childhood dementia INITIATIVE

Early diagnosis of childhood dementia: challenges, importance, and opportunities for improvement

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Acknowledgments

In the spirit of reconciliation, Childhood Dementia Initiative acknowledges the Traditional Custodians of country throughout Australia and their connections to land, sea and community. We pay our respects to their elders past and present and extend that respect to all Aboriginal and Torres Strait Islander peoples today.

Childhood Dementia Initiative considers the voices of families as central to improving awareness and understanding of childhood dementia, and to creating change. We thank and acknowledge the parents and families who contributed to this report.

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Abbreviations

CLN2: Neuronal ceroid lipofuscinosis type 2 (a type of Batten disease)

EMA: European Medicines Agency (European Union)

ERT: enzyme replacement therapy

FDA: Food and Drug Administration (USA)

HSCT: haematopoietic stem cell transplant

LSDP: Life Saving Drugs Program (Australia)

MPS: mucopolysaccharidoses (a group of inherited lysosomal storage disorders)

NPC: Niemann-Pick disease type C

PBS: Pharmaceutical Benefits Scheme (Australia)

TGA:Therapeutic Goods Administration (Australia)

Executive Summary

Childhood dementia is caused by over 145 genetic disorders and affects approximately 1 in 2,900 births. Half of the children with these conditions die before age 10, and most do not reach adulthood. Early diagnosis is crucial yet remains a significant challenge.

Early diagnosis of childhood dementia enables:

- Access to treatments, clinical trials and emerging therapies which are available for some types of childhood dementia and have a narrow therapeutic window
- Accelerated therapeutic development through recruitment of participants to clinical trials that are most likely to benefit
- Reduced diagnostic odysseys, avoiding unnecessary stress and anxiety, tests and inappropriate interventions
- Timely access to appropriate care, early intervention and reproductive family planning

Major barriers to early diagnosis include:

- Limited awareness among healthcare professionals
- Non-specific initial symptoms leading to misdiagnosis, delayed referral to specialists, and long waiting times to see specialists
- Lack of centres of expertise, guidelines and access to timely genomic testing to expedite diagnosis
- Most childhood dementia conditions are not currently detected through screening programs such as newborn bloodspot screening

To improve diagnostic outcomes, key recommendations include:

- Expansion of newborn screening to include additional suitable childhood dementia conditions, incorporating genomic technologies
- Establish and fund an expanded reproductive carrier screening program
- Develop a red flag system and clear referral pathways from primary care to specialists supported by awareness and education resources for health professionals
- Invest in biomarker research for early detection and monitoring
- Establish fast tracked, defined, expedited pathways for diagnosis
- Improve support for families during and after diagnosis

All of these actions to improve diagnosis of childhood dementia must be driven and supported by a **national centre of expertise**. These changes are essential to enable earlier intervention, better outcomes, savings within the health system and improved quality of life for affected children and their families.

1. Background

Childhood dementia is caused by more than 145 genetic disorders which are estimated to affect 1 in every 2,900 births.[1] Half of the children living with a childhood dementia disorder will die before they are 10 years old, most will not reach adulthood, and all will die prematurely.[1]

The disorders that cause childhood dementia are rare, diverse and difficult to diagnose, which combined with low awareness, results in delayed diagnosis for families. The average delay to diagnosis reported in literature from around the world is 2 years after the onset of symptoms.[1] For some conditions the median time to diagnosis has been reported to be even longer, for example 6 years for alpha-mannosidosis,[2] 8 years for galactosialidosis[3] and 16 years for cerebrotendinous xanthomatosis.[4]

A survey of families in New South Wales found that more than 50% of children with dementia attended over 15 appointments with different healthcare practitioners before receiving an accurate diagnosis, and for 30% the diagnosis process took more than 5 years.[5] Late diagnosis of childhood dementia prevents children from accessing vital treatments and entering clinical trials, slows therapeutic development, leads to unnecessary medical procedures and potentially harmful medications, and deprives families of crucial early support services and reproductive family planning options.

The US-based EveryLife Foundation quantified the cost of delayed diagnosis for rare genetic conditions in terms of medical costs and productivity loss. For X-linked adrenoleukodystrophy (X-ALD, a childhood dementia disorder), they reported the cost was US$302K per patient cumulatively for the years of delay.[6] Timely diagnosis of X-ALD was found to be especially important as there is a potentially life-saving treatment available. However, even in the absence of treatments for other conditions, they found timely diagnosis can have a profound impact, ultimately improving health and reducing the burden of the diagnostic odyssey on patients and families.

This report explores the importance of early diagnosis of childhood dementia and the challenges and opportunities for improving the diagnostic process. This commentary was informed by published literature, the Childhood Dementia Knowledgebase[7] and expert clinical opinion. Throughout this document, we present valuable insights into the experiences of families whose children were diagnosed with dementia, gathered through multiple consultations conducted in 2023 and 2024.

2. Early Diagnosis: Importance and Current State

2.1 Access to treatments, clinical trials and emerging therapies

The window of time where therapeutic intervention might be most effective is largely unknown for most 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 is likely to be too late.[8] Once neurodegeneration has started, halting or slowing it is extremely difficult and repairing the damage to the brain is currently impossible. It can be assumed that the earlier a treatment can be administered, the greater the potential for providing good ongoing quality of life for the child and family.

There are limited treatment options for children with dementia, but the treatments that do exist require early diagnosis for optimal outcomes (Appendix A and B and Supplementary Table 1).[9]

"My child was diagnosed the day before their second birthday and had a bone marrow transplant very rapidly thereafter. It is not curable but I'm very aware that we are a lot luckier than some in the world of childhood dementia, a lot luckier than most, thanks to early treatment."

- Mother of a child with Hurler Syndrome, who finished year 12 last year and is currently living independently.

There are also new, innovative therapies including gene therapies under development and in clinical trials, offering great hope for the future. Typically, clinical trials for new treatments have strict recruitment criteria, designed to include patients most likely to benefit from the intervention. This selective approach aims to demonstrate the treatment's efficacy more clearly and increase the likelihood of successful outcomes. However, most children are not diagnosed until after the clinical trial inclusion criteria age, and are thus too late to participate in trials of potential treatments (Appendix C).

"An earlier diagnosis would have meant that my daughter would have been eligible for a trial that has since become a treatment."

- Mother of a child who was diagnosed too late to access a clinical trial.

2.2 Accelerating therapeutic development

In the absence of early diagnosis, clinical trials rely on recruitment of younger siblings of children diagnosed with childhood dementia. This is not only devastating for the older sibling, but also contributes to the slow

recruitment to clinical trials and impacts the financial viability of drug development for childhood dementia. If children early enough in their disease progression can't be recruited to clinical trials this can result in clinical trials failing and potentially effective therapies being shelved.[9] These challenges also discourage pharmaceutical companies from taking on the development of treatments for these disorders.

This highlights the critical need to diagnose childhood dementia earlier to accelerate the development of new therapies.

2.3 Access to early care, support and family planning

Early diagnosis of childhood dementia is valued by families, even when there are no disease modifying treatment options or clinical trials. This is often called "the value of knowing". It not only shortens the stressful diagnostic odyssey for parents seeking answers to their child's symptoms but also ensures equitable, high-quality care and support.

Delayed diagnosis is also **costly for the health system**. A survey of families in New South Wales found that more than 50% of children with dementia attended over 15 appointments with different healthcare practitioners before receiving an accurate diagnosis.[5] During that time unnecessary, invasive tests and inappropriate interventions are imposed on the child and their family.

"We did lots of irrelevant tests. And our form of childhood dementia can be diagnosed with a blood test, one simple blood test."
- Parent of a child with dementia.

An early diagnosis empowers families to plan for the future, addressing crucial aspects such as reproductive family planning, finances, career decisions, and housing. Moreover, it allows for timely implementation of early intervention services, like occupational and speech therapy, which can help maintain the child's skills for as long as possible.

"We've got a dietitian that's critical. We've got speech pathologists that work on communication and feeding. We've got a physio and an OT. Early allied health intervention has supported her development and helped us manage daily care."
- Mother of a child with dementia on the need for a comprehensive early intervention approach.

Due to the genetic nature of childhood dementia, it is estimated that around 15 to 20% of families affected by childhood dementia have more than one child with the condition*. Earlier diagnosis allows families to understand their risk for future pregnancies and plan accordingly, including the possible use of IVF techniques to reduce the risk.

"If my daughter had been diagnosed earlier I would have had access to information and reproductive family planning that would mean that I only had one child with dementia rather than two."
- Mother of two children with dementia.

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*Estimate based on the knowledge that most of the childhood dementia disorders are inherited in an autosomal recessive pattern which confers a 1:4 risk of the condition to each pregnancy and assuming an average of 2 children per family. However, some childhood dementia disorders (e.g. Rett syndrome) are not inherited, they are caused by spontaneous mutations so it is highly unlikely that there will be more than one child with these conditions in a family. A proportion of children would have conditions severe enough to be diagnosed in infancy, so genetic counselling may be possible.

3. Case studies

Early diagnosis	Late diagnosis
A family's experience with childhood dementia was uniquely shaped by their pre-existing knowledge of Sanfilippo syndrome, as the father had lost his sibling to the condition in childhood. Despite this family history, multiple doctors dismissed the mother's requests for genetic testing during pregnancy, assuring her she wouldn't be a carrier. Following their child's birth, the mother's persistence in seeking testing led to an early diagnosis at three months old. "I asked lots of doctors about whether or not I should be tested. And they all said, "you won't be a carrier", the mother recalled, highlighting the challenges of advocating within the medical system. Their early diagnosis enabled access to a clinical trial and gene therapy treatment at age one, leading to significantly different outcomes than typically expected. The diagnosis impacted various aspects of family life, from social connections to medical management. Some friends struggled to cope with the diagnosis and withdrew, while others provided crucial support. The family made conscious choices	A family's seven-year quest for answers began when their daughter started showing developmental changes around age two. Initially presenting with sleep issues, their concerns grew when she began losing her previously acquired language skills, going from knowing about 20 words to losing them entirely. The path to diagnosis was complicated by multiple misdiagnoses, with five different medical opinions ranging from typical developmental delay to ADHD. "We got five different diagnoses. The first diagnosis was she's fine... once she becomes five years old or older, she'll start speaking," the father recalled, reflecting on the frustration of being repeatedly dismissed by different specialists. The impact of delayed diagnosis was devastating. During the seven years it took to receive a correct diagnosis of Sanfilippo syndrome, a childhood dementia condition, valuable time for early intervention was lost. She was too old, and her disease too far progressed, for any clinical trials. By the time the family finally accessed support services and specialised schooling, their daughter's condition had progressed significantly. "Every time we went to

about privacy and information sharing, particularly regarding their child's medical status. The experience highlighted systemic issues in genetic counselling and testing. "If someone had told me those numbers, I would have insisted that I got tested. But people downplayed what I was asking based on ignorance," the mother reflected, emphasising the importance of accurate genetic risk information. The case demonstrates the vital importance of early diagnosis and intervention, while also highlighting the ongoing challenges families face even with optimal treatment access. It underscores the need for better genetic counselling, improved support systems for families in unique medical situations, and recognition of the long-term impacts on family wellbeing.	find the answer, we waited to get it. But already the time's gone," dad explained. By age fifteen, she was no longer able to walk, talk or follow simple instructions. Previously beneficial therapies like physio and speech pathology were no longer effective. The case highlights the devastating impact of diagnostic delays on both child and family. While support services were eventually secured, including physio and speech therapy, the progressive nature of the condition meant many opportunities for intervention were missed. It demonstrates the critical importance of early diagnosis and the need for medical professionals to take parental concerns seriously when developmental regression is observed.

NOTE: the children in these case studies have the same childhood dementia disorder and live in the same city

4. Barriers to Timely Diagnosis and Solutions

The pathway to diagnosis of childhood dementia typically involves a combination of early clinical symptom assessment, brain imaging, detection of biochemical markers in urine and blood, and genetic testing. Given the non-specificity of initial presenting symptoms, the rarity of the individual diseases and general lack of awareness in the medical community, commonly, children are misdiagnosed with autism, developmental delay, attention deficit hyperactivity disorder (ADHD) and others, before reaching a definitive diagnosis.

"We had five working diagnoses at one time, and none of them made sense."

- Mother of a child who had childhood dementia.

4.1 Delays within the health system

4.1.1 Delayed referral to specialists

Parents frequently report that their initial concerns about their child's development were not initially recognised by healthcare professionals as they are non-specific and difficult to distinguish from more common neurodevelopmental disorders. This, combined with a lack of guidelines and referral pathways results in a series of appointments with various providers before finally obtaining a referral for specialist diagnostic testing. Tragically, it often takes a noticeable regression in the child's skills to prompt such a referral, by which time valuable intervention time has been lost.

"I think as a parent, sometimes you kind of get dismissed and treated like you're silly. But we know our kids best, and if you know your child's going backwards, something is wrong."

- Parent of a child with dementia.

The development of a **red flag system and appropriate and consistent referral pathways to appropriate specialists supported by a national centre of expertise is needed**. This will enable faster referral to specialists for fast tracked diagnostic testing.

Research into blood biomarkers which could be used as a screening tool to differentiate childhood dementia from neurodevelopmental conditions when symptoms first arise is another avenue worth investigating. This is being explored to differentiate adult onset neurodegenerative conditions from psychiatric

disorders.[10] This could offer a pathway to expedite referral for diagnostic testing for those with childhood dementia, and also be used to monitor disease progression and response to treatments.

4.1.2 Lack of defined diagnosis pathways and centres of expertise

Once referral to a specialist is made, wait times can often be frustratingly long and vary depending on location. This protracted process can have significant emotional and practical consequences for affected families.

The establishment of defined, expedited pathways for diagnosis with appropriate triage systems is needed. Diagnosis by specialist clinicians, should be supported by a national centre of expertise. This would ensure the best use of available diagnostic techniques to reduce the time to diagnosis.

4.1.3 Delayed access to diagnostic testing

Access to diagnostic testing can also be delayed for many. For example, one family waited four years to access genetic testing that ultimately gave them an answer.[11]

In Australia, since 2020, access to Medicare funded genomic testing for children under the age of 10 with intellectual disability or global developmental delay of at least moderate severity has been available. This test can be ordered by general and specialist paediatricians. Since November 2023 Medicare funded genomic testing has also been available, via specialist clinicians, for patients suspected to have mitochondrial disease, a subset of whom will have childhood dementia. However, in the year since the mitochondrial disease genome sequencing item numbers were introduced, they have only been utilised 126 times, indicating possible underutilisation of this test[12]. It was estimated that 400 adults and 52 children nationally would utilise the test within the first year of listing.[13]

Despite their potential, these complex genomic tests face several challenges that hinder their full utilisation.[14] The consent process is often lengthy and complex. Many doctors are unfamiliar with ordering these tests, and interpreting the results can be difficult or create uncertainty. These factors may contribute to reluctance in ordering the tests and work is ongoing to produce resources to support clinicians. Additionally, strict eligibility criteria such as “aged 10 years or younger”, and “global developmental delay of at least moderate severity”, exclude some patients from accessing these diagnostic tools. Furthermore, the waiting period between test order and results can be frustratingly long.

Therefore, a **review of genomic testing eligibility criteria and funding arrangements is warranted to gain access for those children that are currently falling through the cracks. Access to genetic counselling for families and genetics services to support clinicians ordering genomic testing must be**

ensured, as well as increased resourcing of diagnostic laboratories to shorten turnaround times. The establishment of a national centre of expertise and introduction of defined pathways and resources, as mentioned above, will also help diagnosing clinicians navigate diagnostic testing.

"It took us 7 years to know what she has"
- Mother of a child with dementia.

Due to the genetic nature of childhood dementia, often there will be multiple individuals affected by the condition in one family. As such, **cascade testing of other family members should be offered as soon as possible after diagnosis**. Families report that this is often not the case, and they have to fight for this to be made available.[5] Early access to cascade testing will enable early diagnosis of siblings, and restore reproductive confidence for extended family members.

"We need to get these children seen earlier and by the right specialists, because that's the only way that we're going to be able to access a potentially disease modifying treatment for them."
- Pediatrician, VIC.

4.2 Limited newborn and reproductive carrier screening

4.2.1 Newborn screening

Newborn bloodspot screening (NBS) has been available to babies in all states and territories in Australia since the 1960s. Approximately 99% of babies are screened every year – more than 300,000 babies. **Most childhood dementia conditions are not currently detected through screening programs such as newborn bloodspot screening.** The Australian Newborn Screening Program currently screens for 30 conditions in all states and territories and another 4 are in the process of being implemented. This results in the detection of more than 300 babies each year who then have access to early, life-saving and life-changing treatments. Approximately half of these babies would otherwise suffer progressive brain damage and childhood dementia. This includes babies diagnosed with conditions such as phenylketonuria (PKU) and maple syrup urine disease which have well established and accessible treatment options.

There are 5 childhood dementia conditions that are screened in other countries, but are not screened in Australia: X-linked adrenoleukodystrophy, biotinidase deficiency, Hurler syndrome (MPS I), Hunter syndrome (MPS II) and Krabbe disease (Supplementary Table 1). X-linked adrenoleukodystrophy has been recommended by the Medical Services Advisory Committee (MSAC) for addition to Australia's NBS programs, and implementation is underway. Hurler and Hunter syndromes are currently under review by MSAC for

possible addition to the Australian newborn screening programme while the Health Department is gathering technical advice on biotinidase deficiency. Pilot studies of NBS for metachromatic leukodystrophy are producing robust results and the test is currently being implemented in one state in the USA.[15,16] Health economic modelling has been conducted for many of these conditions and shown that newborn screening is likely to be cost effective.[17–19]

Newborn screening for other conditions where treatments are available or imminent, are currently being piloted. This includes CLN2, Sanfilippo syndrome, Gaucher disease, cerebrotendinous xanthomatosis, GM1 gangliosidosis and Niemann-Pick disease types A and C (Supplementary Table 1).[20]

Urgent expansion of newborn screening to include additional suitable childhood dementia conditions is needed so that children in Australia can benefit from early interventions. This is crucial due to the narrow therapeutic window and broader benefits as outlined in section 2 and illustrated in the case study on pages 10 and 11.

Genomic newborn screening (NBS) technology is being explored to expand screening even further, with multiple pilots underway in Australia and abroad. This technology could potentially screen for hundreds of genetic conditions in a single test. However, interpreting genetic data requires careful consideration, as the relationship between certain genetic variations and diseases is not yet fully understood. The sensitivity of genomic NBS is currently estimated to be around 80% for inherited metabolic disorders, whereas traditional biochemical methods detect close to 100% of cases.[21,22] The feasibility of genomic newborn screening is expected to improve as more data is collected and approaches that combine biochemical and genomic technologies are also being explored.[23,24]

The implementation of genomic NBS necessitates a reconsideration of screening principles and governance, including models of consent, data storage and security, and the inclusion of conditions without available effective treatments.[25] There is strong community support for newborn screening, even in the absence of a treatment,[26–28] however the opinions of medical professionals are mixed.[29] New models to implement genomic NBS must consider how best to support affected children and their families diagnosed pre-symptomatically without treatment options and how to accelerate their access to potential treatments through clinical trials. Despite these challenges, expanding NBS through genomic testing has the potential to deliver widespread benefits in the future, including avoiding lengthy diagnostic processes, enabling participation in clinical trials, and informing reproductive decision-making.

With appropriate processes and informed consent in place, genomic NBS could be transformative for communities affected by childhood dementia and other genetic conditions. **Further investment is needed to pursue implementation of genomic NBS**, and address the aforementioned issues.

Expansion of newborn screening programmes, either using traditional methods or genomic technology, necessitates inclusion of education initiatives, access to genetic counselling and clinical services for successful delivery. Clinical services must be well-resourced and have the capacity to support newly diagnosed families and deliver timely access to available treatments and clinical trials.

"Information is everything. We could have known before we conceived. However, we were in the right place at the right time and because we got information in a timely fashion we could access a clinical trial. I would love it to be on the heel prick test so that all children can benefit from early diagnosis."
- Mother of a child who was able to access a gene therapy trial for her child due to early diagnosis.

4.2.2 Reproductive carrier screening

While reproductive carrier screening is primarily performed before or during pregnancy to assess reproductive risk, it can play a valuable role in diagnosing rare genetic conditions such as those that cause childhood dementia. When carrier screening identifies carriers at high risk of having a child with childhood dementia, this information can enable early diagnosis of rare conditions in offspring and inform reproductive decision-making.

Recent advances in genomic technology have expanded reproductive carrier screening panels to include hundreds of rare conditions. The Australian Reproductive Genetic Carrier Screening Project (Mackenzie's Mission) screened 9,107 Australian couples for genetic variants that cause more than 750 rare genetic conditions.[30] Of these couples, 175 (1.9%) were identified as having an increased chance of having a child with a genetic condition, including at least 19 couples at risk for childhood dementia disorders. This equates to approximately 1 in 500 couples being at high risk of having a child with dementia.

The information from the Mackenzie's Mission screening was highly valued by the participating couples and most of the couples have since chosen a reproductive option with the aim of avoiding having a child with the condition.[30] It is important to note that not all childhood dementia disorders can be detected through reproductive carrier screening, including disorders such as Rett syndrome.

Reproductive carrier screening is currently limited to just three conditions under Australia's public healthcare system, none of which cause childhood dementia (spinal muscular atrophy, cystic fibrosis and fragile X). Only 20% of the couples identified in Mackenzie's Mission were at high risk of one of these 3 conditions.[30]

While expanded panels testing for hundreds of additional conditions exist, they are only available to those who can afford substantial out-of-pocket costs. Stakeholders are calling on the Government to **establish and fund an expanded reproductive carrier screening program**, so that this vital medical information can be equally accessible to all prospective parents.

5. Supporting families through diagnosis

Receiving a diagnosis is a life-changing event for both children with dementia and their families. Seeking and receiving a diagnosis is confusing and fraught, and often exacerbated by delays and inadequate information and communication.

From diagnosis and across a child's remaining life, a family faces severe and ongoing grief, loss and chronic sorrow. Tragically, most families report that they were not connected with psychological support,[5] a failing that further compounds the catastrophic impacts of the diagnosis. Formal peer support networks that can give essential psychosocial and practical assistance are not available either.

"It took 5-6 years for my child to be diagnosed although she started showing symptoms from 18 months. When she was diagnosed, we were told that it was degenerative, progressive and that there was no treatment and that if she made it to 21, she would be doing well and not to go looking for a miracle cure because there wasn't one."
- Parent of a child with dementia

Families report that basic information on what to expect or how to manage care was lacking. The onus falls on parents to proactively research their child's condition and seek out specialists worldwide who could advise on care. Many families are unfortunately not connected to information on possible clinical trials or emerging treatments, have to research for themselves and bring this information back to their doctor. **Specialist multidisciplinary input is needed to support diagnosing teams, provide information for health professionals and parents and provide clear pathways to connect families to support services, including peer support.**

"After diagnosis, we don't support them very well because we are busy with a lot of patients – but they need to be seen frequently after it because they go through the phases of grief and shock"
- Paediatric neurologist, WA.

6. Summary of recommendations to improve the diagnostic process

Enhancing the diagnostic process is crucial on multiple fronts. Earlier diagnosis opens doors to vital treatments, clinical trials, and emerging therapies while simultaneously accelerating therapeutic development. Streamlined diagnostics would also alleviate the immense strain that late diagnosis places on families and healthcare systems, by avoiding long stressful diagnostic odysseys filled with unnecessary tests and inappropriate interventions. Early diagnosis ensures timely access to proper care and early intervention, and gives families the opportunity to plan for their future.

To reduce the time to diagnosis and make the process less traumatic for families the following actions are required:

- Expansion of newborn screening to include additional suitable childhood dementia conditions, incorporating genomic technologies (with appropriate governance)
- Establish and fund an expanded reproductive carrier screening program
- Development of a system of red flags and appropriate referral and triage pathways from primary health care to appropriate specialist clinicians
- Investment in research to discover and validate biomarkers which could be used as a screening tool in early symptomatic children and to monitor progression and response to treatments
- Establishment of defined, expedited pathways for diagnosis
- Review of genomic testing eligibility criteria and funding arrangements to gain access for those children that are currently falling through the cracks
- Increased access to genetic counselling for families, including cascade testing of other family members, and genetics services to support clinicians ordering genomic testing
- Improved support for families during and after the diagnostic process including information and resources, and psychological and peer support.

All of these actions should be driven by, and supported by **a national centre of expertise.** The establishment and funding of such a centre will provide clinical advice, education, resources, guidelines and models of care to improve the diagnostic process for all families.

Consultation with experts including health professionals and families is needed to design solutions that most efficiently address the barriers to improved diagnosis of childhood dementia.

In addition, there is a need to ensure access to treatments approved overseas and experimental therapies through clinical trials for children with dementia, and for more research to discover new and improved treatments. As we improve the diagnosis of these children, we need to be able to offer them access to safe and effective treatments and cures and early interventions to improve quality of life.

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

- Mother of a child with dementia.

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Appendices: The therapeutic landscape for childhood dementia disorders

Appendix A. Approved treatments

Approximately 20% of children born with a childhood dementia disorder have treatment options which may improve their survival and quality of life if diagnosed and treated early (Supplementary Table 1). Treatments include bone marrow or haematopoietic stem cell (HSCT) transplants for some conditions including X-linked adrenoleukodystrophy, metachromatic leukodystrophy, alpha-mannosidosis, Hunter and Hurler syndromes (mucopolysaccharidosis types I and II) and Krabbe disease. HSCT is most effective if performed pre-symptomatically and risks versus benefits must be considered on an individual case basis, as the procedure is associated with significant morbidity and mortality.

Medical care has improved in recent years to reduce that risk. In a recent study of 62 children with mucopolysaccharidosis undergoing HSCT according to international guidelines, the 5-year overall survival and event-free survival have been reported to be 95.2 and 90.3%, respectively.[31] In addition, children had a lower risk of developing graft-versus-host disease if they were treated at a younger age.

HSCT is particularly challenging for infantile Krabbe disease, as this is a very rapidly progressive form of childhood dementia and treatment with HSCT should ideally occur within the first 30 days of life, which can be difficult to achieve even if diagnosed soon after birth through newborn screening[32]. Processes need to be put in place to enable early HSCT treatment of babies diagnosed with Krabbe diseases through newborn screening and meanwhile, gene therapy treatments are moving through the pipeline that may address this challenge.

Five enzyme replacement therapy (ERT) medications are currently approved in some countries for use in childhood dementia disorders; however, four of these therapies are only given intravenously and are unable to cross the blood–brain barrier (Supplementary Table 1). This renders them largely ineffective for CNS disease processes and does not address the dementia aspects of these conditions. Research is ongoing to target these ERT medications to the brain. The fifth product, Brineura® (cerliponase alfa), delivered by intraventricular administration, targets a type of Batten's disease (CLN2). It has been shown to slow progression of motor and language deficits and new evidence suggests that pre-symptomatic treatment offers improved outcomes.[33,34]

For other disorders treatment options include supplementation of critical enzyme cofactors, which are deficient or the administration of small molecule drugs targeting the disease pathology, and similarly, early diagnosis and treatment is critical (Supplementary Table 1).

Appendix B. Treatments approved overseas and coming soon

There are effective treatments for some types of childhood dementia approved overseas but not available to Australian children, including:

- Libmeldy™/Lenmeldy™ gene-modified cell therapy for metachromatic leukodystrophy (approved in the EU in 2020 and USA in 2024).
- Skysona™ gene-modified cell therapy for X-linked adrenoleukodystrophy (approved in the USA in 2022).
- Daybue™ (trofinetide) for Rett syndrome (approved in the USA in 2023).
- Nulibry™ (cPMP) for molybdenum cofactor deficiency type A (approved in the USA in 2021 and EU in 2022).
- Chenodeoxycholic acid (CDCA) for cerebrotendinous xanthomatosis (approved in the EU in 2017).
- Zavesca™ (miglustat) for Niemann-Pick type C (TGA approved in 2010 but not reimbursed through the PBS or LSDP).
- Miplyffa™ (arimoclomol) for Niemann-Pick type C (approved in the USA in 2024), to be used in combination with Zavesca™ (miglustat).
- Aqneursa™ (N-acetyl-L-leucine) for Niemann-Pick type C (approved in the USA in 2024).

Not all of these treatments are considered curative, however, in clinical trials improvements were seen in symptom management and/or slowed disease progression.

Access to gene-modified cell therapies such as Lenmeldy/Libmeldy and Skysona is challenging in Australia. This therapy involves harvesting a child's stem cells, introducing a working copy of the gene into these cells in the laboratory, and then infusing them back into the child. Therefore, in addition to local regulatory approval and reimbursement, local laboratories will need to be established and accredited to process the cells, or shipping procedures for the cells to and from the US or Europe will need to be tested and approved.

Several additional potential treatments are progressing through the development pipeline. For instance, in the USA the FDA will soon consider cyclodextrin for Niemann-Pick type C and multiple companies are expected to submit applications for regulatory approval of gene and enzyme replacement therapies for childhood dementia conditions, including Sanfilippo and Hunter syndromes, in 2025. Ultragenyx

Pharmaceuticals submitted their application for accelerated approval of AAV-9 gene therapy for Sanfilippo syndrome type A (UX111) to the FDA in December 2024 and the clinical trial continues to produce positive results.[35–37]

The therapies listed above are not currently available or difficult to access in Australia, and historically Australians wait on average 5 years to receive reimbursed access to new medicines after they are registered overseas.[38,39] Access arrangements need to be put in place for therapies shown to be effective until they are TGA approved and funded by the Government, coupled with studies to continue gathering evidence of safety and effectiveness in these early access patients. Early diagnosis will be important to enable children to get the most benefit from these effective treatments when access arrangements are made.

Despite the development of emerging treatments in a minority of childhood dementia disorders, effective treatments remain unavailable to most children across the world, and, where available, extend partial benefits only. Moreover, a number of these therapies such as HSCT and gene therapies come with a high degree of risk, underscoring the need for more research to discover improved treatments. Investment in infrastructure to deliver emerging treatments will also be required.

Appendix C. Clinical trials

Clinical trials are crucial for children with dementia, as they often represent the sole avenue for accessing potential disease-modifying treatments. These trials offer potential benefit, not only for the participants but are also essential for developing treatments that may benefit the broader patient population in the future.

Typically, clinical trials for new treatments have strict recruitment criteria, designed to include patients most likely to benefit from the intervention. This selective approach aims to demonstrate the treatment's efficacy more clearly and increase the likelihood of successful outcomes.

For example, a gene therapy trial for Sanfilippo syndrome type A (UX111 being developed by Ultragenyx) has shown that the children treated under the age of 2 (17 out of 28 children who participated in the trial) continue to show cognitive development gains beyond the age where patients usually start regressing.[36,37] Unfortunately, clinical benefits were not as robust in children dosed at more advanced stages of their disease, however retention of meaningful functional abilities at the time of last assessment has recently been reported[37]. This resulted in the inclusion criteria being modified in subsequent studies to only include younger children.

Most children are not diagnosed until after the inclusion criteria age, too late to participate in trials of potential treatments. For example:

- The cut off age for two Sanfilippo syndrome gene therapy trials was 2 years of age (NCT02716246, NCT04201405), yet children are diagnosed on average at 4 years of age.[40]
- Trials of enzyme replacement (NCT04573023) and gene-modified cell therapy (NCT05665166) for Hunter syndrome have had age cutoffs of 3.5 years and 12 months of age respectively. Children with Hunter syndrome are diagnosed at 3.5 years of age on average.[40]
- The trial of gene therapy for GM1 Gangliosidosis (NCT03952637) has an age cut off of 12 months of age, but is diagnosed on average at 16 months.[40]

As stated above in section 2.2, In the absence of early diagnosis, clinical trials rely on recruitment of younger siblings of children diagnosed with childhood dementia. This has devastating impacts on families, and also affects the viability of therapeutic development as detailed on page 8 of this report.

Supplementary Table 1: Approved treatments for childhood dementia disorders and newborn screening status

Disorder	% of incidence	Treatment and evidence for early diagnosis need	Newborn screening (NBS) status Australia [41]	Newborn screening status globally[20]
Biotinidase deficiency	2.4%	Biotin supplements can prevent development of neurological symptoms. If treated after onset of optic atrophy, hearing loss, or cognitive deficits these are usually irreversible.[42]	Identified for NBS technical advice.	Screened in multiple jurisdictions globally. Added to USA's Recommended Uniform Screening Panel (RUSP) in 1984.
X-linked adrenoleuko-dystrophy (X-ALD)	3.2%	HSCT* is most effective when undertaken early in the disease course; in the absence of NBS, ~50% of boys are diagnosed too late to be eligible for HSCT.[43] Gene-modified cell therapy approved USA[8], only asymptomatic or mildly symptomatic patients eligible for treatment.	MSAC supported adding X-ALD to Australia's NBS programs in 2024, implementation underway.	Screened in multiple jurisdictions globally. Added to RUSP in 2016.
MPS I (Hurler syndrome)	2.1%	HSCT* younger age at transplantation, before the age of 2, is a major predictor of superior cognitive development posttransplant.[45,46] Aldurazyme® (Enzyme Replacement Therapy; ERT)^[47] only reimbursed in Australia for less severe forms that do not have neurological involvement.	Referred to the MSAC health technology assessment process.	Screened in multiple jurisdictions globally. Added to RUSP in 2015.
MPS II (Hunter syndrome)	1.65%	Elaprase® (ERT)^[48], HSCT*, early treatment, before 5 years of age, gives better outcomes.[49–51]	Referred to the MSAC health	Screened in multiple jurisdictions globally. Added to RUSP in 2022.

			technology assessment process.	
MPS VII (Sly syndrome)	0.09%	MEPSEVII™ (ERT)^[52] , not approved in Australia.		Not screened anywhere in the world. Included in pilot studies.
Globoid cell leukodystrophy (Krabbe disease)	1.2%	Haematopoietic stem cell transplant (HSCT) can improve survival and neurological function if performed in first weeks of life, although varying degrees of neurologic impairments remain*[32,53]	Decision June 2024 NOT TO progress to health technology assessment for NBS.	11 US states currently screen newborns for Krabbe and added to the RUSP in 2024.
CLN2 (Batten disease)	1.7%	Brineura® (ERT via intraventricular infusion).[33,54,55] Evidence of treatment being superior if started pre symptomatically.[33,54]	Decision June 2024 NOT TO progress to health technology assessment for NBS.	Not screened anywhere in the world. Included in pilot studies.
Metachromatic leukodystrophy	2.3%	HSCT* most effective in later-onset disease treated pre-symptomatically. May not benefit the most common late-infantile subtype. [56] Gene-modified cell therapy approved by the EU and USA.[57] Only 15–20% of all diagnoses occur within the treatment window without newborn screening.[17]		Not screened anywhere in the world. Included in pilot studies and planned implementation in Illinois in 2024.
alpha-mannosidosis	0.2%	Lamzede®^ (ERT not approved in Australia), HSCT*, early diagnosis and early initiation of treatment (with ERT and/or HSCT) are essential to attain maximal benefits[58]		Not screened anywhere in the world.

Niemann-Pick disease type C	2.3%	Zavesca® (migulstat). Access limited in Australia. Miglustat has been shown to halt or slow disease progression, but benefit is variable.[59] Favourable outcomes have been reported from early treatment.[60] Two new treatments approved in the USA in Sept 2024 - Miplyffa™ (arimoclomol) and Aqneursa™ (N-acetyl-L-leucine), not available in Australia.		Not screened anywhere in the world. Included in pilot studies.
Cerebrotendinous xanthomatosis	0.7%	Chenodeoxycholic acid (CDCA)/cholic acid.[61] CDCA difficult to access in Australia. Early diagnosis and treatment are imperative to prevent potentially irreversible neurological damage[62]		Not screened anywhere in the world. Included in pilot studies.
Molybdenum cofactor deficiency type A	0.9%	Cyclic pyranopterin monophosphate (cPMP, not available in Australia).[63] Treatment before the onset of significant encephalopathy results in good long-term developmental outcomes[64]		Not screened anywhere in the world.
Menkes disease	1%	Copper–histidine supplementation. Response to treatment variable and only effective when administered soon after birth.[65]		Not screened anywhere in the world. Included in pilot studies.
Biotin-thiamine-responsive basal ganglia disease	NA	Biotin and thiamine, treatable if recognised early and managed appropriately. Severe infantile form may not respond to treatment.[66]		Not screened anywhere in the world. Included in pilot studies.[67]

SLC5A6 deficiency	NA	Biotin, pantothenate, and lipoate, treatment early within the disease course important.[68,69]		Not screened anywhere in the world.
Cerebral folate deficiency	NA	Folinic acid, substantial improvement in neurologic findings when started at a young age and presymptomatic treatment can prevent regression[70]		Not screened anywhere in the world.
Total	**19.6%**			

NA - data on incidence not available for these ultra-rare conditions

*Haematopoietic stem cell transplant (HSCT) is employed at a limited number of paediatric centres. Benefit is variable and needs to be weighed against the significant risks including graft failure, infections, and graft-versus-host disease, that can lead to death.

^Intravenous treatment not effective against the neurological aspects of the disease

List of abbreviations

RUSP: Recommended Uniform Screening Panel (USA); HSCT: haematopoietic stem cell transplant; ERT: enzyme replacement therapy; MSAC: Medical Services Advisory Committee; X-ALD: X-linked adrenoleukodystrophy; MPS: mucopolysaccharidosis; CLN: ceroid lipofuscinosis, neuronal.