childhood dementia INITIATIVE

State of Childhood Dementia 2022

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Acknowledgements

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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And we would particularly like to extend our heartfelt gratitude to the families of children with childhood dementia who have so generously shared their stories.

Cover image: Sebby who died at 22 months from childhood dementia

Contents

"An end to childhood dementia would save other families the heartbreak of watching their children suffer as their minds slip away."

Karen, mum to twins Amelia and Makenzie (pictured) who have childhood dementia.

Executive Summary

Childhood dementia is a global problem that needs a global solution.

Right now, over 700,000 children and young people are suffering and dying slowly from dementia. They are without access to the care or therapies they urgently need. The majority of these children will not live past the age of 18; their short lives are defined by pain and suffering. And yet, most people have never heard of childhood dementia. Until now, each of the 70+ rare genetic conditions causing childhood dementia have been considered and viewed individually, with little awareness, research or support. This siloed approach has resulted in insufficient investment and advancement in therapeutic development, a lack of appropriate care and support for children and their families, and inadequate recognition of childhood dementia in health policies worldwide.

Collectively addressing childhood dementia is a world-first approach.

Considering the childhood dementia disorders as a collective provides opportunities for greater scale, impact and improvement of policy, services and therapy development. It represents a paradigm shift in how these children are viewed, cared for and treated. This approach has proven to be successful for diseases such as adult dementia and paediatric cancers. For example, over the last 50 years, in countries such as Australia, survival rates for childhood cancer increased from 10% to 80% (O'Leary et al., 2008) and tailored support for children and their families significantly improved.

This report explores the current state of childhood dementia across policy responses, research progress and the support available for children and families. There are significant barriers in all of these areas to achieving much-needed outcomes for children with dementia globally.

Addressing childhood dementia as a collective is a paradigm shift with profound potential.

Childhood dementia is not a health priority.

Despite the high burden of disease associated with childhood dementia, not one of the global policies, action plans or national strategies established to address dementia recognise children as a subset of the dementia population. The inclusion of childhood dementia in policy statements is essential to improve outcomes for children with dementia and ensure that their health and wellbeing are prioritised.

Research is inadequate, fragmented and grossly underfunded.

For most children with dementia there are no treatments available beyond symptom management. In contrast to disorders with comparable numbers, such as cystic fibrosis, there is limited research and clinical trial activity. The research that does occur is generally fragmented with little collaboration across disorders. Addressing these issues will dramatically accelerate the development of much needed treatments and cures for children with dementia.

Care and support is limited and does not meet families' needs.

The burden of childhood dementia on those people who care for them is immense and families' needs are not currently met by health and social systems. A lack of appropriate and responsive care pathways exists and there is limited awareness and understanding among health professionals. Improvements to the systems of care and support will significantly improve the quality of life for children with dementia and their families.

The following key recommendations respond to these barriers and would transform and accelerate progress for children with dementia globally:

- Recognise and include children with dementia in dementia policies, strategies and practice
- Undertake systemic change informed by lived experience
- Increase research funding and clinical trial activity
- Increase collaborative research and shared infrastructure
- Improve health and social care systems to meet families' needs
- Enable earlier diagnosis
- Educate health and social care professionals

There have been some early signs of progress toward addressing childhood dementia in Australia, and as such, some of the findings outlined in this report are specific to that country. However, the challenges and opportunities identified are globally applicable. We are calling on all researchers, policymakers and health and social care professionals across the world to adopt the framework for change, outlined on pages 10 and 11, in order to improve the lives of children with dementia.

Childhood Dementia Overview

Childhood dementia results from progressive brain damage and is caused by over 70 rare genetic disorders. All children with dementia face one common challenge: childhood dementia is progressive. Over months, years or decades, as their brains are damaged more and more, they progressively lose skills they've already developed such as the ability to write, read, talk, walk and play. Their brains also lose the ability to keep the body functioning properly and, eventually, to keep the body alive.

50,000
every year:
The estimated number of
babies born
with a condition that
causes childhood dementia

One in every
2,800 babies
are born with a condition that causes childhood dementia

This is MORE THAN are born with well-known conditions like CYSTIC FIBROSIS

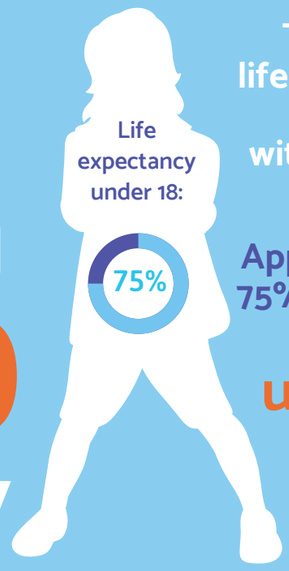
Just like adults with dementia, children with dementia suffer from:

- Memory loss
- Confusion
- Trouble concentrating, understanding, learning and communicating
- Personality changes
- Severely disturbed sleep
- Behavioural issues such as hyperactivity
- Emotional issues like anxiety and fear

Childhood dementia

affects an estimated

700,000
people globally



The average life expectancy for children with dementia is just 28.

Approximately 75% have a life expectancy under 18 years

Every 11 minutes,
someone dies from childhood dementia.

48,300 die
prematurely each year.

In Australia

people in Australia are living with childhood dementia.

Childhood dementia causes around
90 deaths a year.

This is a similar number to deaths from cancer (ages 0-14)

This is a similar prevalence to MOTOR NEURONE DISEASE

Noah's Story

"Noah is from the idyllic island of Bali. He was fostered at 11 hours old and then adopted by Geoff and I, his Australian family, while we were living and working in Bali. He was a happy and healthy baby and met all his milestones. He spent his days going to the beach, riding horses, playing with friends and his beloved giant groodle dog, Nyame. His world was full of joy and laughter.

Noah absolutely loved performing. He just loved dancing, singing and was front and centre at kinder and school concerts, loving the audience and proud of remembering his steps.

As a family, we travelled throughout Bali and Indonesia. Noah loved it. He loved adventures and going on boats and planes. He loved food and lived for spicy dishes and 'nasi' rice.

Noah was always smiling and never cried – not ever – nor did he ever throw tantrums. We used to say he is calm and almost zen because he is Balinese, and many share these gentle and kind traits.

In hindsight, these characteristics may have been a symptom. There were other things too. Like an ever so slightly slurred speech (almost an American accent) and the occasional facial tick when he was tired. Any concerns I had, as a first-time mother, were always dismissed by others as being overprotective or living in a bilingual home (English & Indonesian).

Noah started having noticeable problems jumping and keeping up with his peers from about 3 1/2 to 4 years old. He loved horse riding, but when he got on the horse, it made him so happy, that he passed out. We later found out he had cataplexy and narcolepsy brought on by joy and happiness. Noah then started having problems breathing and developed pneumonia too many times to count. We travelled all over Indonesia searching for answers but with no luck. The adoption process took almost 5 years, and while we loved our life in Bali, we could not travel to Australia for tests or a diagnosis. The government does not grant passports for children undertaking international adoption for fear that families will simply leave the country and not return.

"The diagnosis was a most devastating and heart-breaking experience. It was a complete shock and very difficult to understand that our son would never grow up or grow old."

Noah and I finally arrived in Australia in 2019 and, after 5 months of tests, he was diagnosed with Niemann-Pick Type C (NPC). NPC is a rare degenerative genetic disorder that is fatal. The body slowly malfunctions to the point where it can no longer go on. At this time, Noah was very unsteady on his feet. He could no longer run without falling over. He lost words and began answering questions with either single words or gestures. He also coughed and choked when eating. Up to 6 hours a day was spent slowly feeding, one small mouthful at a time. Around this time was when we first heard the words 'childhood dementia'. As so many of his symptoms were unknown to me, the word 'dementia' stood out. It highlighted the severity of his disease.

The diagnosis was a most devastating and heart-breaking experience. It was a complete shock and very difficult to understand that our son would never grow up or grow old. I can't put into words the pain. As Noah was neurologically symptomatic, he was given only a few short years to live.

Noah's NPC is very aggressive and has taken so much from him in the last few years. He can no longer walk, talk or even sit up. This is because he has ataxia and muscular hypotonia. He is fed via a tube in his tummy because he cannot swallow any of the food he loves so much (dysphagia). He has loads of scary seizures (epilepsy, cataplexy) and can't express to anyone how he feels anymore. We try to interpret his slight gestures and what they mean and act accordingly. I talk to him about activities and which he may prefer. Sometimes he can kick his legs if it is something he wants to do or give me a sideways glance, meaning, "no way, mum!"

His future is very uncertain, and every day, he loses a little more control of his body and brain. He now requires 24-hour support to help him with movement, self-care, and live his best life. He no longer recognises people and places but is most happy doing the things he used to love as a 2 or 3-year-old. He loves music, especially anything Zumba, movies, and people from his past and shows his recognition."

- Jane, Noah's mum

We are very sad to share that Noah died while this report was being written. He was 8.

Framework for Childhood Dementia Systems Change

The **evidence-informed framework for change for childhood dementia** outlined here incorporates care, research and advocacy. The intersection between each of these areas is critical to achieving the outcomes needed:

- Treatments and cures for childhood dementia
- Equitable and quality care for people with childhood dementia
- Recognising childhood dementia as a health policy priority

The interdependent nature of the three areas is key to the model.

Increased funding and activity in the research space are necessary for the development of treatments and cures. However, awareness, policy change and the inclusion of families' perspectives and needs are also critical to enable research.

Improved interventions and emerging therapies rely on early diagnosis and effective care systems to test and implement research breakthroughs.

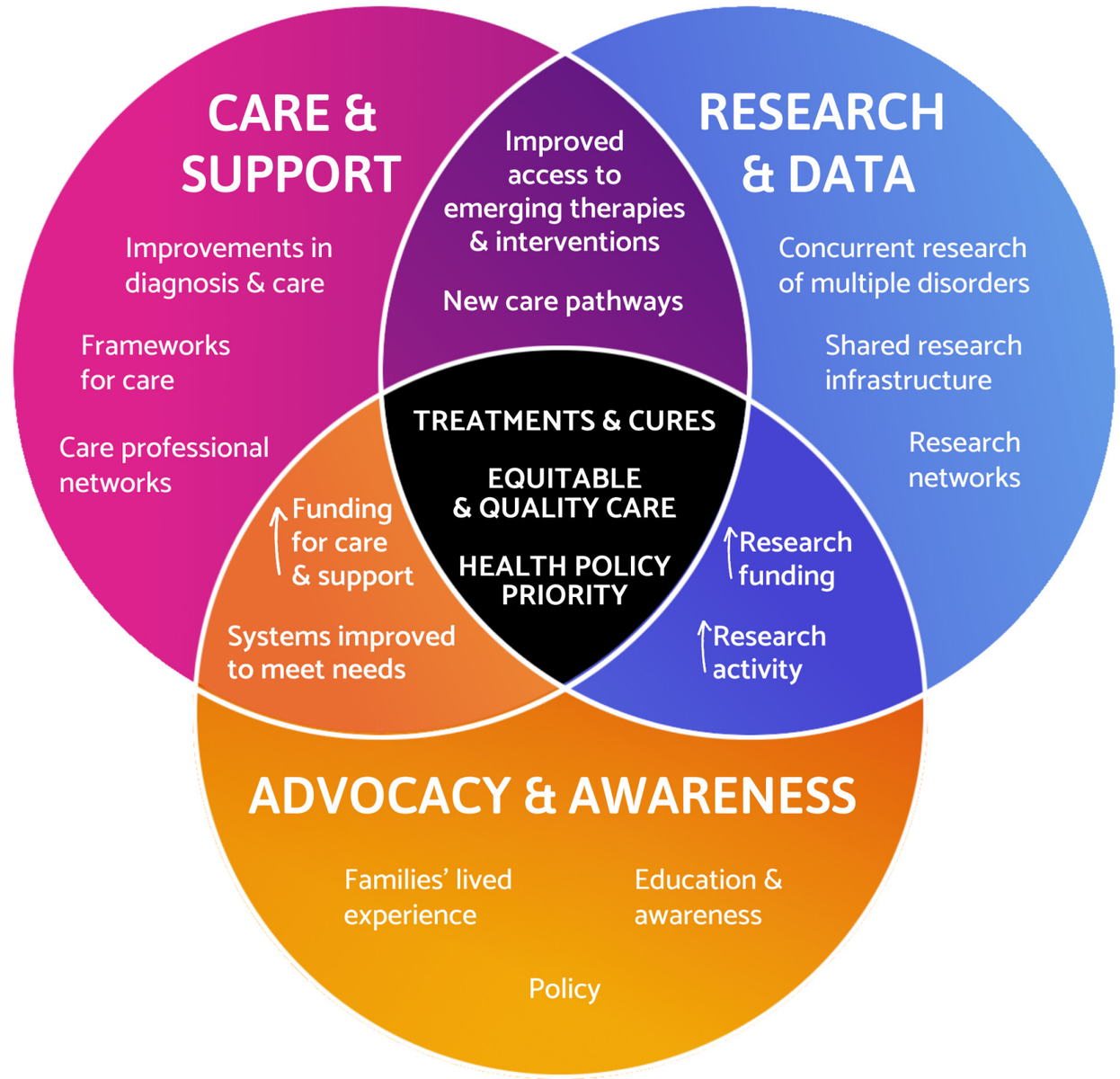
Improvements to care and support need to be informed by lived experiences of families, the latest research, and the capability and expertise of the health and social care systems.

Underpinning this framework are the key principles of evidence, people and co-design. To drive system change, the body of comprehensive **evidence** must first be developed and validated by three key sources: the lived experience of the families of children with dementia; experts working in the field; and empirical data. Evidence required to drive system change for childhood dementia ranges from psychosocial impacts, epidemiological and health system data, research benchmarks, current system issues and opportunities, policy frameworks and funding.

Systems primarily consist of **people,** so gathering the right organisations and stakeholders to **co-design,** implement and embed sustainable solutions is critical. The networks required to drive system change for childhood dementia are diverse and evolving. It includes, but is not limited to, families, researchers and research institutions, health and social care service providers, dementia specialists, policymakers and funders.

The intersection between each of these areas is critical to achieving the outcomes needed.

Figure 1 Framework for Childhood Dementia Systems Change



Advocacy & Awareness

Childhood dementia is not a health priority.

Childhood dementia is currently overlooked both as a health and social issue. As a result, it is excluded from the very plans and policies that could best help address it: global policies, action plans and responses to dementia. This is despite childhood dementia being described in medical literature since the beginning of the 20th century (Girard et al., 1945) and a major study being carried out in the 1990s to define and measure the impact of childhood dementia (Nunn et al., 2002).

By comparison, significant advances have been made to understand adult dementia and its impact. This has driven significant investment globally to improve care and develop treatments. It's important that this focus extends to childhood dementia.

The World Health Organization (WHO) Global action plan on the public health response to dementia 2017 - 2025 (World Health Organization, 2017), makes no reference to childhood dementia. Nor do any of the national dementia plans developed by WHO member states or the global peak body for dementia, Alzheimer's Disease International.

In any of the key global policy documents available, the only references to children are about children or grandchildren of people with dementia, environmental risk factors that can begin in childhood, children in caregiving roles, and the need to educate children about dementia in adults.

Advocacy to government and policymakers is critically needed to address the needs of this neglected sub-population of the dementia community.

Childhood dementia burden of disease

In 2020 Childhood Dementia Initiative partnered with health economists at THEMA Consulting to publish a childhood dementia burden of disease study (Tilden et al., 2020). The study identified over 70 genetic conditions that cause dementia in childhood and conservatively quantified, for the first time, their tremendous and negative collective impact on children, families and the community. Significantly, it revealed that **childhood dementia is relatively common**, with an estimated incidence of one in every 2,800 births and affecting approximately 2,273 people in Australia. This incidence and prevalence are **comparable with well-known diseases such as cystic fibrosis and motor neurone disease** respectively (Massie et al., 2000; Deloitte Access Economics Report, 2015) and can be extrapolated to reveal startling global figures: an estimated 700,000 affected people and 50,000 births every year (Childhood Dementia Initiative, 2020). The study reported that **childhood dementia is severe, complex and life-limiting, and that it necessitates extensive health and supportive care** for patients who often die before adulthood and have an average life expectancy of just 28.

Childhood dementia affects an estimated 700,000 people. Every year, around 50,000 babies are born with a condition that causes childhood dementia.

It also found that there are no effective treatments or cures for most childhood dementia disorders.

The study also projected childhood dementia's economic cost in Australia: AU$3.9 billion between 2021 and 2030, an average of AU$389 million annually. This economic cost of childhood dementia, while significant, is most likely underestimated due to the short life expectancy and lack of available treatment options. **The burden of childhood dementia is therefore disproportionately met by the families caring for children**. Furthermore, the indirect costs incurred by carers of children with dementia are also underestimated since research has shown that rare genetic paediatric conditions are associated with significant negative health impacts on parents, which results in a 'flow on' effect to the healthcare system (Wu et al, 2020).

THEMA Consulting's landmark analysis brought to light the acute impacts of childhood dementia and highlighted the significant unmet need. Understanding the collective impact of childhood dementia, the shared disease mechanisms and commonality of care needs presents significant opportunities to accelerate research towards treatments and cures; streamline and improve services for equitable and quality care; and position childhood dementia as a health policy priority.

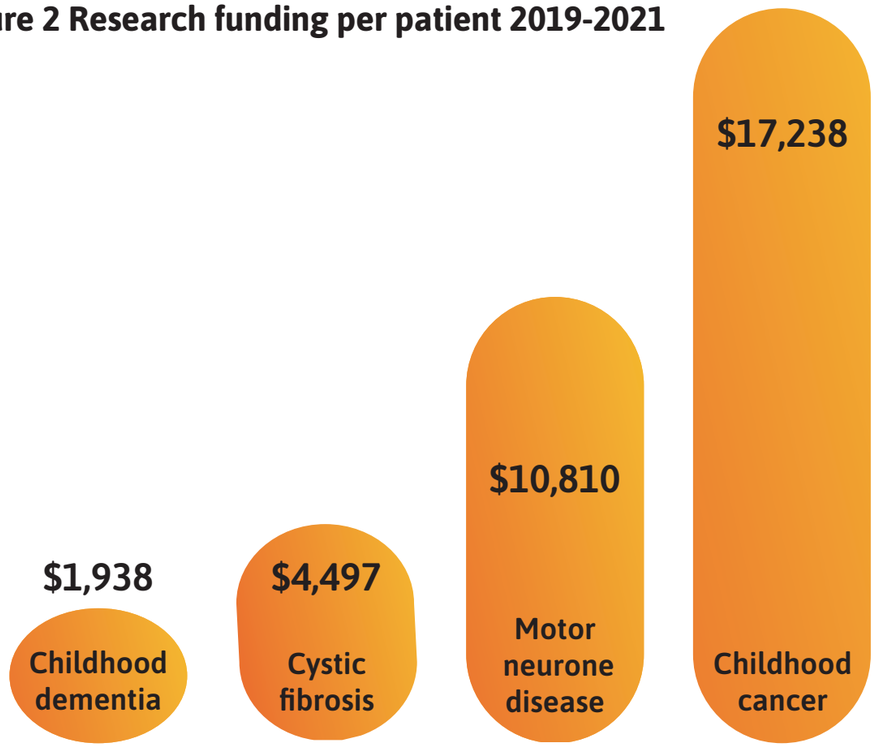
"Recognising these conditions as dementia gives people a connection and way to understand their severity. These children are not in the playground, mainstream school or supermarket. They are at home with their parents who are trying to help them die comfortably."

- Anna mother of Sebby (pictured) who died at just 22 months

Research Funding in Australia: from inequity to world-first progress

Analysis of Australian Government research funding via the Medical Research Future Fund (MRFF) and the National Health and Medical Research Council (NHMRC) shows that, between 2019 and 2021, childhood dementia received much lower levels of funding than comparative disease groups. Childhood dementia received 20 times less funding for research than childhood cancer, with a comparable number of children dying in Australia each year. When analysed **per patient, childhood dementia received 9 times less funding[10] than childhood cancer[11], 6 times less than motor neurone disease and 2 times less than cystic fibrosis** (Figure 2)[12].

Figure 2 Research funding per patient 2019-2021



Investment in research is critical to the development of effective treatments and cures. In 2022, the Australian Federal Government's MRFF announced it would direct AU$3M in funding to research into childhood dementia therapies and treatments. **This is the first government funding of its kind in the world** and a great first step towards addressing the historical neglect in research funding. Much more is needed.

In Australia

In 2020, the Australian Federal Government endorsed the National Strategic Action Plan for Rare Diseases, recognising the need for research into rare diseases to be collaborative, person-centred and systematically address gaps. The Framework for System Change for Childhood Dementia aligns with this Plan.

Childhood dementia did not feature in any policy statements in the 2022 Federal Election. However, dementia organisations in Australia are global leaders. The peak body, Dementia Australia, and leading service provider, HammondCare (provider of Dementia Support Australia) both specifically recognise childhood dementia as a type of dementia.

The family voice

The lived experience of families is central to making improvements in health and social care systems and when influencing policy and research. The family voice must be heard, understood and amplified in order to create appropriate and effective policy recommendations and consumer-centred reforms. The experiences of all families impacted by childhood dementia must be accurately represented, including minority communities and bereaved families. The collation and publication of lived experience contributes to the knowledge base of anyone involved in the care and treatment of children with dementia and enables them to respond accordingly.

In 2021 and 2022, Childhood Dementia Initiative and Palliative Care Australia co-hosted roundtables with families affected by childhood dementia to inform the Commonwealth Paediatric Palliative Care National Action Plan. The outcomes of these focus groups are documented in Childhood Dementia Matters (Childhood Dementia Initiative, 2021), available publicly. One of the key priorities identified during this process was the need for increased understanding of childhood dementia. **Caregivers reported that there was little to no understanding of the condition in the community and the health system**, placing an exhausting burden on parents to be their child's advocate and constantly explain their condition. One parent shared: "No one understands regression".

> **"No one understands regression."**
>
> - Parent participating in roundtable on palliative care in Australia

Due to the reported inadequacy of information resources and limited understanding of their child's condition across systems and services, **awareness and education** resources are urgently required for health and social care professionals, people living with childhood dementia and the broader community. A sustainable approach to education is key. **Childhood dementia education should be integrated into existing infrastructure and curricula to enable an informed, skilled workforce in the future.**

Recommendations

Include children with dementia in dementia policies, strategies and practice

In order to drive systemic change to address the devastating suffering of children with dementia and their families, appropriate policy frameworks are critical. This ranges from local health and social care strategies to global dementia policies, strategies and care protocols. Children with dementia must be acknowledged and responded to with appropriate policy in the World Health Organization's dementia strategies, as well as national dementia strategies globally and the strategies guiding peak bodies such as Alzheimer's Disease International.

Undertake systemic change informed by lived experience

The lived experience of families is central to making improvements in health and social care systems and must influence policy and research priorities. It is essential that the family 'voice' is amplified, heard and understood in order to create appropriate and effective policy recommendations and consumer-centred reforms. This includes bereaved families and families in minority commmunities and rural and regional areas.

[10] Childhood dementia research includes projects focussing on individual childhood dementia disorders, for example Rett syndrome, and a proportion of mitochondrial disease research (25-40% depending on the focus of the project).

[11] Prevalence assumes children with cancer are receiving active treatment for 5 years on average. Between 2017 and 2021 (5 years) there were 5748 children diagnosed 0-19 years old with cancer and 727 deaths. Therefore, it is estimated that 5021 Australian children are receiving active treatment for cancer at any one time. (https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia)

[12] Prevalence of cystic fibrosis and motor neurone disease from (Ahern et.al, 2021) and (Deloitte Australia, 2015) respectively.

Research & Data

Childhood dementia research is inadequate, fragmented and grossly underfunded.

Research into childhood dementia is inadequate, fragmented and grossly underfunded. To accelerate the development of treatments and cures, it is critical that research activity and funding increase and that concurrent research on multiple disorders is undertaken.

Concurrent research of multiple disorders

Globally, research into childhood dementia disorders remains disparate and siloed in nature. Single disorders are typically researched in isolation and, consequently, infrastructure is replicated. This is despite research that suggests overlapping cellular processes are occurring among the various childhood dementia disorders (Alessenko and Albi, 2020; Pará et al., 2020) that could be targeted in the development of treatments. In addition, similar techniques, disease models and equipment can be used to study the cells of the brain to understand these disorders and develop treatments. Cross indication approaches will lead to enhanced efficiencies and greater benefit for children with dementia and may also assist research into adult dementia and other neurodegenerative disorders (Qureshi et al., 2020; Torres et al., 2019; Platt et al., 2018).

Research Activity

A 2022 study to better understand the landscape of childhood dementia research globally (Research Australia, 2022) revealed just 353 childhood dementia clinical trials have been undertaken across 48 countries.[13] **The inadequacy of this clinical trial activity is especially striking in relation to other better-known disease groups.** The number of childhood dementia clinical trials per patient was 18 times less than cystic fibrosis, 12 times less than childhood cancer and 4 times less than motor neurone disease (MND).[14]

In Australia

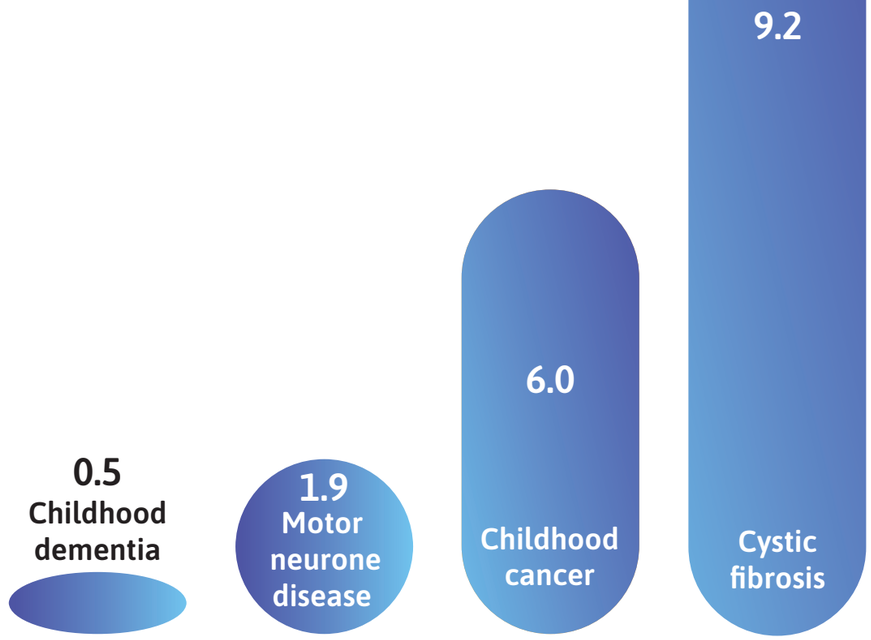
Two Australian research projects focussed on concurrent research of the collective group of childhood dementia disorders:

Researchers led by Professor Ralph Martins, a world-renowned Alzheimer's disease expert at Edith Cowan University in Perth, are working to discover biomarkers for childhood dementia. Biomarkers are substances in bodily fluids, such as blood, that can be measured to track the progression of disease, and importantly, determine if a new potential treatment is having a beneficial effect in clinical trials.

Research led by Associate Professor Michelle Farrar at University of NSW is examining the shared symptoms between childhood dementia disorders, through a literature review and family surveys. This research will help inform the development of therapeutics and optimisation of best-practice management.

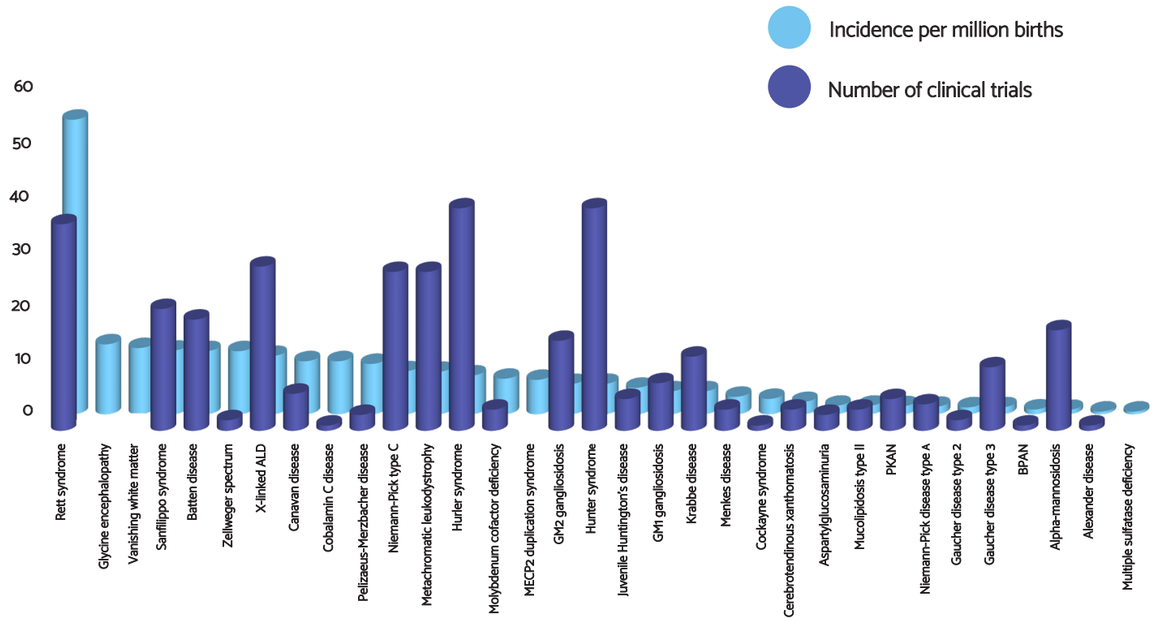
"Just two years ago, Angelina's school work showed full pages of neat writing, underlining, answering of questions and problem-solving. Now Angelina is lucky to write a few words or read simple sentences."
- Niki (above left), mum to Angelina (above right)

Figure 3 Clinical trials per 1000 patients globally



[13] Only clinical trials registered with clinicaltrials.gov were analysed as this is the largest and most accessible database. Some trials may not be registered with this database.
[14] Global prevalence of cystic fibrosis and motor neurone disease from (Guo et al., 2022) and (Xu et al., 2020) respectively. For childhood cancer, it was assumed that active treatment, maintenance therapy or close surveillance lasts for 5 years on average and global incidence and mortality obtained from (Force et al., 2019).

Figure 4 Clinical trials compared to incidence of childhood dementia disorders



Improving access to emerging therapies and interventions via clinical trials is an important outcome of the framework for change as outlined on pages 10 and 11. Clinical trial activity has transformed patient outcomes for comparable disorders in developed countries. A combination of research and advances in disease management have seen life expectancy of cystic fibrosis patients, for example, increased from the first few years of life in the mid-twentieth century, to at least 50 today (Scotet et al., 2020). Similarly, over the last 60 years, the survival rates for childhood cancer rose from 10% to over 80% (O'Leary et al., 2008; Ward et al., 2019).

In addition, the **clinical trials that are occurring for childhood dementia are out of step with need.** Some relatively common disorders have little or no clinical trial activity (Figure 4) and **more than half of the childhood dementia disorders currently have no clinical trial options available to patients anywhere in the world**. It is hoped that the collective consideration of the childhood dementia disorders will address this inequity and increase research activity across the spectrum of disorders.

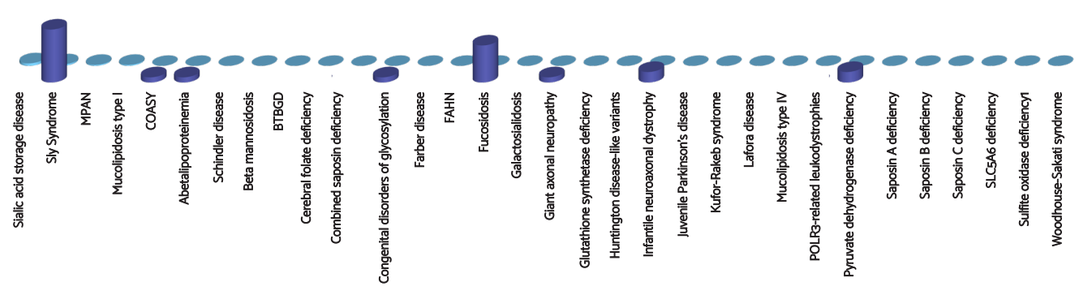
Worryingly, as seen in all rare diseases (Chowdhury et al., 2021), **new clinical trial activity slowed since the beginning of the COVID-19 pandemic** (Supplementary Figure 1) and there has also been a sharp downturn in the biotech market driven by broader economic, clinical, and regulatory setbacks across the whole sector (Pagliarulo, 2022). Given the already inadequate levels of clinical trial activity, this requires increased effort to streamline research and advocate for a regulatory environment to support innovation in this space.

Encouragingly, gene therapies make up a sizable proportion of clinical trials (Figure 5). This is increasing every year (Supplementary Figure 1) and signals progress towards cutting-edge treatments and cures that target the root causes of childhood dementia. Gene therapies aim to replace the dysfunctional gene causing childhood dementia with a healthy version of the gene.

The highest proportion of trials focused on testing small molecule drugs (40%). These are relatively simple drugs which makes them more affordable and less complicated to develop. These drugs may not all be curative but could

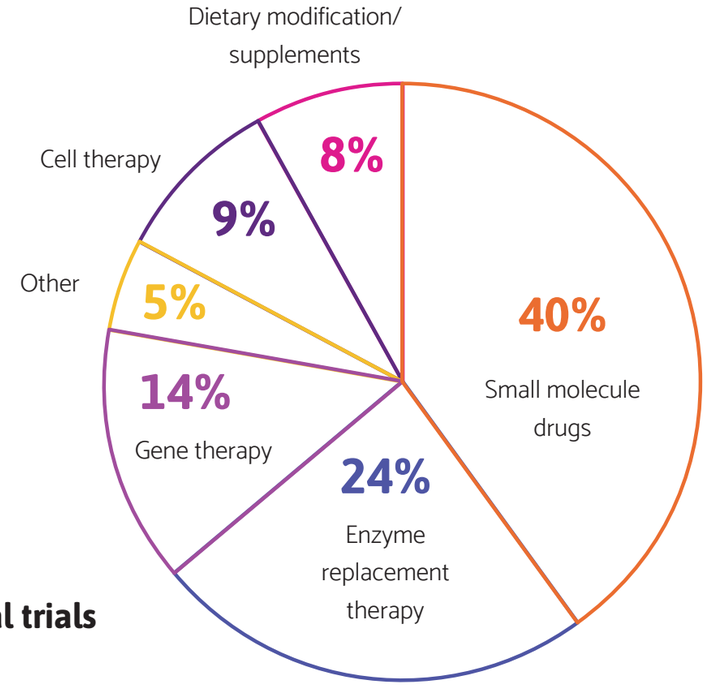
"There is no better time than now to address childhood dementia. Finally, we have a coalescence of brilliant advocates for children and families in desperate need of support and hope. Moreover, advances in the capacity to make a diagnosis earlier in the course of the disease, and the development of innovative novel genetic and other therapies, now make us really optimistic about being able to help children affected by these devastating disorders."

- Professor John Christodoulou, Professor and Chair of Genomic Medicine at the Murdoch Children's Research Institute and the University of Melbourne, and member of Childhood Dementia Initiative's Scientific and Medical Advisory Committee



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 attributes, however, they have only ever been tested in clinical trials one disorder at a time. This means that **opportunities are being missed for more patients to benefit from potential treatments** (Supplementary Table 1).

Figure 5 Types of potential treatments tested in clinical trials

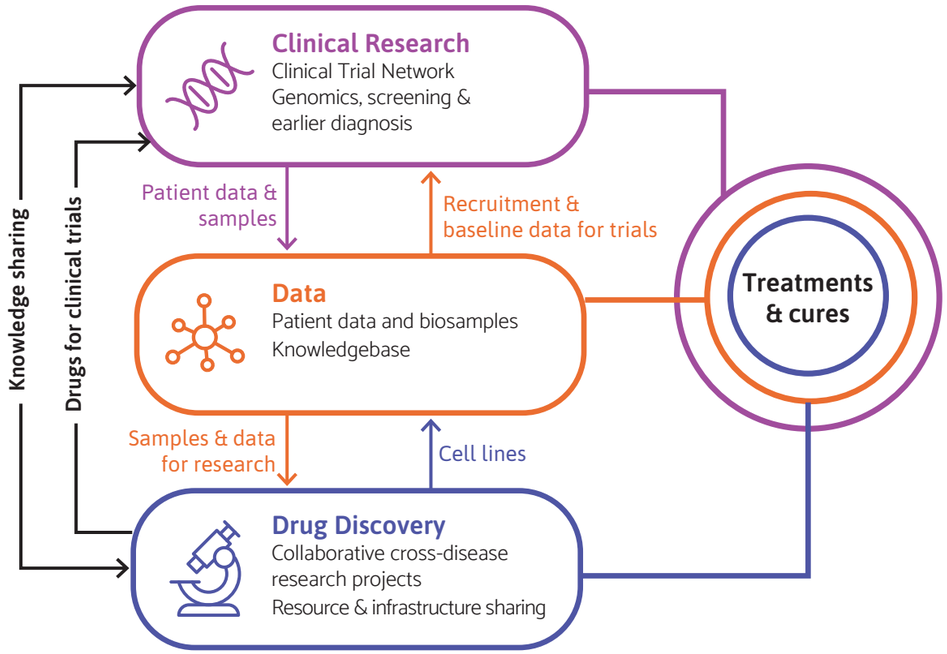


Collaborative Research

Collaborative research is critical to address fragmentation and increase resource and knowledge sharing across disciplines, diseases, and institutions. This includes networks and collaboration between lab-based scientists discovering potential new treatments and cures, and clinician researchers working to diagnose patients and conduct clinical trials (Figure 6). The collection, storage and sharing of patient data and biosamples is crucial to accelerating this research and plays a central role. In addition, collation of data about the childhood dementia disorders into a knowledgebase will support both drug discovery and clinical research (see below).

In early 2022, the inaugural Childhood Dementia Symposium was held in Sydney, Australia. It was the first meeting of its kind, bringing together 75 clinicians, researchers, industry, and patient representatives. The symposium enabled the formation of a network for collaborative research. The benefits of this network were quickly evident. Experts from this network, with a range of backgrounds, were able to form new collaborations and respond to an Australian Federal Government call for grant applications (see page 14) with diverse and innovative proposals, and research initiatives across multiple disorders.

Figure 6 Collaborative research model

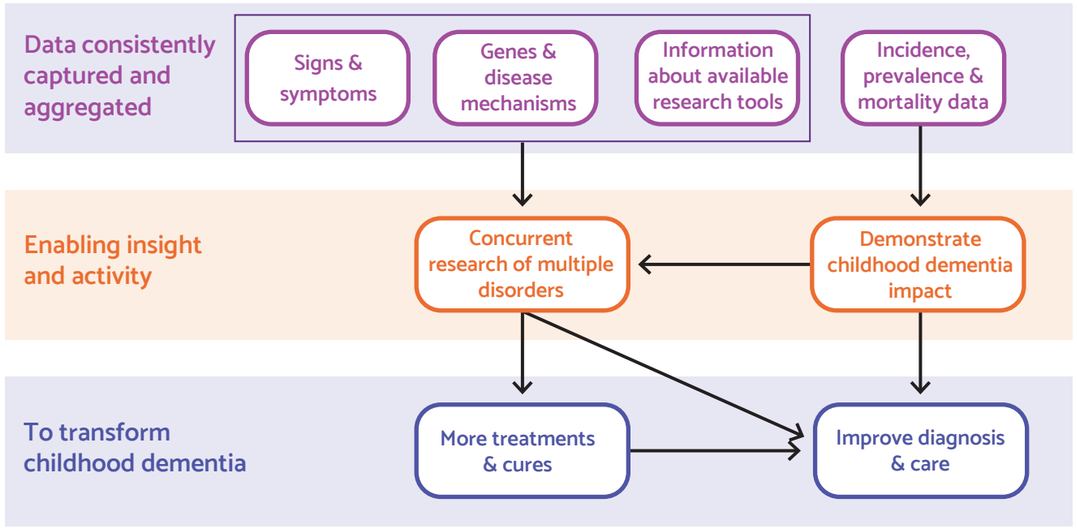


Shared research infrastructure

In order to create efficiencies in research and accelerate progress, shared infrastructure is required, the Childhood Dementia Knowledgebase is one example of this. It contains key statistics such as incidence, prevalence, life expectancy, and age of onset and diagnosis for each of the 70+ conditions that cause childhood dementia. It provides data on the collective impact of childhood dementia that can be used for advocacy and research funding applications. The relational database also contains information including genetic cause, signs and symptoms, and disease mechanisms for each disorder. This powerful resource gives the ability to identify disorders with a particular symptom or which are amenable to a certain treatment approach, encouraging the concurrent study of multiple childhood dementia disorders.

The Knowledgebase has been used by many researchers to plan new and innovative research projects. It was designed as a public resource for all clinicians and researchers to interrogate for their research.

Figure 7 Childhood Dementia Knowledgebase elements and outcomes



Find the Knowledgebase at: www.childhooddementia.org/knowledgebase

Recommendations

Increase research funding and clinical trial activity

Large-scale funding is urgently needed for research which concurrently studies multiple childhood dementia disorders and develops new therapeutics. This will enable more clinical trials, and ultimately, accelerate the development of treatments and cures. Innovative clinical trial designs are also required to streamline testing of more potential treatments for a greater number of childhood dementia disorders.

Increase collaborative research and shared infrastructure

Collaboration and shared resources and infrastructure are required to accelerate the development of new treatments and cures. This is especially important for advanced therapeutics, which have enormous potential but are costly. Advanced therapeutics, such as gene therapy, aim to target and correct the genetic change in a small group of patients. Economies of scale can be created by sharing platform technology and infrastructure across disorders, giving children access to treatments that otherwise would have been too expensive to develop.

Care & Support

Care and support for childhood dementia is limited and does not meet families' needs.

Once diagnosed, a child might live with dementia for months, years or even decades and the impacts of childhood dementia on families worldwide are substantial. Families face a unique set of challenges: the complex nature of the disorders that cause childhood dementia coupled with the ongoing management of dementia symptoms.

There is currently a dearth of knowledge around the needs and experiences of children with dementia and their families. There is an urgent need to build this evidence base to drive improvements in diagnosis and care. **Emerging evidence shows that the specific psychosocial needs of children with dementia and their families are currently not being met by health and social systems.**

Family accounts and emerging research findings suggest that the major challenges faced by families include:

- Significant delays in receiving accurate diagnoses
- Medical teams they come into contact with lack relevant knowledge
- Issues accessing timely therapies
- A deficit of care pathways and the need for parents "to constantly battle" to gain access to appropriate care
- Insufficient coordination of care across health and social care services
- Inadequate levels of awareness, compassion and respect across health and social care professionals

The University of New South Wales (UNSW) conducted a world-first systematic review (Nevin, et al., 2022), the first of its kind, assessing the global literature available **regarding the psychosocial impact of childhood dementia on children and families.** The findings of this study, coupled with ongoing consultation with families of children with dementia (Childhood Dementia Initiative, 2021), provide this first view of the shared psychosocial impacts of childhood dementia disorders on parents. The systematic review draws from literature from developed countries around the world, hence outcomes can broadly be applied to this population.

The emerging themes indicate that caregivers endure perpetuating uncertainty and chronic social and psychological isolation due to limited medical knowledge and insufficient healthcare support for their child. The key areas of concern are the severity of caregiver burden and that health and social systems are not effectively meeting the needs of families.

Severity of caregiver burden

Childhood dementia is a chronic, life-limiting condition that requires increasingly complex care, often over many years, even decades. Emerging research shows that the impacts on mental health and overall quality of life for carers of children with dementia are more significant than the impacts of caring for children with other chronic diseases like cancer (Grant et al., 2013, Nevin et al., 2022). Childhood dementia is an unpredictable condition with no cure and an inevitably shortened life expectancy. Parents watch their children progressively decline, interrupted by disease-related traumatic events - this is highly distressing and causes significant social isolation.

Over time, children become reliant on full-time supportive care. In the absence of appropriate and responsive care pathways and support services, parents are left to step in to fill the gaps.

"I know as a parent how isolating it can be and there are days where you feel completely hopeless. I want to make other families, like ours, living with childhood dementia feel supported and have hope for a future with more research and treatments available to overcome this disease."

- Renee (right), with her children Holly, Austin and Hudson, all of whom have a disorder that causes childhood dementia.

The caregiving burden is immense with one study indicating that mothers spent, on average, 88 hours per week caring for their child[15] (Ammann-Schnell et al, 2021). Behavioural challenges associated with dementia, including aggressive behaviours, hyperactivity, agitation, inability to communicate and toileting challenges are particularly draining and distressing for parents, who frequently report a lack of available information and support to assist with management and coping (Hoffmann et al., 2020).

Caregivers experience heightened emotional, social, practical and financial stressors throughout their caregiving journey. Further evidence is required to deepen our understanding of these impacts.

Family needs not met by health and social systems

Emerging research highlights the extensive challenges families face navigating their child's care, accessing timely therapies and support services, and connecting with healthcare professionals who are knowledgeable regarding their child's condition. **A lack of awareness and understanding across health professionals contributes to a number of significant issues including:**

- A protracted timeframe to diagnosis and a lack of timely referral to appropriate care and support once diagnosed
- The requirement for parents to become the experts on their children's conditions and constantly educate health professionals caring for their children, a role that families report as 'exhausting'
- Parents report health professionals lack awareness and understanding of their children's healthcare needs and the associated caregiver burden
- A lack of recognition of the impacts of a child's diagnosis on other members of their family, and thus a lack of connection to appropriate supports
- A lack of understanding of dementia symptoms, resulting in the use of terms such as 'behavioural issues' which triggers exclusion from services such as respite care

In the absence of care pathways and responsive health and social care systems, **parents take on the roles of care coordinator and advocate for their children and families.** Parents describe these roles as taking over their lives and leaving little space for anything else. Without policy and practice to guide care, families report gaps in what they need and a lack of coordination between services. It appears likely that there are vast inequities in care and support due to the requirement for individuals to act as advocates.

[15] Average age of children in this study was 11.6 years. For comparison, an Australian survey showed that mothers spent 14 hours per week on average caring for children aged 5 to 11 and 6 hours per week caring for children aged 12 to 14 (Australian Bureau of Statistics, 2006).

Evidence indicates that transitions between life stages and/or between key systems are major pain points. For example, parents report positive experiences once connected with palliative care, but timeliness of referral is vastly inconsistent. The transition from children's to adult health and disability systems results in a multitude of issues, often leaving families with reduced support at a time when care needs increase.

A more comprehensive qualitative and quantitative study is required to understand families' unmet needs, and identify key gaps in health and social system delivery that will enable system improvement. In partnership with consumers, UNSW has proposed a mixed methods study with caregivers and health professionals that will provide this deep insight into the Australian childhood dementia environment. Partners represented in the project include, Childhood Dementia Initiative, Dementia Australia, Rare Voices Australia, HammondCare, Palliative Care Australia and THEMA Health Economics. At the time of publication, this project was pending funding.

As the body of evidence begins to grow, **frameworks for care will translate research findings into practice**, with clear implementation plans and evaluation processes.

The value of the Dementia Lens

Behavioural and psychological symptoms of dementia (BPSD) is a key feature for people who have dementia. Given the lack of effective treatments available, care and support of children with dementia is largely focused on symptom management. Families report that the existing systems and services do not understand the needs of a child with BPSD or the regressive nature of dementia. Future policy and practice must distinguish childhood dementia from conditions such as intellectual disability, head injury or encephalitis where normal development is slowed, or where skill loss is transient or static. Enduring and progressive loss of previously acquired skills and the associated BPSD, hallmark characteristics of childhood dementia, must be recognised and responded to in health and social care systems to enable appropriate, quality care and avoid the exclusion of these children from services due to 'behavioural issues'.

Early indicators suggest that viewing the childhood dementia disorders through a 'dementia lens' is likely to increase understanding of the behaviours, challenges and needs of a child with dementia, and to deliver immediate improvements to existing care and support. Benefits have been reported from allied health services who have adopted clinical practice to take a dementia-informed approach.

Childhood dementia around the world

It is expected that the incidence of childhood dementia around the world will be similar in all countries (Uvebrant et al., 1992), however, there are some notable exceptions. The **Ashkenazi Jewish population, for example, has a very high risk of childhood dementia disorders** including Canavan disease, Tay Sachs disease, Niemann-Pick disease type A and Mucolipidosis type IV (Risch et al., 2003). Parents with Ashkenazi Jewish ancestry have an approximately two-fold higher risk of having a baby born with a childhood dementia disorder. Preconception carrier screening programs in Jewish communities in countries including Australia, Canada, the USA, and Israel, have resulted in dramatically reduced incidence of these disorders.

A UK study found higher rates of childhood dementia in people of South Asian descent (Devereux et al., 2003) and an Australian study found a higher prevalence of mitochondrial disorders in people of Lebanese descent (Skladal et al., 2003). **Carrier screening should be made widely accessible** for any couple planning to have children who would like to understand their risk. As shown by the success of the screening in the Ashkenazi Jewish population and results of the MRFF-funded Mackenzie's Mission project (Delatycki M, personal communication, 29 Sept 2022), this could significantly reduce the incidence of childhood dementia in the future.

It is important to note that in **developing countries** where access to healthcare is poor, **children are likely to die younger without the palliative supports** that are available in developed healthcare systems, and therefore the prevalence of childhood dementia will be lower.

"Thinking about my young patient living with a form of childhood dementia demystified my approach. I could empathise more as I was now dealing with something that is so much more common and understood. I began to think, 'is she scared, anxious, agitated?' In her therapy, we reverted to old familiar activities and instantly there was calm."

- Kate Montgomery, Speech Pathologist, Director - Communicare Speech, Language and Learning Services

The importance of early diagnosis

Early diagnosis is not only critical for the delivery of equitable and quality care, it also plays a key role in the development of much needed therapeutic interventions for children with dementia. The window of time where therapeutic intervention might be most effective is largely unknown for the childhood dementia disorders. It is thought, however, that in many cases if a child is presenting with symptoms significant enough to lead to diagnosis, it may be too late (Sevin and Deiva, 2021). This presents a tragic dichotomy for the development of treatments and cures. If pre or early symptomatic children are not able to be identified to participate in clinical trials, demonstration that a particular intervention is effective is not possible which means that therapeutics are not made available for children with these conditions. Expanding and improving newborn screening programs and rapid diagnosis pathways for childhood dementia disorders would make great strides towards breaking this tragic predicament.

Early diagnosis also restores reproductive confidence for families both within the immediate family of an affected child as well as their broader family.

In Australia

Adapting clinical practice for improved diagnosis and care

Professor Katrina Williams, a prominent neurodevelopmental paediatrician at Monash Health in Melbourne, is leading a project that aims to diagnose children with developmental regression earlier and provide early intervention and support. This project encompasses childhood dementia and other conditions, including autism. The researchers partnered with Childhood Dementia Initiative to ensure the project meets the needs of the childhood dementia community as they are at the most severe end of developmental regression.

Recommendations

Enable earlier diagnosis

Access to early diagnosis through newborn screening and rapid diagnosis pathways is needed to improve the development and access to emerging therapies as well as optimal care and support. Earlier diagnosis also informs future reproductive and other planning decisions for families that have a child diagnosed with dementia.

Educate health and social care professionals

Broad awareness of childhood dementia is required across health, disability and education settings to support early diagnosis and ongoing responsive care. Those working with children with dementia need a deep understanding of family needs, emerging research and changing policy and practice. Workforce education must be embedded in systems and structures ensuring ongoing sustainable change.

Improve health and social care systems to meet families' needs

Further research into the psychosocial impacts on families and their experiences of health and social care systems is urgently needed to address families care and support needs. Outcomes of this research will inform the development of frameworks for care that will guide improvements in systems and services to better meet needs.

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Appendix

List of childhood dementia disorders

Lysosomal diseases

Lysosomal disorders of lipid metabolism and transport

- Combined saposin (prosaposin) deficiency
- Farber disease
- Gaucher disease (type 2)
- Gaucher disease (type 3)
- Globoid cell leukodystrophy (Krabbe disease)
- GM1 gangliosidosis (type 1 and 2)
- GM2 gangliosidosis - AB variant
- GM2 gangliosidosis (Tay Sachs disease)
- GM2 gangliosidosis (Sandhoff disease)
- Metachromatic leukodystrophy
- Multiple sulfatase deficiency
- Niemann-Pick disease type A
- Niemann-Pick disease type C
- Saposin A deficiency
- Saposin B deficiency
- Saposin C deficiency

Glycoproteinosis

- Alpha-mannosidosis
- α-N-acetylgalactosaminidase deficiency (Schindler disease (type I))
- Aspartylglucosaminuria (AGU)
- Beta-mannosidosis
- Fucosidosis (type I and II)
- Galactosialidosis (cathepsin A mutation)
- Mucolipidosis type I (sialidosis type II)
- Mucolipidosis type II (i-cell disease)
- Mucolipidosis type IV

Mucopolysaccharidoses

- MPS I (Hurler syndrome)
- MPS II (Hunter syndrome)
- MPS III (Sanfilippo syndrome)
- MPS VII (Sly syndrome)

Other lysosomal diseases

- Neuronal ceroid lipofuscinoses (NCLs or Batten disease); 14 subtypes (except those that are adult onset CLN 4, 11, 13)
- Sialic acid storage disease

Other disorders of lipid metabolism and transport

- Abetalipoproteinaemia
- Cerebrotendinous xanthomatosis

Disorders of amino acid and other organic acid metabolism

- Canavan disease
- Glutathione synthetase deficiency
- Glycine encephalopathy / nonketotic hyperglycinemia
- Holocarboxylase synthetase deficiency
- Sulfite oxidase deficiency

Appendix

List of childhood dementia disorders continued.

Vitamin-responsive inborn errors of metabolism

- Biotinidase deficiency
- Biotin-thiamine-responsive basal ganglia disease
- Cerebral folate deficiency
- Cobalamin C disease (Cbl-C)
- Molybdenum cofactor deficiency
- SLC5A6 deficiency

Disorders of mineral absorption and transport

- Menkes disease
- Wilson disease

Peroxisomal disease

- X-linked adrenoleukodystrophy
- Zellweger spectrum disorder

Other Inborn errors of metabolism

- Mitochondrial disorders (including but not limited to: Leighs, KSS, MELAS and Alpers-Huttenlocher syndrome).
- Congenital disorders of glycosylation (subset of e.g. CDG1E, CDG1J, CDG2A)
- Lafora disease

Leukodystrophies not otherwise categorised

- Alexander disease (type I)
- Pelizaeus Merzbacher disease
- POLR3-related leukodystrophies
- Vanishing white matter disease

Neurodegeneration with brain iron accumulation

- Beta propeller protein associated neurodegeneration (BPAN)
- Coenzyme A synthase protein-associated neurodegeneration (COASY)
- Fatty acid hydroxylase-associated neurodegeneration (FAHN)
- Kufor-Rakeb syndrome
- Mitochondrial membrane protein-associated neurodegeneration (MPAN)
- Pantothenate kinase-associated neurodegeneration (PKAN)
- Woodhouse-Sakati syndrome (DCAF17)

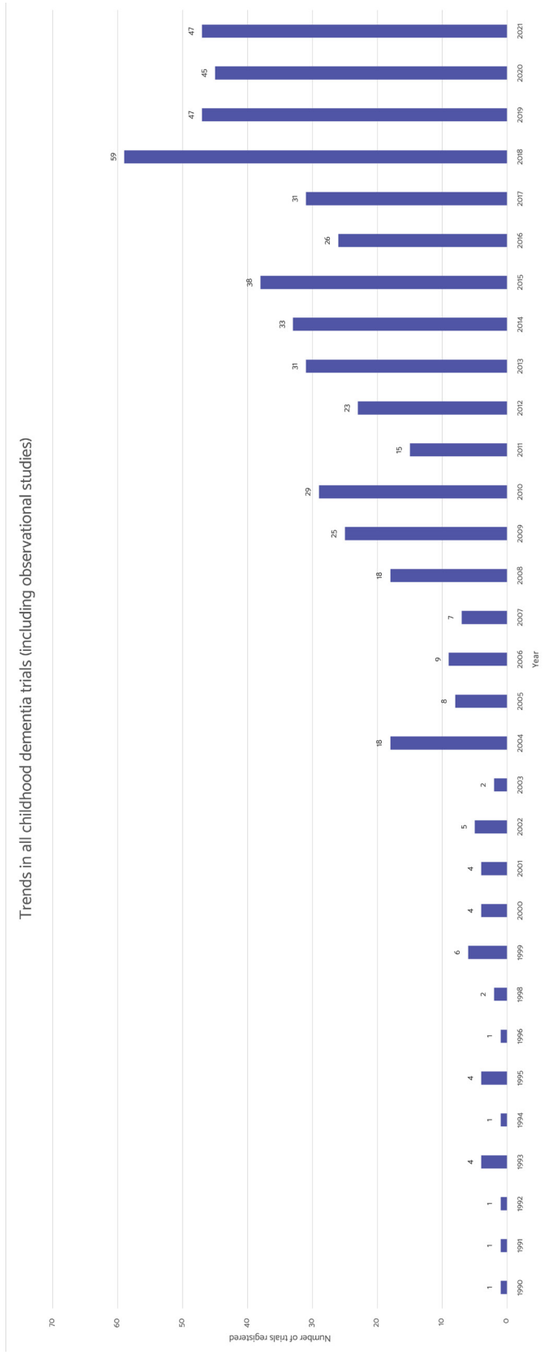
Neurodegenerative diseases not otherwise categorised

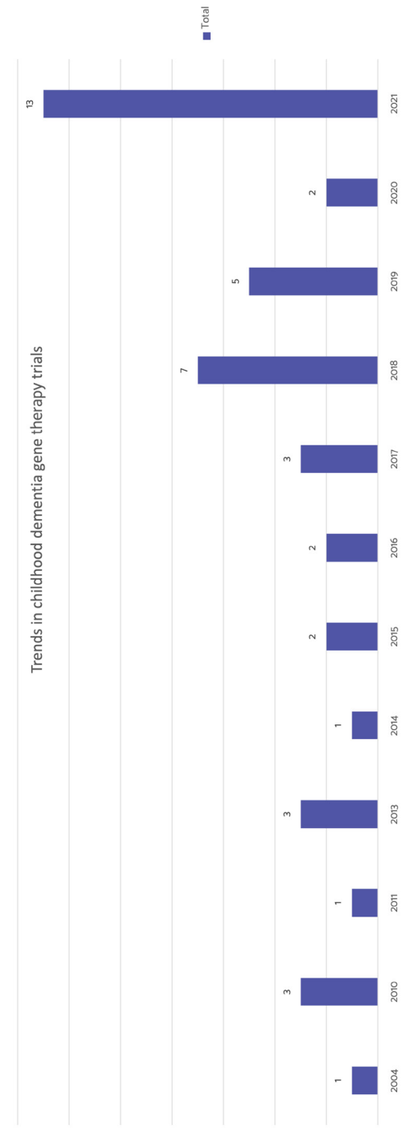
- Cockayne syndrome
- Giant axonal neuropathy
- Huntington's disease (juvenile form)
- Infantile neuroaxonal dystrophy
- Juvenile Parkinson's disease PARK19A (DNAJC6)
- MECP2 duplication syndrome
- Other HD-like variants (particularly HDL3)
- Rett syndrome

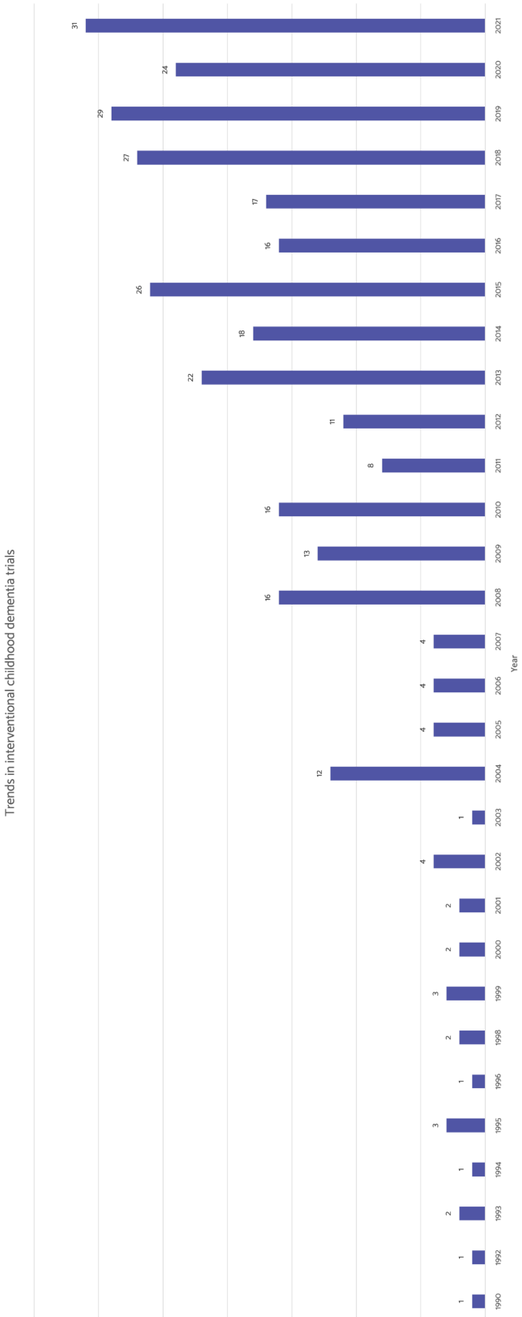
NOTE: this list is constantly evolving and new disorders will be added over time. Some of these disorders are highly variable and not all children will experience dementia.

Supplementary Information

Supplementary Figure 1: Trends in childhood dementia clinical trials over time







Supplementary Information

Supplementary Table 1: Examples of drugs that have been tested in clinical trials for individual types of childhood dementia in isolation but may have broad applicability across multiple disorders

Drug category/mechanism of action	Drug name	Types of childhood dementia in clinical trials
Inhibitors of lipid accumulation	Desipramine	Infantile Neuroaxonal Dystrophy, Rett syndrome
	Miglustat	CLN3, Tay sachs, Sandhoff, Niemann-Pick disease type C*
	Eliglustat	Gaucher disease type 3
	Venglustat	Sandhoff and Tay Sachs disease
Anti-inflammatory/immune modulators	Mycophenolate mofetil	CLN3
	Anakinra	Sanfilippo syndrome (MPS III)
	Fingolimod	Rett syndrome
	OP-101 (HD-N-acetyl cysteine)	X-linked Adrenoleukodystrophy
	ABI-009 (sirolimus albumin-bound nanoparticles)	Leigh Syndrome
Antioxidant/mitochondrial modulators	Vatiquinone/EPI 743	mitochondrial diseases, Cobalamin C disease, Rett syndrome*
	Cysteamine Bitartrate	mitochondrial diseases
	KL1333	mitochondrial diseases
	Sonlicromanol/KH176	mitochondrial diseases
	IW-6463	MELAS
	Idebenone	MELAS
Cannabinoids - neuroprotective	Cannabidiol	Rett syndrome
Chaperone	Arimoclomol	Gaucher disease type 3, Niemann-Pick disease type C*
Fatty acid	Triheptanoin	Rett syndrome
	RT001	Infantile Neuroaxonal Dystrophy
Insulin-like growth factor-1	rIGF-1	Rett syndrome
	Trofinetide (IGF-1 neuropeptide)	Rett syndrome
Mood stabiliser - neurotrophic and neuroprotective	Lithium	Niemann-Pick disease type C, Huntingtons, Canavan disease*
PPAR agonist	MIN-102	Cerebral Adrenoleukodystrophy
	PLX-200	CLN3
Sigma-1 Receptor agonist	pridopidine	Huntingtons disease
	ANAVEX2-73	Rett syndrome
NMDA receptor antagonist	Dextromethorphan	Rett syndrome
	Ketamine	Rett syndrome

* each disorder had/has it's own clinical trial
CLN3= Classic juvenile neuronal ceroid lipofuscinosis aka Batten disease, MELAS=Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes (a type of mitochondrial disease)