CHILDHOOD DEMENTIA GLOBAL LANDSCAPE ANALYSIS

Guiding High Value Investment in Global Childhood Dementia Research

May 2022

RESEARCH AUSTRALIA

CONNECTING • ENGAGING • INFLUENCING

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Research Australia is the national alliance representing the entire health and medical research pipeline, from the laboratory to patient and the marketplace.

Our vision: Research Australia envisions a world where Australia unlocks the full potential of its world-leading health and medical research sector to deliver the best possible healthcare and global leadership in health innovation.

Our mission: To use our unique convening power to position health and medical research as a significant driver of a healthy population and contributor to a healthy economy.

Our role:

Engage
Australia in a conversation about the health benefits and economic value of its investment in health and medical research.

Connect
researchers, funders and consumers to increase investment in health and medical research from all sources.

Influence
government policies that support effective health and medical research and its routine translation into evidence-based practices and better health outcomes.

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Glossary: List of Childhood Dementia Disorders

The table below lists the 70+ individual genetic disorders that were included in Research Australia's global landscape analysis as agreed upon with Childhood Dementia Initative in October 2021. We are cognisant that this list is evolving. Where needed, the disorders have been grouped with sub-types included.

Disorder Searched	Sub types included
Abetalipoproteinaemia	
Alexander Disease	Type I
Alpha-Mannosidosis	
alpha-N-acetylgalactosaminidase Deficiency (Schindler Disease Type I)	
Aspartylglucosaminuria (AGU)	
Batten Disease	CLN1
	CLN5
	CLN10 (neonatal) - Congenital Onset
	CLN2 (1 – 6 y) - Late-infantile Onset
	CLN6 (18 mos – 8 y) - Late-infantile Onset
	CLN7 (2 – 7 y) - Late-infantile Onset
	CLN8 (5 – 10 y) - Late-infantile Onset
	CLN3 (4 – 7 y) - Juvenile Onset
Beta-Mannosidosis	
Beta-propeller protein-associated neurodegeneration (BPAN)	
Biotinidase deficiency	
Biotin-Thiamine-Responsive Basal Ganglia Disease	
Canavan Disease	
Cerebral Folate Deficiency	
Cerebrotendinous Xanthomatosis	
Cobalamin C Disease	
Cockayne Syndrome	

Coenzyme A synthase protein-associated neurodegeneration (COASY)	
Combined Saposin (Prosaposin) Deficiency	
Congenital Disorders of Glycosylation	Congenital Disorder of Glycosylation Type Ie
	Congenital Disorder of Glycosylation Type Ij
	Congenital Disorder of Glycosylation Type IIa
Farber Disease	
Fatty acid hydroxylase-associated neurodegeneration (FAHN)	
Fucosidosis	Type I
	Type II
Galactosialidosis (Cathepsin A Mutation)	
Gaucher Disease	Type 2
	Type 3
Giant axonal neuropathy	
Globoid Cell Leukodystrophy (Krabbe Disease)	
Glutathione Synthetase Deficiency	
Glycine Encephalopathy	
GM1 Gangliosidosis	Type 1
	Type 2
GM2 Gangliosidosis	AB Variant
	Tay Sachs Disease
	Sandhoff Disease
Holocarboxylase synthetase deficiency	
Huntington's Disease (Juvenile Form)	
Huntington Disease-Like Variants	particularly HDL3 and HDL4

Infantile Neuroaxonal Dystrophy/PLA2G6-Associated Neurodegeneration (PLAN)	
Juvenile Parkinson's Disease PARK19A (DNAJC6)	
Kufor-Rakeb Syndrome	
Lafora Disease	
MECP2 duplication syndrome	
Menkes Disease	
Metachromatic Leukodystrophy	
Mitochondrial disorders	Alpers-Huttenlocher syndrome
	Kearns-Sayre syndrome (KSS)
	Leigh Syndrome
	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
	Neuropathy, ataxia, and retinitis pigmentosa (NARP)
Mitochondrial membrane protein-associated neurodegeneration (MPAN)	
Molybdenum Cofactor Deficiency	
MPS I (Hurler Syndrome)	
MPS II (Hunter Syndrome)	
MPS III	Mucopolysaccharidosis type IIIA
	Mucopolysaccharidosis type IIIB
	Mucopolysaccharidosis type IIIC
	Mucopolysaccharidosis type IIID
MPS VII (Sly Syndrome)	
Mucolipidosis Type I (Sialidosis type 2)	
Mucolipidosis Type II (i-Cell Disease)	
Mucolipidosis Type IV	
Multiple Sulfatase Deficiency	

Niemann-Pick disease type A (NPA)	
Niemann-Pick disease type C (NPC)	
Pantothenate kinase-associated neurodegeneration (PKAN)	
Pelizaeus Merzbacher Disease	
POLR3-Related Leukodystrophies	
Pyruvate Dehydrogenase Deficiency	
Rett Syndrome	
Saposin A Deficiency	
Saposin B Deficiency	
Saposin C Deficiency	
Sialic Acid Storage Disease	
SLC5A6 deficiency	
Sulfite Oxidase deficiency	
Vanishing White Matter Disease	
Wilson Disease	
Woodhouse-Sakati Syndrome	
X-linked Adrenoleukodystrophy	
Zellweger Spectrum Disorder	

CHILDHOOD DEMENTIA GLOBAL LANDSCAPE ANALYSIS

Guiding High Value Investment in Global Childhood Dementia Research

Introduction

The Childhood Dementia Initiative has identified the need for systemic change in how research into childhood dementia is undertaken and funded. In particular, there is a need for a global vision to drive research and advocacy to urgently disrupt the impact of childhood dementia on children and families across the world.[1] Research Australia has been commissioned to assist in identifying research that can support this global vision.

To enable greater scientific impact by the Childhood Dementia Initiative, it is necessary to get a global picture of the research being undertaken in Childhood Dementia and the opportunities for scientific collaboration.

Research Australia is the national alliance representing the entire health and medical research pipeline from the laboratory through to the patient and the marketplace. Research Australia has demonstrated expertise in guiding policy for health and medical research, including providing credible, politically neutral, policy advice for over 20 years. Our perspective always includes promoting high quality research at all stages of the research pipeline, from fundamental research right through to health service delivery, with the ultimate goal of improving Australians' health outcomes.

We are pleased to partner with the Childhood Dementia Initiative on this project to identify high-value research investment opportunities and emerging therapies globally, that are vital to diagnosing, treating and hopefully, one day, curing childhood dementia.

Research Australia has conducted a three stage project:

1. A detailed Search Strategy – carefully designed and tested to empower the Childhood Dementia Initiative team to independently identify global research activity and investment opportunities.
2. Pilot Search – preliminary observations from a pilot search of five disorders agreed upon by Childhood Dementia Initiative and Research Australia, which has also assisted in iteratively refining the Search Strategy.

[1] Childhood Dementia Initiative (2021), Childhood Dementia National Action Plan *Funding Request*

3. Global Landscape Analysis – a global picture of the research being conducted into the more than 70 individual genetic disorders that make up childhood dementia, the opportunities for scientific collaboration and identification of areas where more research is a priority.

The following document provides an overview of the Search Strategy and presents the findings of the global landscape analysis.

A better understanding of who is conducting clinical research globally will highlight research gaps, leading to smarter investment by government, industry and philanthropy. Understanding the gaps and opportunities in childhood dementia research will encourage more conscious and effective use of limited resources by researchers themselves, ensuring research is complementary and therefore more efficient and effective.

This will also allow further research investment, from government, philanthropy and industry, to be guided by a benchmark of what activity currently exists. This information will identify new opportunities for the Childhood Dementia Initiative to promote and enable research that concurrently investigates multiple childhood dementia disorders thereby achieving economies of scale and scope. It will also enable the Childhood Dementia Initiative to foster and harness collaborative and diverse networks.[2]

Driving world first action

Health and medical research is part of an ecosystem sustained by many participants and multiple funding streams. The breadth of medical research undertaken in Australia makes it difficult to track progress in particular disease areas. This is especially true for childhood dementia – a complex and confronting diagnostic group of more than 70 individual genetic disorders.

Research into childhood dementia disorders remains disparate and siloed, with research usually focused on a single disorder. This creates the risk of duplication and neglect of some disorders relative to others.

Childhood Dementia Initiative is driving world first action to reframe the way experts, systems and policy makers' view and respond to these disorders; focusing on the commonality (dementia) rather than the underlying genetic cause. The Inaugural Challenging Childhood Dementia Symposium[3] held in March 2022 recommended the following:

- Research is needed to identify common mechanisms that could be targeted across multiple childhood dementia disorders;
- Increase collaboration and knowledge sharing across disciplines, diseases and institutions;
- Achieve a nationally coordinated approach to childhood dementia clinical trials with a central point of contact for trial sponsors and streamlined feasibility, governance and ethics;
- A cohesive, coordinated approach to research funding is needed to tackle the scale and scope of childhood dementia unmet need; and
- More incentives for pharmaceutical companies to conduct trials in Australia.

[2] Childhood Dementia Initiative (2020). Childhood Dementia: the case for urgent action. Page 6.
[3] https://www.childhooddementia.org/news/successful-inaugural-challenging-childhood-dementia-symposium

This project is an important opportunity to promote and enable research that concurrently investigates multiple childhood dementia disorders; and to foster and harness collaborative and diverse networks.

Overview of Search Strategy

To get a clear picture of childhood dementia research activity, Research Australia has developed a detailed Search Strategy that includes the search terms and taxonomy needed to identify published research and clinical trials that have been undertaken in childhood dementia in the last 5 years.

The Search Strategy has been carefully designed and tested to empower the Childhood Dementia Initiative team to independently run the search in following years to update the information for both scientific and consumer audiences.

Through testing the Search Strategy multiple times, Research Australia has identified that the free database, PubMed can be searched in order to identify relevant literature. This ensures that the Search Strategy delivered to Childhood Dementia Initiative is readily and freely accessed and replicable by a wide range of parties, not just the scientific community.

Clinical trial listings also brings a wealth of knowledge valuable to the Childhood Dementia Initiative. While negative studies are often not published in the academic literature, these are important in the context of rare disorders as they can indicate strategies that should be low priorities for funding and show other groups working in this area that may present further partnership opportunities for Childhood Dementia Initiative. Clinical trial listsings can show both groups planning clinical trials that have not yet been published and those that have conducted studies that may not have been published due to negative results.

The Search Strategy has been set up as a broad sweep for advocacy and stakeholder linking purposes; it is is not a systematic review. The aim is to identify researchers and clinicians, groups and institutes (such as hospitals and universities) interested in and conducting research and providing treatment for this group of rare disorders. Using the results of a search conducted by Research Australia in the first year as a foundation, the Childhood Dementia Initiative can repeat the search in future years, building a dataset that will be valuable to both scientific and consumer audiences.

As agreed upon with Childhood Dementia Initiative, clinical registries have been excluded from this search, meaning some observational studies may not be captured. Identifying relevant patient registries and patient data is a much larger, separate project.

For practical reasons, articles will be included if they are in English, and the PubMed search has been limited to the past 5 years. Exclusions include basic science and preclinical research; incidence and prevalence studies and studies looking at psychosocial and allied health interventions (as these are covered in other projects funded by Childhood Dementia Initiative); and literature discussing presentation without suggesting an intervention. It is also not within the scope of this project to map the published studies or case reports to specific clinical trials registered.

Research Australia's full Search Strategy is contained in Attachment A. This details the search terms, inclusion and exclusion criteria, filters, and data extraction.

Global Landscape Analysis

This analysis of published articles and clinical trials will enable Childhood Dementia Initiative to understand the distribution of research across the 70 plus disorders that make up childhood dementia to understand the research gaps and how Childhood Dementia Initiative can work to fill these gaps.

Despite the large number of paediatric neurological disorders known to cause childhood dementia, collectively, childhood dementia itself, as a diagnostic group of diseases, has received little recognition or attention in the medical and scientific literature. Instead, the individual disorders are most often considered as discrete conditions rather than as part of the broader superordinate class.[4]

The need to extend research on one disorder to multiple disorders was raised at Childhood Dementia Initative's Symposium recently.[5] This project enables Childhood Dementia Iniative to identify the breadth of research being conducted and opportunities for this research to extend to multiple disorders.

Please see Attachment B for the comprehensive spreadsheet of results from this landscape analysis. The results of this landscape analysis were obtained from using the Search Strategy described in the previous section (developed and conducted between November 2021 and May 2022).

Distribution of research across childhood dementia disorders

Some disorders are receiving considerably more attention than others. This analysis enables the Childhood Dementia Initiative to understand the gaps in existing research which need to be addressed and areas where new research investment is needed.

The table below outlines the range of trials currently listed for the disorders that are known as childhood dementia.

Number of clinical trials registered	Disorder
20 +	Hunters syndrome Hurler syndrome Metachromatic leukodystrophy Niemann-Pick disease Type C X-linked adrenoleukodystrophy
10-20	Gaucher disease Type 3 Globoid Cell Leukodystrophy MPS III (Sanfilippo Syndrome) Niemann-Pick disease Type A

[4] Childhood Dementia Initiative (2020). Childhood Dementia in Australia: quantifying the burden on patients, carers, the healthcare system and our society. THEMA Constulting Report. Page 3.
[5] https://www.childhooddementia.org/news/successful-inaugural-challenging-childhood-dementia-symposium

Number of clinical trials registered	Disorder
10-20 (cont.)	Rett Syndrome Sly Syndrome (MPS VII) Wilson disease
1-10	Abetalipoproteneaemia Alexander Disease Type 1 Beta-Mannosidosis Beta-propeller protein-associated neurodegeneration Biotinidase deficiency Canavan Disease Cerebrotendinous Xanthomatosis Cobalamin C Disease Cockayne Syndrome Congenital disorders of glycosylation Fatty acid hydroxylase-associated neurodegeneration Fucosidosis Gaucher disease Type 2 Giant axonal neuropathy Glycine encephalopathy GM1 gangliosidosis Holocarboxylase synthetase deficiency Huntington's Disease (Juvenile Form) Infantile neuroaxonal dystrophy Lafora Disease Menkes disease Mitochondrial membrane protein-associated neurodegeneration Molybdenum Cofactor Deficiency Mucolipidosis I, II and IV Pantothenate kinase-associated neurodegeneration (PKAN) Pelizaeus Merzbacher disease

Number of clinical trials registered	Disorder
1-10 (cont.)	Pyruvate dehydrognase deficiency Sialic acid storage disease SLC5A6 deficiency Sulfite oxidase deficiency Vanishing white matter disease Zellweger spectrum disorder
no relevant trials or articles were found	Biotin-Thiamine-Responsive Basal Ganglia Disease Cerebral Folate Deficiency Coenzyme A synthase protein-associated neurodegeneration Combined Saposin Deficiency Farber Disease Galactosialidosis Glutathione Synthetase Deficiency Huntington disease-like variant Juvenile Parkinson's Disease PARK19A Kufor-Rakeb Syndrome MECP2 duplication Multiple sulfatase deficiency Saposin A , B, C deficiencies Schindler Disease Type 1 Woodhouse-Sakati syndrome POLR3 related Leukodystrophies

Identifying the childhood dementia disorders being neglected enables Childhood Dementia Initative to set clear advocacy targets to push for more strategic and impactful research investment, from government, philanthropy and industry. This data set also identifies opportunities where research conducted in one disorder could be extended to others. Please note the number of trials includes multiple trials for an individual drug, e.g. extension studies, and subtrials in different countries of regions that are registered separately.

Types of research

Tracking progress in studies identified through the analysis, the Childhood Dementia Initiative can identify high-value research investment opportunities and potentially access emerging therapies globally, which is vital to treating these disorders in real time.

There is some clinical trial activity ranging from Phase I to Phase IV studies for the majority of disorders, as well as some cross-cutting observational research.

The vast majority (>90%) of trials conducted across the disorders are Phase 1 and/or Phase 2. There is more Phase 3 activity (>5 trials) in some disorders, including:

- GM2 gangliosidosis
- Hunter syndrome
- Niemann-Pick disease Type C
- X-linked adrenoleukodystrophy

A wide variety of intervention types are being tested and discussed for childhood dementia including:

- novel chemical drugs
- enzyme replacement therapies
- gene therapies
- immunotherapies
- dietary/supplement therapies
- drug repurposing
- standard and modified stem cell transplantation
- other stem cell therapies
- ferrochelating therapy
- radiation
- devices

For those areas where there is research in a particular disorder, there is usually a wide range of different intervention types (i.e. a combination of gene therapies, chemical drugs, biologicals, stem cell therapies, dietary supplements, etc) under investigation. The following disorders are all examples of diseases where more than one type of therapy is under investigation :

- Batten disease
- Beta-Mannosidosis
- Beta-propeller protein-associated neurodegeneration (BPAN)
- Canavan Disease
- Cockayne Syndrome
- Congenital disorders of glycosylation
- Fucosidosis
- Gaucher disease Type 2
- Gaucher disease Type 3
- Globoid Cell Leukodystrophy
- GM1 gangliosidosis
- GM2 gangliosidosis

- Holocarboxylase synthetase deficiency
- Hunters syndrome
- Hurler syndrome
- Infantile neuroaxonal dystrophy
- Kufor-Rakeb Syndrome
- Metachromatic leukodystrophy
- MPS III (Sanfilippo Syndome)
- Mucolipidosis I, II and IV
- Niemann-Pick disease Type A
- Pelizaeus Merzbacher disease
- Pyruvate dehydrognase deficiency
- Rett Syndrome
- Sly Syndrome (MPS VII)
- Vanishing white matter disease
- X-linked adrenoleukodystrophy
- Zellweger spectrum disorder

In other disorders, there is a focus on one particular therapeutic type. The table below outlines the disorders for which only one broad type of intervention is being investigated.

Therapeutic Type	Disorder/s
Drug therapies only[6]	Biotinidase deficiency Cobalamin C Disease Fatty acid hydroxylase-associated neurodegeneration Galactosialidosis Glutathione Synthetase Deficiency Huntington disease-like variant Menkes Disease Mitochondrial membrane protein-associated neurodegeneration Niemann-Pick disease Type C Pantothenate kinase-associated neurodegeneration (PKAN) Sulfite oxidate deficiency Wilson disease
Diet/supplements only	Abetalipoproteneaemia Glycine encephalopathy Lafora Disease Sialic acid storage disease SLC5A6 deficiency
Radiation only	Huntington's Disease (Juvenile Form)

[6] Please note the searchable spreadsheet at Attachment B details the types of drugs being investigated.

Gene therapies only	Giant axonal neuropathy[7]

Mitochondrial disease

Mitochondrial disease is reported on separately for two reasons. First, it was not clear whether all identified trials were relevant to childhood dementia, so we have presented it for further analysis by the expert Childhood Dementia Initiative team. Second, mitochondrial diseases are a cluster of diseases that reveal their own internal pattern.

A search was conducted for five mitochondrial diseases:

- Alpers-Huttenlocher
- Kearns-Sayre
- Leigh syndrome
- MELAS
- NARP

There was variation in the level of activity associated with each of these conditons, ranging from no trials identified (NARP), to 20 trials (MELAS). As with other conditions, the majority of trials reported at Phase II studies, although there is some Phase III activity in MELAS, Alpers-Huttenlocher and Leigh syndrome.

A variety of different intervention types are being investigated – most notably drugs and dietary interventions.

[7] this is the one disease for which there was *only* a gene therapy being investigated. Many of the other diseases (on previous page) included gene therapies. These details are contained in the searchable spreadsheet at Attachment B.

Areas of potential collaboration

Health and medical research is undertaken in a complex ecosystem, with private sector, not-for-profit and public sector involvement in both the conduct and funding of research. Research Australia sought to understand who has undertaken the bulk of the research into childhood dementia disorders, who has funded it, and where the opportunities for strategic partnerships lie.

Investigators and institutions

Health and medical research is often conducted within silos. This analysis has identified the experts, internationally, who could be engaged by the Childhood Dementia Initiative for further consideration.

Where trials are being conducted, there is usually a spread of chief investigators and institutions rather than one single, obvious centre of excellence.

This analysis shows institutions where research programs are already well established and can be leveraged for other disorders. There are some investigators that are active across multiple trials and/or disorders and might represent 'centres of excellence'. The table below outlines both Australian and overseas researchers.[8]

Investigator	Institution	Disorder/s researched
Patrick Aubourg; Caroline Sevin	Assitance Publique-Hopitaux de Paris, France	X-linked adrenoleukodystrophy Metachromatic leukodystrophy Canavan Disease
Paul Harmatz	Children's Hospital and Research Center, California, USA	Sly Syndrome (MPS VII) Niemann-Pick disease Type C Hunters syndrome MPS III (Sanfilippo Syndrome)
Kaustuv Bhattacharya; Arthavan Selvanathan	Children's Hospital at Westmead, Australia	Aspartylglucosaminuria
Hisham Abdel-Azim	Children's Hospital Los Angeles, USA	Hurler syndrome Fucosidosis Niemann-Pick disease Type A
Maria Escolar	Children's Hospital of Pittsburgh; UPMC, USA	GM1 gangliosidosis Pantothenate kinase-associated neurodegeneration (PKAN)

[8] Please note clinical trial registries do not list the Primary Investigators at every clinical trial site. There may be investigators involved that are not listed here.

Paul Szabolcs	Children's Hospital of Pittsburgh; UPMC, USA	Globoid Cell Leukodystrophy X-linked adrenoleukodystrophy Hurler syndrome
Randy Windreich	Children's Hospital of Pittsburgh; UPMC, USA	Globoid Cell Leukodystrophy
Adeline Vanderver	Children's Hospital of Philadelphia, USA	Vanishing white matter disease Alexander Disease
James Heubi	Cincinnati Children's Hospital Medical Center, University of Cincinnati, Ohio, USA.	Zellweger spectrum disorder X-linked adrenoleukodystrophy
Wu Landy	Department of Medicine, Frankston Hospital, Melbourne, Victoria, Australia.	Wilson disease
Mohamad Abdulrazak	Department of Medicine, Hunter New England Area Health, Newcastle, New South Wales, Australia.	Wilson disease
Joanne Kurtzberg	Duke University, USA	X-linked adrenoleukodystrophy GM1 gangliosidosis Hunters syndrome Hurler syndrome MPS III (Sanfilippo Syndrome) Metachromatic leukodystrophy Fucosidosis Globoid Cell Leukodystrophy Alpha-Mannosidosis Batten Disease GM2 Gangliosidosis Mucolipidosis Type IV Pelizaeus Merzbacher disease Niemann-Pick disease Type A

Suzanne Ilstad	Duke University, USA	Alpha-Mannosidosis
Yong-Hui Jang	Duke University, USA	Infantile neuroaxonal dystrophy
Gian Luca Forni	Ente Ospedaliero Ospedali Galliera, Italy	Mitochondrial membrane protein-associated neurodegeneration Pantothenate kinase-associated neurodegeneration (PKAN) Fatty acid hydroxylase-associated neurodegeneration Kufor-Rakeb Syndrome
Forbes Porter	Eunice Kennedy Shriver National Institute of Child Health and Human Development, USA	Niemann-Pick disease Type C
Ettore Salsano	Fondazione IRCCS Istituto Neurologico Carlo Besta, Italy	Alexander Disease Type 1
Kumaran Deiva	Hospiteau Universitaires Paris-Sud, France	MPS III (Sanfilippo Syndrome)
Paul Orchard	Masonic Cancer Center, University of Minnesota, USA	MPS III (Sanfilippo Syndrome) Metachromatic leukodystrophy Fucosidosis Globoid Cell Leukodystrophy Sly Syndrome (MPS VII) Alpha-Mannosidosis Aspartylglucosaminuria (AGU) Beta-Mannosidosis Batten Disease GM2 Gangliosidosis Mucolipidosis Type IV Niemann-Pick disease Type A X-linked adrenoleukodystrophy GM1 gangliosidosis

		Hunters syndrome Hurler syndrome
Weston Miller	Masonic Cancer Center, University of Minnesota, USA	Globoid Cell Leukodystrophy GM2 Gangliosidosis X-linked adrenoleukodystrophy GM1 gangliosidosis
Marc Patterson	Mayo Clinic, USA (Department of Neurology)	Niemann-Pick disease Type C
Julie Stout; Alex Veldman	Monash Health, Clayton, Victoria, Australia	Molybdenum Cofactor Deficiency Niemann-Pick disease Type A X-linked adrenoleukodystrophy Huntington's Disease (Juvenile Form)
Aleksandra Djukic	Montefiore Medical Center, USA	Rett Syndrome
Torayuki Okuyama	National Centre for Child Health and Development, Tokyo, Japan.	Hunters syndrome Hurler syndrome
Carsten G Bonnemann	National Institute of Neurological Disorders and Stroke, Maryland, USA	Giant axonal neuropathy
David Rogers	Nationwide Children's Hospital, Columbus, USA	Batten Disease
Mitchell Cairo	New York Medical College, USA	Batten Disease Niemann-Pick disease Type A X-linked adrenoleukodystrophy Metachromatic leukodystrophy Fucosidosis Globoid Cell Leukodystrophy
William Connor	Oregon Health and Science University, USA	Cerebrotendinous Xanthomatosis

Nathan Selden; Robert Steiner	Oregon Health and Science University, USA	Batten Disease
Jan Smeitink	Radboud University Medical Centre, Nijmegan, Netherlands	Mitochondrial diseases
Anita Goh; Mark Walterfang	Royal Melbourne Hospital, Victoria, Australia	Niemann-Pick disease Type C Rett Syndrome Huntington's Disease (Juvenile Form)
Gheona Alterescu; Ari Zimran.	Shaare Zedek Medical Center, Israel	Canavan Disease Gaucher type 3
Lung-Ji Chang	Shenzhen Geno-Immune Medical Institute, China	X-linked adrenoleukodystrophy Metachromatic leukodystrophy
Gregory Enns	Stanford University, USA	Mitochondrial diseases
Neal Sondheimer;	The Hospital for Sick Children, Toronto, Canada	Zellweger spectrum disorder
Joe TR Clarke	The Hospital for Sick Children, Toronto, Canada	GM2 Gangliosidosis
Lynda Polgreen	The Lundquist Institute, Harbor-UCLA Medical Center, USA	Hunters syndrome Hurler syndrome MPS III (Sanfilippo Syndrome)
Caroline Hastings	UCSF Benioff Children's Hospital Oakland, USA	Niemann-Pick disease Type C
Jaap Jan Boelens	UMC Utrecht, Utrecht, The Netherlands Sylvia Toth Center for Multidisciplinary Follow Up After Hematopoietic Cell Transplantation	Globoid Cell Leukodystrophy X-linked adrenoleukodystrophy
Thomas Klopstock; Feriandas Greblikas	University Hospital, LMU Munich, Germany (Friedrich Baur Institute at the Department of Neurology)	Pantothenate kinase-associated neurodegeneration (PKAN)
Aman Wadhwa; Smita Bhatia	University of Alabama, USA	X-linked adrenoleukodystrophy

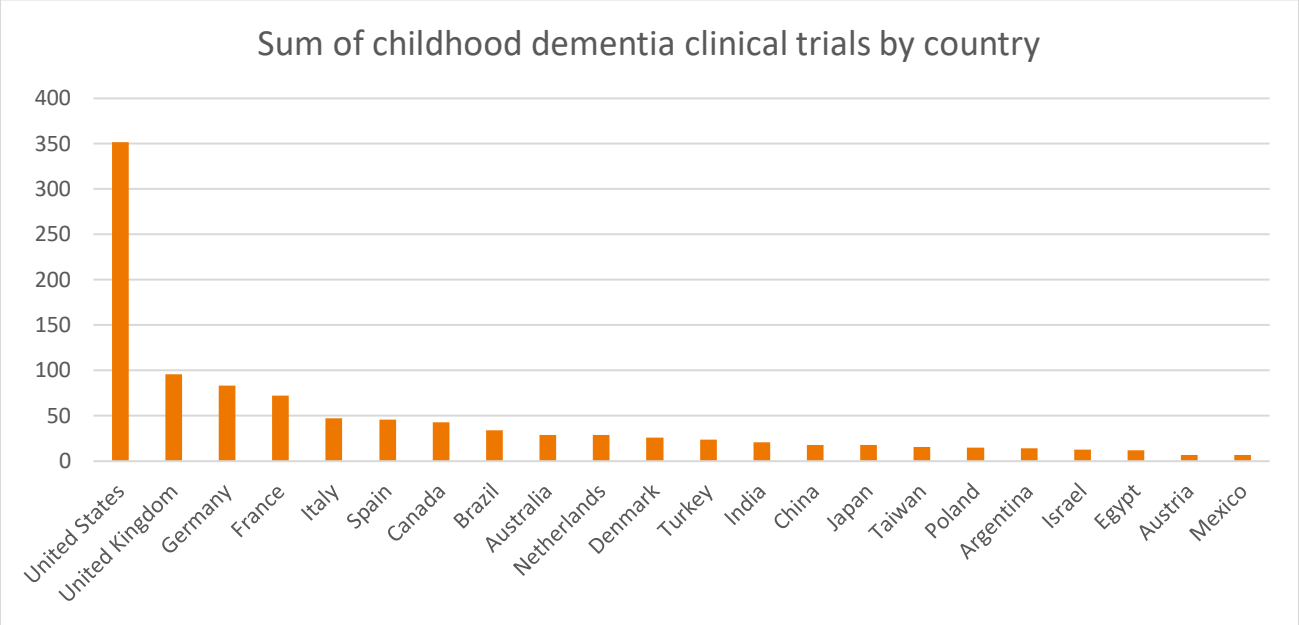
	(Division of Pediatric Hematology and Oncology, Department of Pediatrics)	Hurler syndrome Metachromatic leukodystrophy
Mathew Gentry	University of Kentucky, USA	Lafora disease
Julie Eisengart	University of Minnesota, USA (Department of Pediatrics, Division of Clinical Behavioral Neuroscience)	Hurler syndrome
Troy Lund	University of Minnesota, USA (Department of Pediatrics, Division of Pediatric Blood and Marrow Transplantation)	Aspartylglucosaminuria (AGU) Beta-Mannosidosis Mucolipidosis Type 1 Hurler syndrome
Joseph Muenzer	University of North Carolina at Chapel Hill, USA (Department of Pediatrics)	Hunters syndrome
Ronald Crystal	Weill Cornell Medical College, New York, USA	Batten Disease
Nicholas Smith	Women and Children's Hospital, North Adelaide, South Australia, Australia	X-linked adrenoleukodystrophy Hunter syndrome MPS III (Sanfilippo syndrome)

Geographical comparison

As seen in the table above the current activity of childhood dementia research is dispersed throughout the globe, with certain institutions and investigators having already well established research programs.

The graph below presents the geographical distribution of childhood dementia clinical trials registered on the US based clinical trial registry.[9] Please note Asian countries may not register trials on the US based register if they are not recruiting participants in the USA.

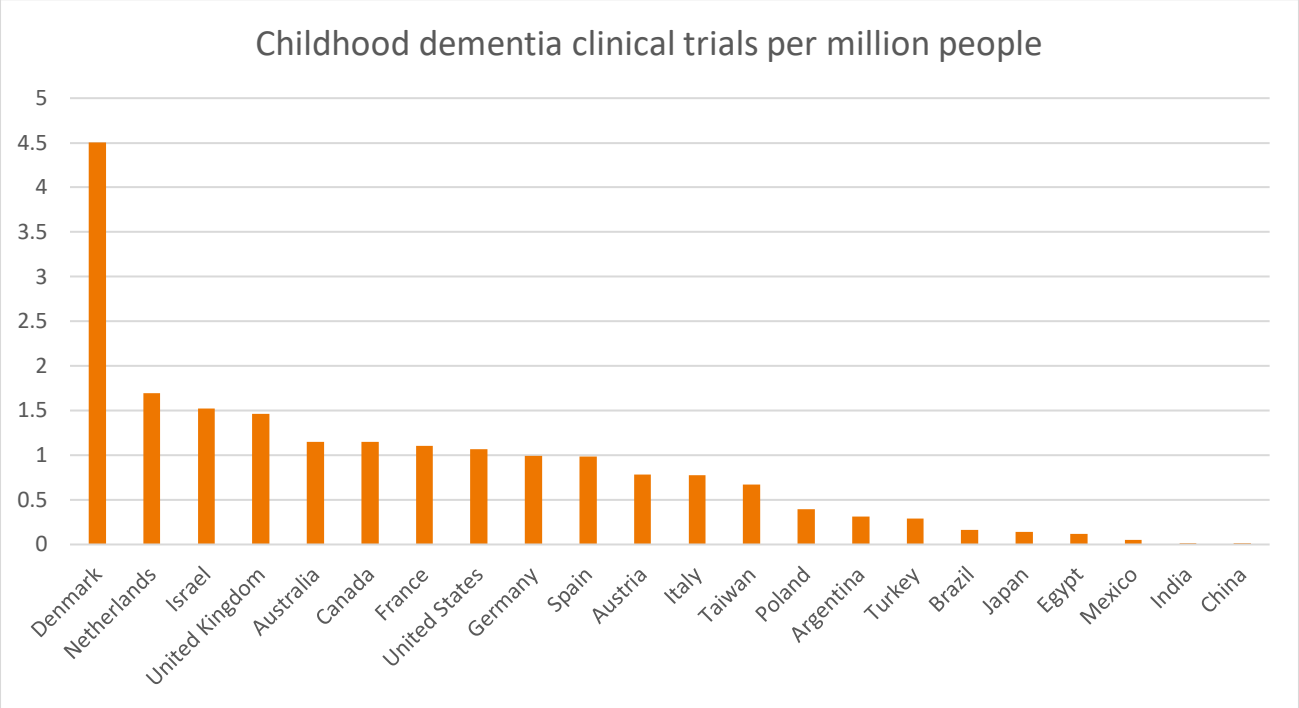
Graph 1: Sum of clinical trials by country[10]



The United States is by far the most active country conducting childhood dementia clinical trials. This data may be skewed due to the source being a US based registry. Australia sits as the 10th most active country for childhood dementia clinical trials. When analysed by the clinical trials per million people the ranking of research activity changes, please see graph below.

[9] Sourced from: https://clinicaltrials.gov/
[10] The number of trials may be underrepresented for some countries as they register trials locally rather than on the US based https://clinicaltrials.gov/. For example, Chinese Clinical Trial Registry (ChiCTR) and The Clinical Trials Registry – India (CTRI).

Graph 2: Clinical trials per million people



The graph above shows Denmark ranking first in the number of childhood dementia clinical trials per million people, Australia moves up to ranking 5th and the United States ranks 8th in comparison. Denmark has a relatively small population (5.8 million) so any increase in the number of trials may skew the ranking. However the relatively high number of trials is most likely due to leadership by clinician researchers such as Allan M Lund.

When compared by the number of clinical trials per million people Australia ranks well, however there are only 14 clinical trials currently active in Australia for childhood dementia, covering just 9 of the 70+ childhood dementia disorders. [11] There is the opportunity to capitalise on the existing base in Australia to harness the potential of childhood dementia research for the estimated 2,300 Australians living with childhood dementia.[12]

[11] These figures are as of June 2022
[12] Childhood Dementia Initiative, 2020, *Childhood Dementia: the base for urgent action.* Available at: https://www.childhooddementia.org/getasset/T2NYDK

Industry

25% of all Australian health and medical research expenditure is in the private sector.[13] While it is difficult to estimate the amount of money spent globally by private companies on childhood dementia research, the importance of this sector for progressing research into childhood dementia cannot be overestimated.

Level of industry activity	Disorder
More than one company involved	Batten Disease Canavan Disease Cerebrotendinous Xanthomatosis Farber Disease Gaucher disease Type 2 Gaucher disease Type 3 Globoid Cell Leukodystrophy GM1 gangliosidosis GM2 gangliosidosis Hunters syndrome Hurler syndrome Kufor-Rakeb Syndrome Lafora Disease Mitochondrial diseases Molybdenum Cofactor Deficiency MPS III (Sanfilippo Syndrome) Mucolipidosis I, II, IV Niemann-Pick disease Type A Niemann-Pick disease Type C Pantothenate kinase-associated neurodegeneration (PKAN) Pelizaeus Merzbacher disease Rett Syndrome Wilson disease X-linked adrenoleukodystrophy

[13] based on Australian Bureau of Statistics (ABS) data, 2017/18. Available at: https://researchaustralia.org/category/hmrfacts/

One company involved	Alexander Disease Type 1 Beta-Mannosidosis Cockayne Syndrome Congenital disorders of glycosylation Fatty acid hydroxylase-associated neurodegeneration Fucosidosis Galactosialidosis Giant axonal neuropathy Holocarboxylase synthetase deficiency Huntington disease-like variant Huntington's Disease (Juvenile Form) Infantile neuroaxonal dystrophy Menkes Disease Metachromatic leukodystrophy Sly Syndrome (MPS VII) Sulfite oxidate deficiency Vanishing white matter disease Zellweger spectrum disorder
No industry activity	Abetalipoproteneaemia Beta-propeller protein-associated neurodegeneration (BPAN) Biotin-Thiamine-Responsive Basal Ganglia Disease Cerebral Folate Deficiency Cobalamin C Disease Coenzyme A synthase protein-associated neurodegeneration Combined Saposin Deficiency Glutathione Synthetase Deficiency Glycine encephalopathy Juvenile Parkinson's Disease PARK19A MECP2 duplication

No industry activity (cont.)	Mitochondrial membrane protein-associated neurodegeneration Multiple sulfatase deficiency (MSD) Pyruvate dehydrognase deficiency Saposin A, B, C deficiencies Schindler Disease Type 1 Sialic acid storage disease SLC5A6 deficiency Woodhouse-Sakati syndrome POLR3 related Leukodystrophies

Industry involvement in childhood dementia research represents a significant opportunity for Childhood Dementia Initiative to seek funding and partnership to progress research into this group of disorders. The following organisations[14] are active in childhood dementia research:

- Aadi, LLC
- Abliva
- Abeona
- Actelion
- Aldagen
- Alexion Pharmaceuticals
- Amicus Therapeutics
- ApoPharma
- ArmaGen
- AXIO Research
- Biogen
- BioMarin Pharmaceutical
- Bluebird Bio
- Cadent Therapeutics
- Cbusinez
- Centogene GmbH
- Cyclo Therapeutics
- Cyprium Therapeutics, Inc.
- DNage B.V
- Edison Pharmaceuticals
- Ente Ospedaliero Ospedali Galliera
- GAAD Medical Research Institute, Inc
- Genzyme, a Sanofi Company
- Green Cross Corporation
- GSK
- Homology Medicines
- Horizon Pharma[15]
- Intra Bio
- JCR Pharmaceuticals
- Kennedy Krieger, Inc
- Khondrion BV[16]
- Magenta Therapeutics
- Mandos
- Minoryx Therapeutics

[14] Please note this is not a complete list because we did not search systematically by funding source. This includes organisations that are both active in just one disorder or active across multiple.
[15] Involved in studying two or more types of mitochondrial disease
[16] ibid

- Neuren Pharmaceuticals, Australia
- Orchard Therapeutics
- Origin Biosciences
- Orpha Labs
- Orphazyme
- Oxford GlycoSciences
- Passage Bio
- Pfizer
- PTC Therapeutics[17]
- Regenxbio
- Retrotope
- Sanagamo Therapeutics
- Sanofi
- Santhera Pharmaceuticals
- Shire
- Takeda Pharmaceuticals
- Talaris Therapeutics
- Travere Therapeutics
- Ultragenyx Pharmaceutical Inc
- Univar BV
- Vtesse, Janssen Research and Development

[17] Involved in studying two or more types of mitochondrial disease

Opportunities for further exploration

Throughout this project, Research Australia has identified several areas for the Childhood Dementia Initiative to implement into future advocacy.

Opportunity 1: Some disorders are receiving considerably more attention than others

Our landscape analysis identifies the distribution of research across the 70 + individual disorders classified as childhood dementia. It is clear that some disorders are being neglected over others. While it is important to consider childhood dementia as a collective rather than discrete conditions, understanding why certain disorders have limited or no research activity (both clinical trials and published articles) over others have will enable Childhood Dementia Initiative to set clear advocacy target to push for more strategic and impactful research investment, from government, philanthropy and industry. The information from this global landscape analysis is also an important foundational database to advocate for a cohesive coordinated approach to research and the funding that underpins it.

Opportunity 2: There are several leading experts and institutions, currently not known by Childhood Dementia, who present opportunities for future strategic partnerships.

Health and medical research is undertaken in a complex ecosystem, with private sector, not-for-profit and public sector involvement in both the conduct and funding of research. This analysis has identified the experts, internationally, who could be engaged by the Childhood Dementia Initiative for further consideration. Where trials are being conducted, there is usually a spread of chief investigators and institutions rather than one single, obvious centre of excellence. There is a key role and opportunity for the Childhood Dementia Initiative to bring these investigators together to increase collaboration and knowledge sharing across disciplines, diseases and institutions.[18]

Opportunity 3: Research being conducted in one disorder could be extended to others

Health and medical research is often conducted within silos. However, we have identified several leading experts globally who have conducted research into more than one of the 70+ childhood dementia disorders. Our analysis also shows institutions where research programs are already well established and can be leveraged for other disorders. Childhood Dementia Initiative has a key role to play in bringing these investigators and institutions together to progress the research of childhood dementia *as a collective*. Research Australia acknowledges the work Childhood Dementia Initiative has conducted prior to this project, including the recent Challenging Childhood Dementia Symposium. The information from this project will enable Childhood Dementia Initiative to continue to promote and enable research that concurrently investigates multiple disorders thereby achieving economies of scale and scope.

Opportunity 4: There is a dynamic industry with an interest in childhood dementia research.

There are opportunities to collaborate with the private sector, including pharmaceutical, biotechnology and medical technology companies, to advocate for private investment in particular kinds of research. While it is difficult to estimate the amount of money spent by these private companies on childhood dementia research, the potential importance of this sector for childhood dementia research cannot be overestimated. Industry involvement in childhood dementia research represents a significant opportunity for Childhood Dementia Initiative to seek funding and partnership to progress research into this group of disorders.

[18] Recommendation from the Inaugural Challenging Childhood Dementia Symposium in March 2022.

Conclusion

This report has presented the key findings from a global picture of the research being conducted into childhood dementia, the opportunities for scientific and industry collaboration, and identification of areas where research conducted into one disorder may be extended to others.

This landscape analysis is a valuable foundation for the Childhood Dementia Initiative to build a full picture in future years. The Search Strategy has been set up as a broad sweep for advocacy and stakeholder linking purposes. Research Australia expects the dataset to evolve over time as the Search Strategy is repeated in the future and we acknowledge there will be hidden research discovered along the way.

Chidlhood Dementia Initiative is leading global action to focus on the commonality of the more than 70 individual genetic disorders rather than the underlying genetic cause.

A better understanding of who is conducting research globally, in what disorders and the areas for collaboration, will encourage more conscious and effective use of limited resources and lead to smarter investment by government, industry and philanthropy.

This information identifies new opportunities for the Childhood Dementia Initiative to promote and enable research that concurrently investigates multiple childhood dementia disorders, thereby achieving economies of scale and scope. It also enables the Childhood Dementia Initiative to foster and harness collaborative and diverse networks.

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