments before 2012 (see Table 1 for more details).

- To date, **23 RPD PRVs** have been redeemed for priority review of 21 different drugs[2] for a variety of diseases, including 6 drugs that treat rare diseases. **Only three** of the drugs for which vouchers were redeemed were among the top 50 drugs by Medicare Part B or D spent in 2022, and **fewer than half** were among the top 100 drugs Medicare Part B or D spent (see Table 2 for more details).[3]

- 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[4] (see Figure 1, Table 2).

Figure 1: Rare Pediatric Disease Priority Review Vouchers Awarded Per Year[5]



[1] Data until April 30, 2024.
[2] Of which 20 have received at least one FDA-approved indication.
[3] Medicare drug spent for total product sales, not limited to the indication(s) for which PRVs were redeemed.
[4] i.e., in 2020 or later.
[5] Data shown until December 31st 2023

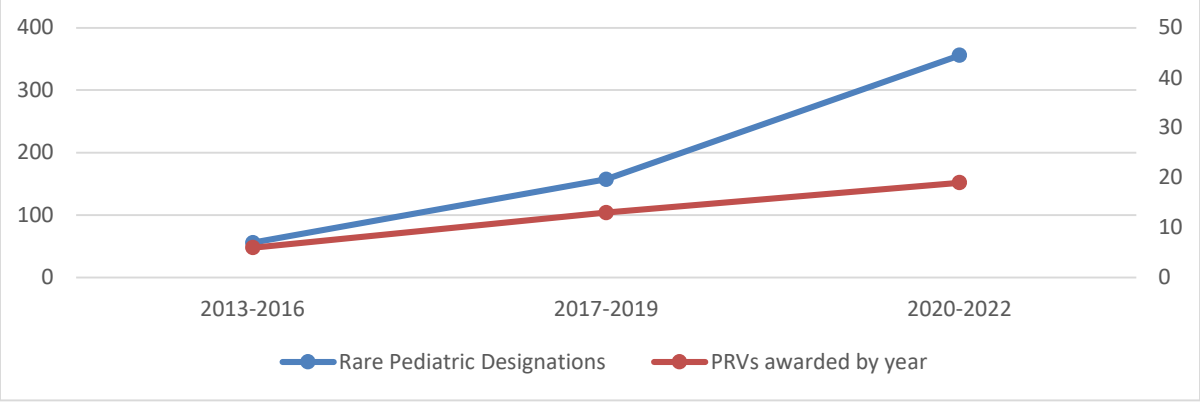
How the RPD PRV Program works

The first PRV program began in 2006 as an incentive to support the development of drugs for neglected tropical diseases and was expanded in 2012 to include rare pediatric diseases.[6] Under this program, companies that develop safe and effective novel therapies for rare pediatric diseases – rare diseases that primarily affect children and are serious or life-threatening in children - 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.[7,8]

Sponsors studying rare pediatric diseases are strongly encouraged to obtain a RPD designation, which typically occurs very early in the drug development program. RPD PRVs are only granted once an NDA or BLA is approved, after extensive clinical studies have shown that the product is safe and effective, and after FDA determines that all other relevant requirements linked to the PRV program are met.[9,10]

To date, the RPD PRV program has helped spur rare disease drug development in pediatric populations, with 53 RPD PRVs awarded for 39 different rare pediatric diseases by April 30th, 2024 (see Table 1). FDA's authority to grant RPD designations is currently set to expire on September 30th, 2024, and the authority to grant RPD PRV upon approval of an NDA or BLA will expire two years later.[11]

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



[6] 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

[7] 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).

[8] 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

[9] Ibid.

[10] Ibid.

[11] 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

The RPD PRV program supports pediatric rare disease drug development

A total of 53 RPD PRVs have been awarded as of April 30, 2024, reflecting a steady upward trend in pediatric rare disease drug development since the program was first authorized for rare diseases in 2012. Among the 39 rare pediatric diseases for which vouchers were awarded, only three 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 to date were awarded since 2019, the year the last prior program assessment by the Government Accountability Office (GAO) ended.[14,15,16] At the time of GAO's analysis, the program had only been in place for 7 years; at that time, 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 development programs incentivized by the RPD PRV program had not yet received FDA approval in 2019.[17]

RPD PRVs are typically sold quickly, and rarely redeemed for 'blockbuster' drugs

An integral component of the RPD PRV program is that companies can sell or transfer RPD PRVs to another company, creating important additional revenue streams for biopharmaceutical companies.[18] To date, 29 of the 53 awarded RPD PRVs have been sold, and others have transferred ownership as part of company mergers or acquisitions.[19] Almost all of the RPD PRV sales to date occurred within a year of award (mostly within 6 months or less), and about half of the sold RPD PRVs have been redeemed to date. This trend is consistent with that seen among RPD PRVs that were not sold. In total, 23 of the 53 awarded RPD PRVs have been redeemed, spread out over the past decade (see Table 3).[20] In most years, between one and three RPD PRVs are redeemed, with a high of 5 RPD PRVs redeemed in 2022. Among the RPD PRVs that have been redeemed, most have been redeemed within 4 years of award, and in many cases RPD PRVs were redeemed within a year or two of award.

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[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 ofRare Diseases. https://link.springer.com/epdf/10.1186/s13023-024-03097-x?sharing_token=tVsd-cxtCuGoLKGG18G02G_BpE1tBhCbnbw3BuzI2ROyCDnBKl_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] Ibid.

[16] Ibid.

[17] Orphanet: About orphan drugs. (n.d.). https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=EN

[18] 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

[19] 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.

[20] 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

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 the 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 case, PRVs were redeemed to speed up the FDA review for two different indications of use), and one drug received a Complete Response Letter (CRL) and is not currently FDA approved.

Of note, only three of the drugs for which RPD PRVs were redeemed were among the top 50 drugs by Medicare Part B or D drug spent in 2022, and only about half are among the top 100 (notably, drug spent is compiled across all FDA-approved indications of use, in many cases including additional uses beyond those for which the RPD PRVs were redeemed; the actual drug spent linked to the redeemed PRV is therefore often a fraction of that shown here). 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 6 different orphan drugs. Moreover, in several instances the drugs for which RPD PRVs were redeemed are the only available therapies for their indication in their given drug class, often representing important innovation in their therapeutic area.

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, 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 data point 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 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 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. For questions, concerns, or access to additional data sets please contact Karin Hoelzer, Senior Director, Policy and Regulatory Affairs at khoelzer@rarediseases.org or Hayley Mason, Policy Analyst, at hmason@rarediseases.org.

Table 1: 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.**[21]	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 .	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.[22]	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**.[23]	~ 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.**[24]	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**	500,000 people worldwide	2	2023, 2024	none

[21] https://www.mda.org/disease/duchenne-muscular-dystrophy
[22] https://www.ncbi.nlm.nih.gov/books/NBK533981/
[23] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7436954/
[24] https://www.cff.org/managing-cf/understanding-changes-life-expectancy

	can be significant, and patients with the most severe form are at major risk of death during the first few years of life.[25]				
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**.**[26]	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.**[27]	1 in 50,000	1	2015	none
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.** [28]	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.**[29]	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.**[30] With current treatment regimens, about 80%–90% of people with ALL will reach a complete remission.[31]	Less than 10,000 per year	1	2017	Arranon; Clolar
Mucopolysaccharidosis 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	1 in 250,000 live births	1	2017	none

[25] https://www.niams.nih.gov/health-topics/epidermolysis-bullosa
[26] https://www.orpha.net/en/disease/detail/582
[27] https://rarediseases.org/rare-diseases/bile-acid-synthesis-disorders/
[28] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10043439/
[29] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10104757/
[30] https://www.lls.org/leukemia/acute-lymphoblastic-leukemia
[31] https://cancer.ca/en/cancer-information/cancer-types/acute-lymphoblastic-leukemia-all/prognosis-and-survival/survival-statistics

	forms. **Severe forms lead to death during the first year of life**.[32]				
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.**[33]	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.**[34]	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.**[35]	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.**[36]	1.5 per million live births	1	2018	none
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.**[37]	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**	approximately 50 cases reported	1	2020	none

[32] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4893087/
[33] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8268668/
[34] https://dravetsyndromenews.com/dravet-syndrome-prognosis/
[35] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4985714/
[36] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9469671
[37] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331358/

	treatment people with POMC deficiency remain obese throughout life.[38]				
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.** [39]	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.**[40]	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.[41]	1 in 100,000 to 200,000 births	1	2021	none
Hypoplasminogenemia	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.**[42]	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**	1 in 100,000 people	1	2022	none

[38] https://medlineplus.gov/genetics/condition/proopiomelanocortin-deficiency/
[39] https://www.tandfonline.com/doi/full/10.1517/21678707.2014.970172
[40] https://www.ncbi.nlm.nih.gov/books/NBK558987/
[41] https://www.childneurologyfoundation.org/disorder/molybdenum-cofactor-deficiency-type-a/
[42] https://primaryimmune.org/understanding-primary-immunodeficiency/types-of-pi/congenital-athymia#:~:text=Without%20a%20thymus%2C%20children%20with,by%20age%20two%20or%20three.

	years of age., mostly due to the cardiac complications of iron overload.[43]				
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.[44]	1 in 40,000 to 60,000 live births	1	2022	none
Achondroplasia	Achondroplasia is the most common skeletal dysplasia, characterized by disproportionated 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.**[45]	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 adrenoleukodystrophy	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.**[46]	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	1 in 300,000 to 1,000,000 live births	1	2023	none

[43] https://www.aafp.org/pubs/afp/issues/2009/0815/p339.html
[44] https://www.cdkl5.com/about-cdkl5
[45] https://www.sciencedirect.com/science/article/pii/S875632822100034X
[46] https://www.childrenshospital.org/conditions/adrenoleukodystrophy-ald#:~:text=Cerebral%20adrenoleukodystrophy%2C%20also%20known%20as,highly%20unlikely%20to%20develop%20CALD.

	alpha-mannosidosis may survive into their fifties.[47]				
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.**[48]	1 in 40,000 people	1	2023	none
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.[49]	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).**[50] **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.[51]	unknown	1	2023	none

[47] https://medlineplus.gov/genetics/condition/alpha-mannosidosis/
[48] https://emedicine.medscape.com/article/1150420-followup#
[49] https://www.rettsyndrome.org/about-rett-syndrome/faqs/
[50] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10432830/
[51] https://pubmed.ncbi.nlm.nih.gov/38280023/

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
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.[52]	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.[53]**	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	Between 1 in 40,000 and 1 in 160,000	1	2024	none

[52] https://www.orpha.net/en/disease/detail/93583
[53] https://ashpublications.org/bloodadvances/article/7/13/3276/494890/Long-term-survival-with-sickle-cell-disease-a

	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.[54] 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.[55]				
WHIM Syndrome	WHIM syndrome is a rare genetic disease that causes the body's immune system to not function properly. WHIM syndrome reduces the number of mature neutrophils and lymphocytes (types of white blood cells important in fighting infection) circulating within the body. **While symptoms vary, patients with WHIM syndrome can have recurrent infections, including pneumonia, sinusitis, and skin infections and are at risk for life-threatening bacterial and viral infections**.[56]	It is estimated to occur in about 1 in 5 million live births. Approximately 60 cases have been reported in the medical literature	1	2024	none

[54] https://medlineplus.gov/genetics/condition/metachromatic-leukodystrophy/
[55] https://www.ninds.nih.gov/health-information/disorders/metachromatic-leukodystrophy
[56] https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-first-drug-whim-syndrome-rare-disorder-can-lead-recurrent-life-threatening-infections

Table 2: The diseases for which RPD PRVs have been redeemed

PRV redeemed for	Year	Therapeutic Area	Rare Disease	Only therapy in this class[57]	Top 50 Medicare spent in 2022[58]	Top 100 Medicare spent in 2022[59]
Ajovy	2018	Migraine	-	-	-	-
Beovu	2019	Macular degeneration	-	-	-	-
Cosentyx	2020	Ankylosing spondylitis	-	-	yes	yes
Descovy	2019	HIV pre-exposure prophylaxis	-	yes	-	yes
Filgotinib [60]	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*	2019; 2022	Rheumatoid Arthritis; Ulcerative Colitis	-	-	-	yes
Skyrizi	2022	Chron's Disease	yes	-	-	yes
Soliqua	2016	Type II Diabetes	-	-	-	-
Tyvaso DPI	2022	Pulmonary Arterial Hypertension	yes	-	yes	yes
Ultomiris*	2018; 2022	Paroxysmal Nocturnal Hemoglobinuria;	yes	yes	yes	yes

[57] In the same therapeutic area as defined by drug class on https://dailymed.nlm.nih.gov/dailymed/
[58] Based on Medicare Part B or Part D spent, whichever is lower; see https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug and https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-b-spending-by-drug
[59] Ibid.
* two different PRVs were redeemed to support different supplemental applications for this product
[60] Has not been approved for use by the FDA

		Myasthenia gravis				
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	-	-	-	-