Childhood Dementia Global Clinical Trial Landscape Analysis

A Childhood Dementia Initiative report

childhood dementia INITIATIVE

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Acknowledgments

In the spirit of reconciliation, Childhood Dementia Initiative acknowledges the Traditional Custodians of country throughout Australia and their connections to land, sea and community. We pay our respect to their elders past and present and extend that respect to all Aboriginal and Torres Strait Islander peoples today. Aboriginal and Torres Strait Islander readers are warned that this report may contain images and words of deceased persons.

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- Tiffany Boughtwood, Australian Genomics (Chair)
- Professor John Christodoulou AM, Murdoch Children's Research Institute and the University of Melbourne
- Professor Michelle Farrar, Sydney Children's Hospital and the University of NSW
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- Associate Professor Leszek Lisowski, Children's Medical Research Institute and the University of Sydney
- Professor Peter Schofield AO, Neuroscience Research Australia (NeuRA)
- Dr Nicholas Smith, Women's and Children's Health Network and University of Adelaide

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Executive summary

Childhood dementia is caused by more than 100 rare genetic disorders which are estimated to affect 1 in every 2,900 births.[1] Half of the children living with a childhood dementia disorder will die before they're 10 years old, most won't reach adulthood, and all will die prematurely. Not only are the lives of children with dementia short, they are also extremely difficult – defined by pain, distress and progressive loss of cognition and abilities. Childhood dementia remains terminal for all children. Survival rates have not notably improved in recent decades. This is unlike other conditions such as childhood cancer, which has seen death rates halve[2], and cystic fibrosis, which has seen life expectancy double[3].

This report explores the current childhood dementia clinical trial landscape, and identifies trends and issues of concern. The level of clinical trial activity was compared to childhood cancer – a group of paediatric conditions that causes a similar number of deaths as childhood dementia each year[1].

For most children with dementia, there are no treatments available beyond palliative symptom management. Clinical trials offer the only opportunity children might have to access potential disease modifying treatments. Trials are also essential for treatments and cures to be made available to the broader patient population in the future.

Despite the huge unmet need, the analysis shows a severe and continued lack of activity to develop treatments and cures for childhood dementia globally. Beyond this deficiency in activity, 2 additional concerning trends were identified: a slowing of clinical trial activity and trials being stifled by bureaucracy and lack of funding.

Key findings

- **Globally, clinical trial activity for childhood dementia slowed** in the 5 year period from 2018 to 2023. This was despite the continued growth of clinical trial activity overall.
- In addition to fewer trials being initiated, **evidence was found of multiple trials halting or failing to initiate at a late stage due to regulatory and/or commercial barriers.**
- **Opportunities for children to enrol in clinical trials globally are lacking.** Per patient, there were 24-fold fewer clinical trials recruiting children with dementia than children with cancer in December 2023. This is consistent with the historic lack of trials. Over the past 23 years, 21-fold fewer trials were initiated per child with dementia compared to childhood cancer.
- **Globally, clinical trial activity is inconsistent with the incidence of the individual disorders.** Some relatively common childhood dementia disorders have little or no clinical trial activity. This is indicative of the fragmented and siloed research landscape.
- **In Australia the disparity was even greater**:
    - Per patient in December 2023, there were 43 times more clinical trials recruiting children with cancer than children with dementia.
    - Of 54 clinical trials recruiting patients globally, only 2 of these trials were listed as recruiting in Australia, and no new trials started in Australia in 2023.

Recommendations

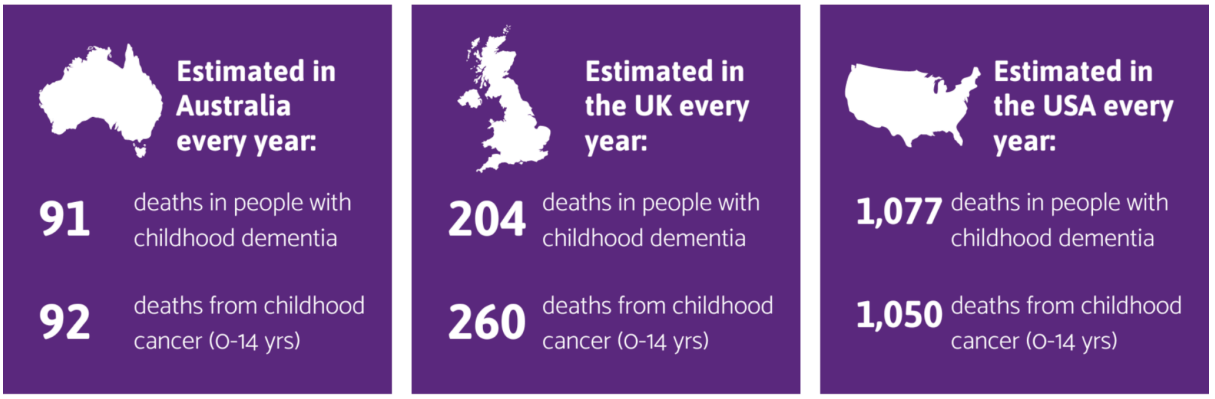
- **Regulatory bodies to ensure that the unique characteristics of this population and great unmet need are taken into account.** This must include allowing a flexible approach to clinical trial designs and the utilisation of surrogate endpoints.
- To address the current and historic inequity, measures must be taken to **improve the commercial viability** of childhood dementia clinical trials including incentives, alternative funding models and improved clinical trial efficiency.
- **Increased funding for research** across the pipeline, from basic to translational research, to increase the development of potential therapeutics for clinical trials. Consideration should be given to relatively neglected subtypes of childhood dementia and to harnessing economies of scale by encouraging concurrent research on multiple conditions in parallel.
- In Australia, urgent action is required to improve clinical trial readiness, infrastructure, and capacity. This will enable locally initiated trials and **attract more trials to Australia** from overseas.

Advances in genomics and drug development in recent decades have put effective treatments for childhood dementia within reach. However, **inadequate research funding, inflexible regulatory processes and commercial constraints are preventing progress.** Action must be taken globally to remove the roadblocks that are denying current and future generations of children born with devastating childhood dementia conditions access to effective therapies.

Introduction

A recent study[1] showed that childhood dementia is caused by more than 145 rare genetic disorders and burden of disease analysis estimated that:

- 1 in every 2,900 babies is born with a childhood dementia disorder. Annually, this equates to 107 babies born in Australia, 240 in the UK, and 1,262 in the USA.
- All children living with a childhood dementia disorder will die prematurely: half before they're 10 years old, 70% before they reach adulthood.
- 91 people in Australia, 204 in the UK and 1,077 in the US died in 2021 due to childhood dementia respectively. For comparison, 92 children aged 0-14 years die annually in Australia from childhood cancer, 260 in the UK and 1,050 in the USA.



Not only are the lives of children with dementia short, but they are extremely difficult.[4–7] As a result of the progressive cognitive decline, children with dementia lose communication skills and experience changes in eating, motor function, sleep, and behaviour as well as complex medical issues. Parents watch their child(ren) suffer increasing levels of confusion, distress, unhappiness, and pain. Childhood dementia is also associated with significant carer stress, anxiety, and challenges in care. Psychosocial challenges are numerous and encompass physical, economic, social, emotional and psychological implications.[4,7]

There are no cures for childhood dementia. Clinical trials offer the only prospect of survival and access to potentially disease-modifying treatments for most children living with dementia today. Analysis of clinical trial activity gives a snapshot of the current opportunities for families to participate in trials. It also gives insight into the inadequate level of research and attention that these disorders have received in recent decades.

This report builds on the *Childhood Dementia Global Landscape Analysis* and *State of Childhood Dementia* reports published in 2022[8,9]. The current analysis includes additional childhood dementia conditions identified, and updated prevalence figures reported, in the childhood dementia burden of disease analysis published in *Brain* in 2023[1].

The level of childhood dementia clinical trial activity was compared to childhood cancer, another severe group of paediatric diseases which cause a similar number of deaths each year in high income countries such as Australia, USA and UK[1]. Approximately 1.3 times more children are undergoing treatment for cancer at any one time than the number living with dementia and this was taken into account in our analysis (Supplementary table 1). Thanks to intensive medical research in recent decades, there have been impressive gains in childhood cancer survival and in high-income countries, more than 80% of children with cancer are cured.[10] Childhood dementia has had no notable overall improvement in survival in recent decades. We endeavour to learn from the progress in childhood cancer and achieve similar impact and improvements in length and quality of life for children with dementia.

Methods

Each individual childhood dementia disorder (as drawn from the most recent burden of disease analysis[1]) was searched in the clinical trials database, clinicaltrials.gov. Analysis included all trials registered before 31 December 2023. First launched in 2000, this database is the most comprehensive record of clinical trials globally and contains listings for almost half a million studies in over 200 countries. Search terms included the disease name, synonyms, and acronyms for each childhood dementia condition. All clinical trials found for each condition were verified to ensure that they were indeed a trial relevant to childhood dementia based on the clinical trials description. This analysis focused on interventional studies and excluded those that were observational, such as natural history studies and patient registries. Trials that were 'withdrawn' – stopped early, before enrolling their first participants - were excluded.

All clinical trial data available on clinicaltrials.gov for 145 childhood dementia disorders was collated into a single spreadsheet. Conditions without any trials available were noted as such.

Analysis of the number of trials for each individual childhood dementia condition was carried out by extracting data pertaining to the number of interventional trials and plotting against the incidence of each condition as listed in Elvidge et al. (2023).

To analyse overall trends in all childhood dementia trials, any duplicate trials were removed such that each trial was represented only once (even if the trial was relevant to more than one childhood dementia condition). The vast majority of the trials that were for more than one condition were trialling cell therapies such as allogeneic hematopoietic stem-cell transplantation. Others included more than one closely related condition such as different types of mitochondrial disease. Trends over time were plotted using the trial start date. Clinical trials in Australia were analysed by filtering by study location.

Note that interventional trials included 'expanded access' trials. All interventional trials were manually categorised into one of 9 intervention categories (cell therapy; gene-modified cell therapy; combination therapies; dietary modification/supplement; enzyme replacement therapy; gene therapy; small molecule drugs; other biological; other), based on the description of the intervention for each clinical trial.

The number of childhood cancer clinical trials was obtained by searching clinicaltrials.gov using the condition/disease search terms "cancer OR leukaemia OR glioblastoma OR lymphoma OR neuroblastoma OR nephroblastoma OR osteosarcoma OR sarcoma OR carcinoma OR medulloblastoma OR glioma OR Hodgkin's" and restricting to interventional trials for children (birth-17) using the available filters. Withdrawn trials were excluded. The estimated patient population sizes for childhood cancer were obtained from relevant publications as described in Supplementary Tables 1 and 2 (Appendix).

Clinical trial activity globally

Number of trials globally

From 2000 to the end of 2023, a total of 386 interventional clinical trials for childhood dementia were registered in clinicaltrials.gov. The number of clinical trials found for childhood cancer was 10,474. In December 2023, 54 trials were listed as recruiting children with dementia and 1,682 for children with cancer. To compare clinical trial activity on the two disease groups meaningfully, the number of trials per patient was calculated (Supplementary Table 1).

Globally, there were 24-fold more trials recruiting children with cancer, than children with dementia, on a per patient basis (Figure 1). This is consistent with the historic lack of clinical trials for patients with childhood dementia. Over the past 23 years, 21-fold more trials were initiated per child with cancer compared to childhood dementia.

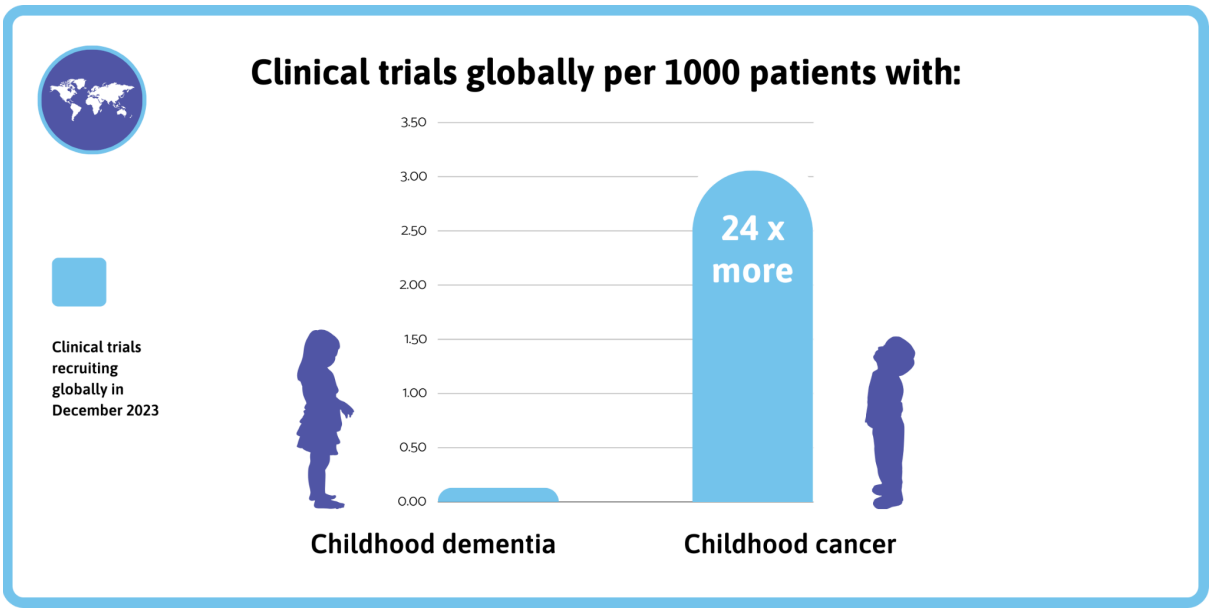


Figure 1: Global comparison of clinical trials recruiting in December 2023
Note: Data drawn from trials registered in clinicaltrials.gov. See Appendix for patient population information.

Change in clinical trial activity over time globally

The early 2000s saw some growth in childhood dementia clinical trials, however, from 2015 onwards, the number of new trials initiated plateaued. This may in part be due to the COVID-19 pandemic which negatively impacted all clinical research activities globally[11]. In addition, the downturn in the global economic market negatively affected the biotechnology sector. **When compared to the number of clinical trials registered in clinicaltrials.gov overall, which continues to grow at a steady rate, a distinct slowing can be seen in childhood dementia trials (Figure 2)**.

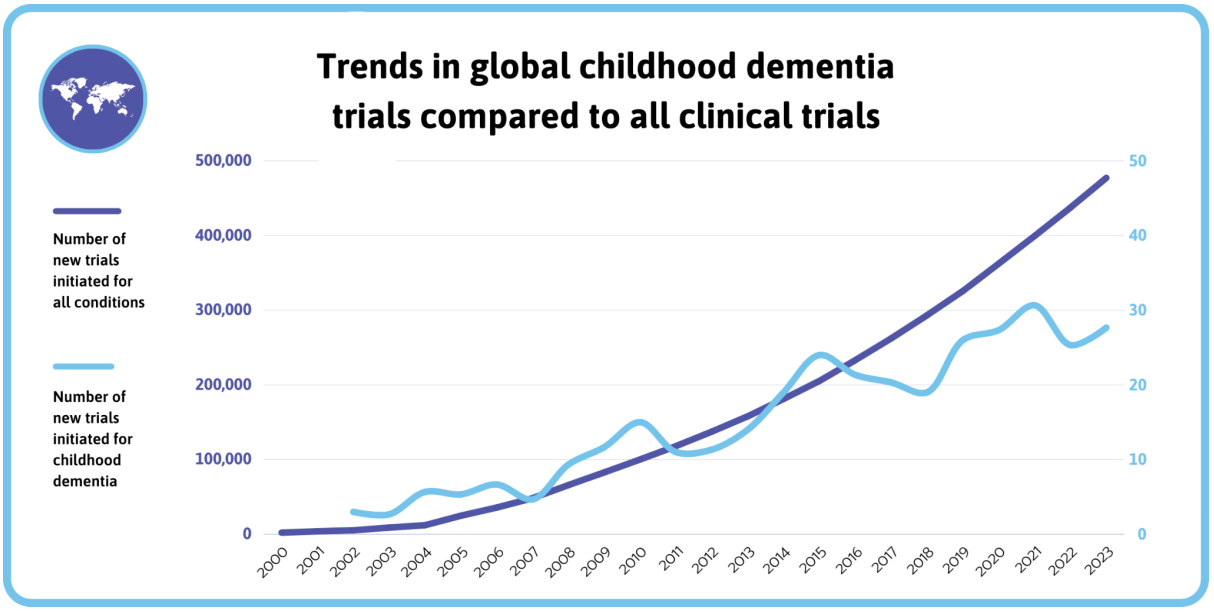


Figure 2: Trends in global childhood dementia trials compared to all clinical trials.
Note: Data for all trials obtained from: https://classic.clinicaltrials.gov/ct2/resources/trends. The childhood dementia line is a 3 period moving average.

In addition to a lack of new clinical trials being initiated globally, there have been worrying reports of therapeutic development stalling at a late stage. Clinical trials are being initiated and then halted or failing to move to the next phase . Others failed to launch despite all preclinical preparations being made including natural history studies, drug production and preclinical studies in animal models. A scan of press releases from companies known to be developing therapeutics for childhood dementia conditions found 10 examples of clinical trials being halted in the absence of negative results and 5 failing to initiate at a late stage (Table 1).

Table 1: Examples of stalled childhood dementia therapeutic clinical development

Company	Clinical trial	Date announced	Comments
REGENXBIO	Batten disease (CLN2) gene therapy	Nov 2023	Positive interim clinical trial data reported in 2023.[12,13] Portfolio prioritisation has halted development and pursuing strategic alternatives.
	Batten disease (CLN2) gene therapy - ocular		
	Hurler syndrome (MPS I) gene therapy		
Allievex	Sanfilippo syndrome (MPS IIIB) enzyme replacement therapy	Jan 2024	Positive results published in a peer reviewed journal in 2023.[14] Program stalled pending negotiations with the FDA.
Taysha GTx	giant axonal neuropathy (GAN) gene therapy	Sept 2023	Clinically meaningful and statistically significant slowing of disease progression in completed phase 1 trial[15]. Discontinued due to challenges with study design feasibility after discussions with the FDA.[16] Rights transferred to clinical trial collaborator National Institute of Neurological Disorders and Stroke (NINDS) in Feb 2024.
	Batten disease (CLN1) gene therapy	Mar 2022	Due to commence phase 1/2 studies in 2022, was on hold due to strategic pipeline prioritisation until Feb 2024 when Taysha provided drug for treatment of a single patient at RUSH University Medical Center

	GM2 gangliosidosis (Tay Sachs and Sandhoff disease) gene therapy	Mar 2022	Positive initial biomarker data in 2 trial participants[17], deprioritised in 2022 and rights returned to Queen's University in Feb 2024
	Leigh syndrome gene therapy	Mar 2022	Natural history complete, deprioritised in 2022, rights returned to the originating institution Feb 2024.
SOBI	Sanfilippo syndrome (MPS IIIA) enzyme replacement therapy	April 2021	Discontinued after 6 patients treated in phase I/II trial due to business reasons. Positive results published in peer reviewed journal in 2022[18]
Lysogene	Sanfilippo syndrome (MPS IIIA) gene therapy	April 2023	Terminated development and bankruptcy announced. Positive results were reported for younger patients[19]
Amicus Therapeutics	Batten disease (CLN3 and CLN8)* gene therapy	February 2024	Rights returned to Nationwide Children's Hospital, next steps uncertain. CLN3 trial produced early positive results.[20] CLN8 preclinical only.
Neurogene	Batten disease (CLN7) gene therapy	February 2023	Initiated natural history study but discontinued prior to clinical trial
Ionis Pharmaceuticals	Lafora disease antisense oligonucleotide	February 2022	Natural history study and preclinical work completed. Discontinued prior to trial[21]
Avrobio	Gaucher disease type 3 gene-modified cell therapy	July 2023	Registered trial with clinicaltrials.gov but this was withdrawn. Discontinued prior to trial[22]

*rights to CLN6 program also returned - clinical trial results showed disease stabilisation was not sustained beyond 2 years, so not included here.

Nine of these trials were still listed as active in clinicaltrials.gov at the time of analysis. There are likely other examples but it is difficult to identify them as this information isn't available in clinicaltrials.gov. Thus, our analysis actually overestimates the clinical trial activity for childhood dementia.

Clinical trial activity in Australia

The first clinical trials for childhood dementia were initiated in Australia in 2008 and since then, the number has remained static with 1 to 2 trials started each year on average (Supplementary Figure 1). No trials started in 2023.

From the inception of clinicaltrials.gov and up to 31 December 2023, 26 clinical trials were registered for childhood dementia in Australia. Seven of these were listed as still active in December 2023 for 5 types of childhood dementia; mucopolysaccharidosis type II (MPS II, Hunter syndrome), mucopolysaccharidosis type IIIA (MPS IIIA, Sanfilippo syndrome type A), Niemann-Pick disease type C, Alexander disease and metachromatic leukodystrophy.

Of 54 clinical trials recruiting patients globally in December 2023, only 2 were listed as recruiting in Australia (Niemann-Pick disease type C and Alexander disease). This means that **less than 2.6% of children with dementia had any prospect of participating in a clinical trial in Australia**. Within that 2.6%, only a small fraction of children would actually be eligible for trials as the inclusion criteria are usually narrow. For example, in the Niemann-Pick disease type C trial, to be eligible, participants must have a severity score between 0.5 and 2 on a 17-point scale.

Clinical trial activity for childhood dementia is grossly deficient in Australia. This is especially apparent when comparing activity with childhood cancer. For childhood cancer, 552 clinical trials have been initiated in the same time period and in December 2023, 123 trials were listed as recruiting.

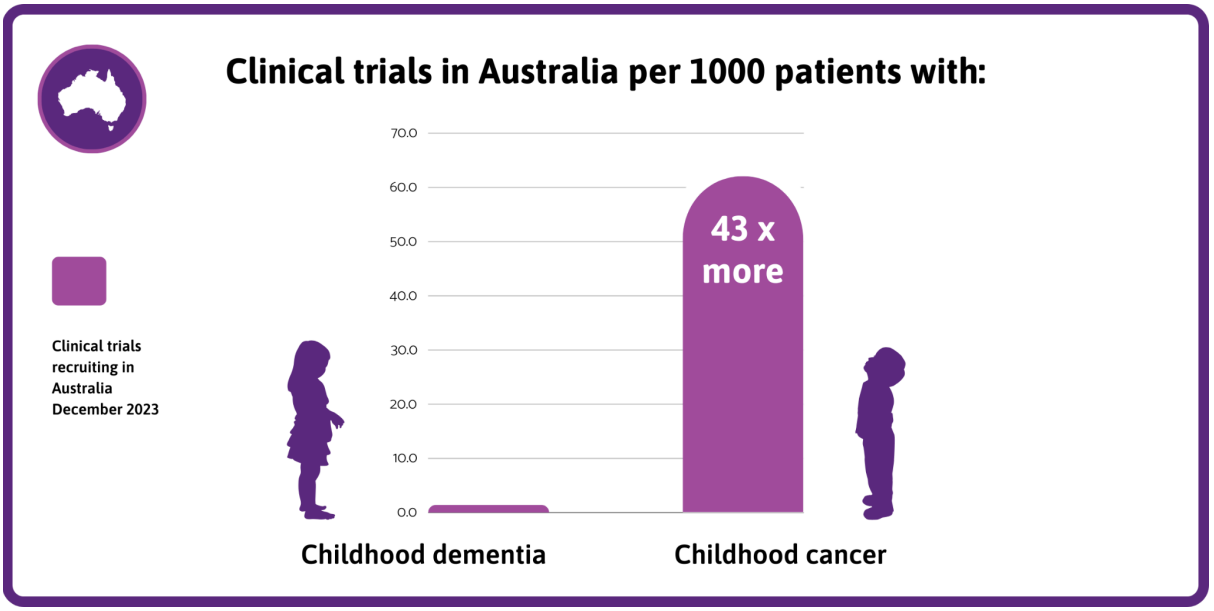


Figure 3: Comparison of Australian clinical trials recruiting in December 2023
Note: Data drawn from trials registered in clinicaltrials.gov. See Appendix for patient population information.

In December 2023, there were 43 times more clinical trials recruiting children with cancer, per patient than those with dementia (Figure 3). Over the past 23 years, 15-fold more trials for children with cancer have been initiated in Australia than for children with dementia (Supplementary Table 2). At the time of the analysis, 33 industry sponsors were active in childhood dementia clinical trials globally. Five of these were active in Australia (Supplementary Table 3). This identifies companies that could be engaged regarding clinical trial opportunities in Australia.

"We're trying our best to find solutions to change such a terminal diagnosis. There are treatments out there. We need to find them and get them to children. We need more research, more resources to make that happen."

Niki, mum to Angelina who has childhood dementia

Clinical trial opportunities vs incidence

Globally, the clinical trial activity that took place over the 2000 to 2023 period was inconsistent with the number of children affected. Some relatively common disorders had little or no clinical trial activity. Of the 10 disorders with the highest incidence, 5 had 2 or fewer clinical trials registered (Figure 4). This indicates the siloed and fragmented nature of childhood dementia pre-clinical and clinical research that needs to be addressed.

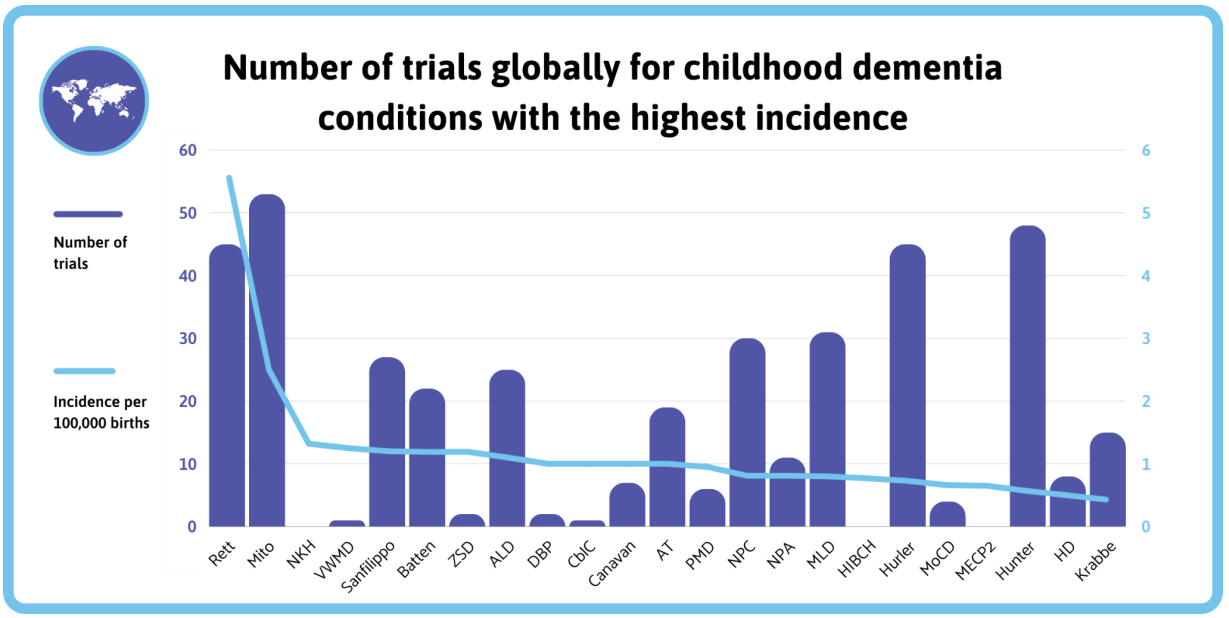


Figure 4

Note: only the 25 highest incidence disorders are plotted here. Includes all trials registered on clinicaltrials.gov between 2000 and 2023 inclusive of completed, terminated, active and recruiting trials.

ABBREVIATIONS
Rett= Rett syndrome
Mito=Mitochondrial disorders
NKH=Nonketotic hyperglycinemia (including variants)
VWMD=Vanishing White Matter Disease
Sanfilippo = MPS III (Sanfilippo syndrome)
Batten = Neuronal Ceroid Lipofuscinoses (NCLs or Batten Disease)
ZSD=Zellweger Spectrum Disorder
ALD=X-linked Adrenoleukodystrophy
DBP=D-bifunctional Protein Deficiency
CblC=Cobalamin C Disease
Canavan=Canavan Disease
AT=Ataxia telangiectasia
PMD=Pelizaeus-Merzbacher Disease
NPC=Niemann-Pick disease type C
NPA=Niemann-Pick disease type A
MLD=Metachromatic Leukodystrophy
HIBCH=Neurodegeneration Due To 3-hydroxyisobutyryl-coa Hydrolase Deficiency
Hurler=MPS I (Hurler Syndrome)
MoCD=Molybdenum Cofactor Deficiency
MECP2=MECP2 duplication syndrome
Hunter=MPS II (Hunter Syndrome)
HD=Huntington's disease (juvenile form)
Krabbe=Globoid Cell Leukodystrophy (Krabbe Disease)
SPG11=Spastic Paraplegia Type 11
Tay Sachs=GM2 Gangliosidosis (Tay Sachs Disease)

Types of potential treatments tested in clinical trials

Treatments that specifically aim to replace a missing protein or enzyme via gene therapy, gene-modified cell therapy or enzyme replacement therapy make up 40% of global childhood dementia clinical trials (Figure 5). These trials offer great promise because they are cutting edge treatments that target the root causes of childhood dementia.

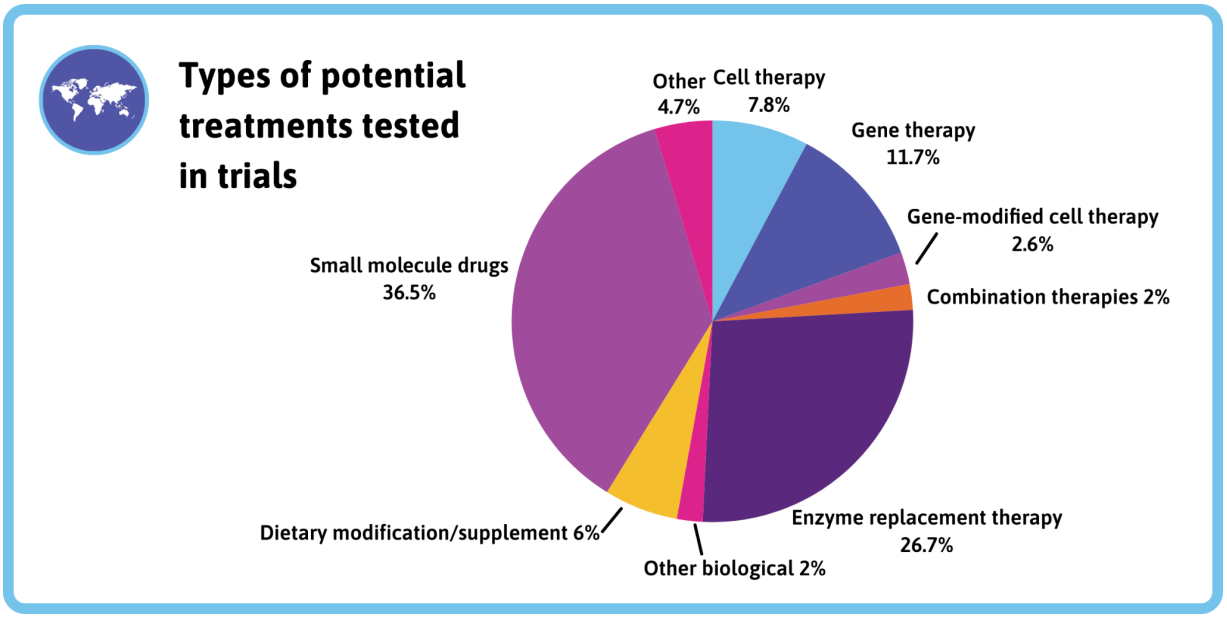


Figure 5: Types of potential treatments tested in childhood dementia clinical trials

Gene therapy, which comprises 12% of childhood dementia clinical trials, aims to introduce a working copy of the dysfunctional gene causing childhood dementia, and offers great hope. These advanced therapeutics give the promise of long-term clinical benefit(s) following a single administration. Most of the gene therapy trials (37 of 45 trials) use adeno-associated virus (AAV) to deliver the gene therapy. The remainder of the gene therapy trials utilise lentivirus (2 trials) or genome editing (2 trials). Four trials are testing another type of genetic therapy called antisense oligonucleotides (ASOs). ASOs require repeat dosing and rather than introducing a healthy copy of the gene, they alter the way that the faulty gene is read.

There were 10 gene-modified cell therapy trials registered. This approach is also known as ex vivo autologous hematopoietic stem cell (HSC) gene therapy. This is where a patient's own stem cells are harvested (for example from the bone marrow) and genetically modified before being returned to the patient. This is expected to have long-lasting effects.

Globally, the number of childhood dementia gene therapy trials grew to a peak of 11 trials initiated in 2021, however this dropped back to 5 in 2022 and 7 in 2023 (Supplementary Figure 2).

Only 2 gene therapies for childhood dementia have ever received regulatory approval:

- Libmeldy (Orchard Therapeutics) for metachromatic leukodystrophy (approved in the European Union, the UK, Iceland, Switzerland, Liechtenstein, Norway and, at the time of publication, was under assessment in the USA with a decision expected in March 2024)
- Skysona (Bluebird Bio) for cerebral X-linked adrenoleukodystrophy (approved in the USA). Skysona was also approved in the EU in July 2021, but authorisation was withdrawn just 4 months later due to difficulty negotiating reimbursement with individual countries.

Even with approval, access remains limited. These gene therapies are only available to citizens of the countries where they are approved, and payment arrangements are still being negotiated with some Governments and insurers (in the USA).

As of December 2023, there had been 103 enzyme replacement therapy (ERT) clinical trials registered in clinicaltrials.gov for childhood dementia disorders. This approach aims to replace a missing enzyme via direct protein infusions at regular intervals, often weekly. ERT drugs have been approved for alpha-mannosidosis, MPS types I, II and VII, Gaucher disease type 3, Niemann-pick disease type A and CLN2 (a type of Batten disease). Except for Brineura for CLN2, which is delivered into the cerebrospinal fluid (intraventricularly), these therapies are not designed to reach the brain and only treat the somatic symptoms of the disease. To address this, 37 trials have been initiated to investigate intrathecal or intracerebroventricular ERT delivery or modified enzymes designed to penetrate the brain. Fifteen of these trials are still ongoing.

Small molecule drugs make up 37% of trials. These are relatively simple drugs which makes them more affordable and often less complicated to develop and make available to patients. These drugs may not all be curative but could significantly slow progression and improve quality of life, especially if administered in combination. Many of these drugs could be widely applicable across multiple childhood dementia disorders with common pathophysiological features, however they are generally only tested in clinical trials one disorder at a time. This means that opportunities may be missed for more patients to benefit from potential treatments.

One exception is a trial that started in 2023 which is testing a small molecule drug for multiple childhood dementia disorders in a basket trial design. AZ-3102, an inhibitor of ceramide production, is being trialled by Azofaros for GM2 Gangliosidosis (Sandhoff and Tay-Sachs diseases) and Niemann-Pick disease type C.

What's the difference between gene therapy and gene-modified cell therapy?

Gene therapy: in the simplest form, involves the introduction of a healthy copy of the dysfunctional gene causing the disease. The gene is often delivered into the cells of the body using a modified viral vector. The viral vector containing the gene is administered into the bloodstream, the spinal cord or directly into the brain. Other strategies such as genome editing, gene silencing or combinatorial strategies are also being developed.

Gene-modified cell therapy: cells are removed from the patient, genetically modified in the laboratory (often using a viral vector) and then returned to the patient. Usually, blood stem cells are used which have the ability to self-renew in a patient's bone marrow and produce new blood cells of all types. It can be thought of as a bone marrow transplant combined with gene therapy or genome editing. It avoids the need for a matched bone marrow donor.

It is hoped that both approaches will give long lasting effects, possibly life-long. The 2 approaches may differ in how widely distributed throughout the body the therapy is, but this is still being investigated.

Discussion

Inequity in clinical trial activity globally

This analysis shows that there continues to be a severe lack of activity to develop treatments and cures for childhood dementia globally. Per patient, childhood dementia has attracted 21 times fewer clinical trials than childhood cancer (per patient globally over the past 23 years). This has resulted in gross inequity of access to therapeutics for children with dementia.

Childhood cancer research has yielded the development of many targeted, effective treatments which has resulted in great gains in survival. The NIH National Cancer Institute in the USA lists 43 drugs approved for childhood cancer.[23] In Australia, death rates from cancer almost halved between 1997 and 2017 in children aged 0–14[2] and in high-income countries, more than 80% of children with cancer are cured[10]. Similarly, for people with cystic fibrosis the life expectancy has doubled from 27 years in 2005 to 56 years for those born in 2016-2020 thanks to both improvements in care and the development of genetic modulation therapies.[3] Babies with spinal muscular atrophy are now screened at birth and treated with gene therapy shortly after, which means that instead of dying by the age of two, these children are walking, and thriving without the need for nutritional or respiratory support[24].

By contrast, childhood dementia has had no notable improvement in survival in recent decades, and any small gains are due to improvements in clinical care to better manage symptoms such as seizures and pneumonia[25], not disease-modifying therapies to slow, halt or reverse the progression of dementia. There is no data available on the change in life expectancy for childhood dementia collectively over time, but data for some individual disorders can be found. For example, one UK study showed an increase in life expectancy from ~13 years in the 1980s to ~16 years in the 2000s for Sanfilippo syndrome type A and no change for Sanfilippo syndrome type B[25] and there has been no change in survival for Rett syndrome over the last 30 years in Australia[26]. Meanwhile the average life expectancy of the general population over the same period increased by an average of 8 years in the UK[27] and 8.5 years in Australia.[28]

This highlights the even greater need for more pre-clinical research and clinical trials for childhood dementia. However analysis of trends in clinical trial activity over time showed a **slowing in clinical trial activity for childhood dementia**. This is both surprising and unacceptable given the great unmet need, advances in genomics and drug development in recent decades and the fact that clinical trials for other indications continued to steadily increase.

Need for improvement in Australia

Unfortunately, Australia did not experience a growth in childhood dementia clinical trials that has been seen in other parts of the world. . On average 2, trials started each year over the past decade and in 2023 no trials were initiated. This is a disturbing trend which **necessitates efforts to bolster clinical trial capacity and readiness to enable locally initiated trials and attract more trials to Australia from overseas**. Clearly, there is capacity for more trials to be held in Australia, given the evidence that there were 43 times more clinical trials recruiting children with cancer, per patient, than those with dementia.

The inquiry into new medicines commissioned by the Australian Government and the resulting report tabled in 2021, "The New Frontier - Delivering better health for all Australians"[29], made recommendations that aim to improve clinical trial infrastructure and access to new medicines in Australia. The Australian Government responded[30] in November 2023 and committed to 26 of the 31 recommendations. Swift and well resourced implementation of the recommendations such as the establishment of a Centre for Precision Medicine and Rare Diseases and streamlined ethics processes will help to attract and deliver more trials. In addition, clinical trial resources and infrastructure are needed specifically for childhood dementia. Clinical research should be embedded as part of best practice clinical care.

Regulatory hurdles

In addition to a lack of new clinical trials being initiated globally, there have been **worrying reports of therapeutic development failing at a very late stage due to regulatory and/or commercial issues**. Evidence was found of clinical trials being initiated and then halted or failing to move on to the next phase, in the absence of negative results and without safety concerns. Others failed to launch

despite all preclinical preparations being made including natural history studies, drug production and extensive preclinical studies in animal models. A rudimentary scan of press releases and news articles found 15 examples to illustrate this (Table 1).

Clinical trial results released by companies[12,13,31] and published in peer reviewed journals[14,32–34] demonstrate positive results, especially in children treated early in their disease course. So, **development of effective therapies for this group of devastating diseases is possible**. There is now an opportunity to transform treatment of childhood dementia that could be missed if the trends reported here aren't reversed.

In press releases, the reasons for halting these trials are mostly "due to business reasons" or "pipeline prioritisation". These worrying signs of a lack of commercial viability, especially for the development of advanced therapeutics like gene therapy, need to be addressed through incentives, alternative funding models and improved clinical trial efficiency.

It is also known that regulatory processes are increasingly becoming a key obstacle. One company cited "challenges with study design feasibility" after meeting with the US Food and Drug Administration (FDA) in a press release[16], others have been vocal in conference presentations about their frustration with regulators. The FDA has insisted on placebo controlled trials even for ultra rare diseases where this is logistically near impossible and unethical given the invasive nature of treatment (e.g. intrathecal injection) and narrow treatment window. It is likely that a child allocated to the placebo arm of a trial will deteriorate during the trial to a point where they are no longer eligible for treatment.

Advocacy groups and pharmaceutical companies are calling for the FDA to increase use of the Accelerated Approval Program.[35–37] This program was designed to allow earlier approval of drugs that treat serious conditions through the use of surrogate endpoints. A surrogate endpoint is a marker, such as substance measured in the blood or a physical sign that is thought to predict clinical benefit but is not itself a measure of clinical benefit. The use of a surrogate endpoint can considerably shorten clinical trial timelines, delivering promising treatments to children sooner and improving the commercial viability of clinical trials. This pathway has been highly successful for other rare diseases such as Duchenne muscular dystrophy. However, the FDA appears to be resistant to allowing this path for childhood dementia disorders.

The shelving of potential therapies so close to the final stages of making them available to patients, not due to safety concerns or ineffectiveness, but due to the inflexibility of regulators and the resultant financial and logistical hurdles for companies is highly questionable ethically. It is also heartbreaking for families and incredibly wasteful of decades of research, mostly funded by patient organisations and governments.

The unique challenges faced in the development of childhood dementia therapies need to be appropriately accommodated by the regulatory bodies, health technology assessment (HTA) agencies and payers in each region to ensure they don't fail at the final hurdle. Implementation of a smoother development and approval path will also encourage more researchers and pharmaceutical companies to enter the childhood dementia field.

Clinical trial infrastructure

Activities to accelerate and increase the efficiency of clinical trials are needed to overcome regulatory and commercial barriers that may discourage or slow therapeutic development. **Investment in more clinical trial tools and infrastructure is required**, including:

- improved outcome measures including patient reported outcome measures;
- discovery and validation of biomarkers and surrogate endpoints;
- collection and sharing of natural history data;
- early diagnosis so that potential treatments can be trialled on children early in their disease progression when the treatment it is likely to be most effective; and
- clinical trial networks or consortia to streamline clinical trials, reduce duplication and increase collaboration.

The collective consideration of all childhood dementia disorders in these activities will enable economies of scale and ensure more children with dementia will benefit.

The International Rare Diseases Research Consortium (IRDiRC) is one collaborative initiative launched in 2011 to help address some of these issues facing rare diseases and although progress has been made, major hurdles still need to be overcome. The European Union recognised the importance of a paediatric trials network with a substantial Horizon 2020 grant. A Bill is currently before the US House of Representatives, to establish and maintain a paediatric trials network, and Australian paediatricians are calling for investment and a coordinated national approach to paediatric clinical trials.[38]

Research funding and fragmentation

There has been a long-standing disparity in the allocation of funding to childhood dementia research compared to other disease groups[39]. As a result, there is a lack of therapeutics being developed for childhood dementia and translated into clinical trials.

The analysis in this report also showed that there is inequity between childhood dementia disorders, with some relatively common disorders having little or no clinical trial activity. This highlights the siloed nature of research for childhood dementia. Concurrent research and drug development for multiple childhood dementia disorders with common pathophysiological features in parallel will help to achieve economies of scale.

This historic inequity and fragmentation must be addressed with **large scale, coordinated and collaborative research funding across all stages of research and across the full spectrum of**

childhood dementia disorders, to feed the clinical trial pipeline and increase the number of therapies reaching patients.

Conclusions and opportunities for change

Treatments and cures are needed to improve the length and quality of life for children with dementia and their families. A collective approach to the 145+ genetic disorders that cause childhood dementia will accelerate the development of therapies for childhood dementia through:

- Increased awareness of the unmet need
- Increased research funding and appropriate regulatory pathways
- Identification of commonalities for research
- Economies of scale and development of shared infrastructure
- Identification of opportunities to collaborate and reduce inefficiencies.

In conclusion, advances in genomics and drug development in recent decades have enabled effective treatments to be within reach for childhood dementia, however inadequate research funding, inflexible regulatory processes and financial constraints are stifling progress. **Action must be taken globally to address research inequity and remove the roadblocks that deny current and future generations of children born with childhood dementia conditions access to effective therapies.**

"What would Mia's life have looked like if she was born in 15 years from now? Will it be a different story for the next generation of children yet to be diagnosed?"

Peta, mum to Mia (pictured), who died with childhood dementia

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Appendix

Supplementary Table 1: Global clinical trials analysis (as of December 31 2023)

	Estimated Global Patient Population	Total number of trials (5)	Trials per 1000 patients	Ratio (total trials)	Recruiting trials (6)	Recruiting trials per 1000 patients	Ratio (recruiting trials)
Childhood dementia	420000 (1)	386	0.9		54	0.1	
Childhood cancer	548400 (2)	8550	15.6	17.0	1384	2.5	19.6
Motor neuron disease	331800 (3)	696	2.1	2.3	121	0.4	2.8
Cystic fibrosis	162428 (4)	1061	6.5	7.1	99	0.6	4.7

(1) Extrapolated from Elvidge et al., 2023[1]
(2) GBD 2019 Adolescent Young Adult Cancer Collaborators[2] estimated: 416 500 estimated total childhood cancers occurring worldwide in 2017 minus 142 300 deaths. Assume 2 year average duration of treatment. Encompasses children and adolescents, defined as ages 0–19 years.
(3) Motor neuron disease has a prevalence of 4.2 per 100,000[3] people and assumes a world population of 7.9 billion.
(4) Cystic fibrosis prevalence from Guo et al., 2022[4]
(5) Only interventional trials were included, withdrawn trials were excluded
(6) Recruiting trials include those that are recruiting by invitation.

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Supplementary Table 2: Australian clinical trials analysis (as of December 31 2023)

	Estimated Australian Patient Population	Total number of trials (5)	Trials per 1000 patients	Ratio (total trials)	Recruiting trials (6)	Recruiting trials per 1000 patients	Ratio (recruiting trials)
Childhood dementia	1394 (1)	26	18.7		2	1.4	
Childhood cancer	1984 (2)	438	220.8	11.8	99	49.9	35
Motor neurone disease	2094 (3)	45	21.5	1.2	9	4.3	3.0
Cystic fibrosis	3616 (4)	109	30.1	1.6	6	1.7	1.2

(1) As estimated in Elvidge et al., 2023[1]
(2) Childhood cancer prevalence = number of children and adolescents aged 0-19 diagnosed in 2020 and 2021 minus the number of deaths in those years assuming 2 years average treatment time, Australian Institute of Health and Welfare (AIHW)[5]
(3) Australian motor neurone disease prevalence as reported in 2015[6]
(4) Cystic fibrosis prevalence from Ahern et al., 2021[7]
(5) Only interventional trials were included, withdrawn trials were excluded
(7) Recruiting trials include those that are recruiting by invitation.

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Supplementary Table 3: Industry clinical trial sponsors active globally

Acasti Pharma Inc. (Ataxia telangiectasia)
Amicus Therapeutics (CLN3)
AO GENERIUM (MPS II (Hunter syndrome))
Aspa Therapeutics (Canavan disease)
Azafaros A.G. (Niemann-Pick disease type C, GM2 gangliosidosis (Sandhoff disease), GM2 gangliosidosis (Tay Sachs disease))
Biohaven Pharmaceuticals, Inc. (spinocerebellar ataxia type 7)
Calico Life Sciences LLC/AbbVie (vanishing white matter disease)
CANbridge (Suzhou) Bio-pharma Co., Ltd. (Gaucher disease type 3)
Cyclo Therapeutics, Inc. (Niemann-Pick disease type C*)
Denali Therapeutics Inc. (MPS II (Hunter syndrome))
Forge Biologics, Inc (globoid cell leukodystrophy (Krabbe disease))
GC Biopharma Corp (MPS II (Hunter syndrome))
IntraBio Inc (ataxia telangiectasia, Niemann-Pick disease type C*)

Ionis Pharmaceuticals, Inc. (Alexander disease (type I)*)
JCR Pharmaceuticals Co., Ltd. (MPS I (Hurler syndrome), MPS II (Hunter syndrome), MPS IIIA (Sanfilippo syndrome), MPS IIIB (coming soon))
Khondrion BV (mitochondrial disorders)
Minoryx Therapeutics, S.L. (X-linked adrenoleukodystrophy)
Minovia Therapeutics Ltd. (mitochondrial disorders)
Myrtelle Inc. (Canavan disease)
Neurogene Inc. (CLN5, Rett syndrome)
Omeicos Therapeutics GmbH (Mitochondrial disorders)
Orchard Therapeutics (metachromatic leukodystrophy, MPS I (Hurler syndrome), MPS IIIA (Sanfilippo syndrome))
Passage Bio, Inc. (globoid cell leukodystrophy (Krabbe disease), GM1 gangliosidosis (type 1), GM1 gangliosidosis (type 2))
Polaryx Therapeutics, Inc. (neuronal ceroid lipofuscinoses (NCLs or Batten disease))
Prevail Therapeutics/Eli Lilly and Company (Gaucher disease type 2)
PTC Therapeutics (Mitochondrial disorders)
Retrotope, Inc. (infantile neuroaxonal dystrophy/PLA2G6-associated neurodegeneration (PLAN))
Sanofi/Genzyme (Gaucher disease type 3, GM2 gangliosidosis (Tay Sachs disease), MPS I (Hurler syndrome))

Takeda/Shire (metachromatic leukodystrophy*, MPS II (Hunter syndrome)*)
Taysha Gene Therapies, Inc. (Rett syndrome)
Transposon Therapeutics, Inc. (Aicardi-Goutières syndrome)
Ultragenyx Pharmaceutical Inc (Rett syndrome, MPS III (Sanfilippo syndrome)*)
ZevraDenmark (Niemann-Pick disease type C)

* indicates active trials in Australia

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