childhood dementia INITIATIVE

Running Blind: Data gaps in childhood dementia healthcare

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Childhood Dementia Initiative (2025). Running Blind: Data gaps in childhood dementia healthcare. 12 February 2025. Sydney, Australia.

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.

Thank you to the Childhood Dementia Initiative's Scientific and Medical Advisory Committee who contributed to and edited this report:

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Executive Summary

Childhood dementia affects approximately 1 in 2,900 births and encompasses more than 145 genetic disorders. Half of the children with childhood dementia will die before age 10, and most will not reach adulthood. Despite the devastating impact of childhood dementia, there are significant gaps in data collection and analysis that hamper our ability to improve outcomes for affected children and their families.

This report examines the current state of childhood dementia data collection in Australia and identifies critical gaps in three key areas:

- **Disease Surveillance and Modelling**
  While surveillance studies in Australia and the UK have provided valuable snapshots of childhood dementia's impact, these studies rely on voluntary reporting and often achieve suboptimal case ascertainment. Recent disease modelling estimates suggest a higher prevalence than previously recognised, but comprehensive real-world data remains limited.
- **Patient Registries**
  No dedicated childhood dementia patient registry exists in Australia or globally. While some individual conditions have specific registries, these are often underfunded and capture only a fraction of the childhood dementia population. The absence of a comprehensive registry hinders our understanding of disease progression, treatment outcomes (including identification of clinically relevant outcome measures), and patient needs. It also hinders clinical trial planning and recruitment.
- **Health System Data**
  Current health system coding is inadequate for capturing childhood dementia cases. The ICD-10 system used in Australia has codes accounting for only a third of childhood dementia births. This limitation, combined with fragmented health records across different providers, makes it difficult to track patient outcomes and plan services effectively.

Key Recommendations

1. Create a comprehensive national **clinical quality patient data registry** that combines health professional and patient-entered data, ensures sustainable funding, builds on existing registries, and uses modern technology to efficiently collect and share data while maintaining privacy.
2. **Unlock existing data in health systems** through improved rare disease coding and the development of interim case identification methods.

These improvements are essential for:

- Enabling evidence-based healthcare planning
- Developing clinical best practices
- Supporting clinical trial readiness and clinical research
- Facilitating treatment approval and reimbursement processes.

Implementation will require coordination between multiple stakeholders and sustained investment, but the potential benefits for patient outcomes and healthcare efficiency justify this commitment. Success in addressing these data gaps will be crucial for improving the lives of children with dementia 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're 10 years old, most won't reach adulthood, and all will die prematurely. Not only is there a lack of treatments and cures, but emerging research reveals the impact on families is magnified by the limited capacity of our health and community support systems to meet the needs of children with dementia.[2]

There is very little real-world data collected about these children, which hampers the implementation of systematic improvements, including therapeutic development, for children with dementia and their families.

This report details why data about children with dementia is inaccessible and makes recommendations for improvement.

2. Why is data on childhood dementia needed?

Accurate data on childhood dementia is crucial for multiple aspects of disease management and research advancement. Data on incidence, prevalence, natural history, health system usage, and treatments will enable:

- Informed allocation of healthcare resources based on the demonstrated burden and impact of childhood dementia.
- Health and support service planning.
- Improved clinical best practices and evidence-based disease management protocols.
- Planning of, and recruitment to, clinical trials.
- Informed allocation of research funding into childhood dementia.
- Contribution to global knowledge about childhood dementia and clinical trial readiness. This includes understanding natural history and the development of appropriate clinical trial protocols and outcome measures.
- Real world assessment of clinical effectiveness and cost-effectiveness of emerging therapies, which is needed for drug approval and reimbursement processes.

"There's lots of things that can be done to make an Australian clinical trial site more attractive [for inclusion in a drug trial]. With the rapid progression of childhood dementia, the trials have really tight windows and eligibility criteria, so making sure that data about eligible patients is readily available is essential."
- Nicole Millis, CEO, Rare Voices Australia

Opportunities to participate in clinical trials are extremely limited for children with dementia in Australia. Of 54 childhood dementia clinical trials recruiting patients globally in December 2023, only 2 were listed as recruiting in Australia.[3] As a result, fewer than 2% of children with dementia in Australia can join a potentially life-saving clinical trial. Readily accessible data about children with dementia will attract new clinicals trials. For example, global networks to deliver gene therapy trials are being established with nodes in Brazil, US, UK and United Arab Emirates.[4] Data innovations that demonstrate clinical trial readiness will assist Australia in joining such ground-breaking networks, accelerate research, and deliver new treatments to children with dementia.

Ultimately, comprehensive data collection and analysis aims to improve the diagnosis, management, and treatment of childhood dementia conditions, leading to better outcomes for affected children and their families. To understand how well we are meeting these data needs, we must examine the current state of childhood dementia data collection across three key areas: disease modelling and surveillance, patient registries, and health system data analysis.

3. Childhood Dementia Data: Current State

3.1 Disease modelling

A burden of disease study was published in 2023 used modelling, based on published incidence and life expectancy data, to estimate the collective incidence, prevalence, death rate and average life expectancy of childhood dementia.[1] This study identified 145 genetic childhood dementia disorders and the necessary data for the modelling was available for less than half (70) of them.

The collective incidence was estimated to be 34.5 per 100 000 (1 in 2900 births), median life expectancy of 9 years and prevalence of 16.5 per 100 000 children.[1] The estimated number of premature deaths per year is similar to childhood cancer (0–14 years) and approximately 70% of those deaths will be prior to adulthood.

3.2 Surveillance studies

Surveillance studies involve the distribution of a report card listing diseases of interest distributed at regular intervals, usually monthly, to relevant clinicians e.g. paediatricians. Clinicians are asked to indicate whether they have seen a patient newly diagnosed within the previous month with one or more of the diseases or conditions listed and are asked to complete a clinical case report form.

Surveillance studies in the UK and Australia have gathered data on incidence, age of diagnosis and cause of childhood dementia, albeit with different terminology and slightly different inclusion criteria (Supplementary Table 3).[5,6] These studies have the advantage of gathering detailed information at the point of diagnosis, including those children with dementia of unknown or uncertain cause. However, the methodology relies on voluntary support of consultant paediatricians returning the report cards and clinical case forms and this results in suboptimal ascertainment of cases. The British Paediatric Surveillance Unit (BPSU) and Australian Paediatric Surveillance Unit (APSU) estimate that ascertainment varies between 31% and 94% depending on the study.[7,8]

The Australian Childhood Dementia Study, conducted from 1993 to 1995 through the APSU, identified 80 children with dementia and data was also collected on the impact on day-to-day family functioning.[5] The cumulative two-year prevalence of dementia was estimated to be 5.6 per 100,000 children under 15 years, and the median age at diagnosis was 5.9 years. According to clinicians surveyed, childhood dementia severely impacted families' daily functioning and services and support for families were insufficient.

Surveillance of 'Progressive Intellectual and Neurological Deterioration' (PIND) in children through the BPSU ran from 1997 to 2024 and more than 2000 children were identified.[6] Results published in 2021 reported the prevalence of diseases causing childhood progressive intellectual and neurological deterioration in the UK was 1 in 10,000 live births. There were more than 220 different disorders identified, and the majority of disorders presented early in childhood: 81% before the age of 5 years.

3.3 Patient registries

Patient registries collect, store, and analyse longitudinal clinical, demographic, and patient-reported data for a defined patient population. The primary purposes include identification and tracking of clinically relevant

patient outcomes, monitoring treatment effectiveness, conducting research, improving quality of care, and informing healthcare policy. Patient registries are typically either clinician or patient-led.

Clinician-Led Registries (also sometimes called Clinical Quality Registries):

- Created and managed by healthcare providers, hospitals, or medical institutions.
- Focus primarily on clinical outcomes, treatment responses, and medical data.
- Data collection typically occurs during routine clinical care.
- Often include detailed medical histories, diagnostic information, treatment protocols, and clinical outcomes.
- Generally have stricter data validation processes and standardised medical terminology.
- May be used for clinical care quality improvement initiatives and clinical research.

Patient-Led Registries:

- Initiated and managed by patient advocacy groups, or patient organisations.
- Emphasise patient experiences, quality of life, and patient-reported outcomes.
- Data collection often occurs through self-reporting by patients and/or family members.
- Include information about daily living impacts, symptom management, and personal experiences.
- May capture aspects of the disease experience that clinical registries miss.
- Often more accessible to patients and focused on patient engagement.
- Can be particularly valuable for rare diseases where clinical data may be limited.
- May include social support aspects and patient-to-patient connections.

Both types of registries are valuable but serve different purposes in the healthcare ecosystem, and increasingly, hybrid models are emerging that combine elements of both approaches to provide more comprehensive insights into disease management and patient care. Recruitment and curation of data quality is challenging for both registry types, as families and clinicians often lack time for data entry and updates.[9] Registries with dedicated resourcing, for example research nurses, are able to gather more comprehensive data, though this requires sustained funding. Linkage to electronic health records and artificial intelligence may be able to reduce the data entry burden in the future.

"[It's about] making sure that the information we get about these patients isn't lost because that's the issue with very rare diseases, that information that you learn and families learn, if they're not part of a registry, it doesn't get passed on."
- Paediatric Neurologist, NSW

Linking patient data registries with biobank samples is also highly desirable for the advancement of rare disease therapeutic research and to provide the appropriate resources required for the effective translation of basic research into clinical practice.[10] For example, the Australian Inherited Retinal Disease Register (AIRDR) and DNA Bank aims to characterise the genetic spectrum of inherited retinal diseases and guide research into treatments and cures.[11] One example of how a registry linked to biosamples could be used is in research to discover and validate blood biomarkers. These biomarkers could serve as screening tools in early symptomatic children with dementia to enable early diagnosis and help monitor disease progression and treatment response.

Currently, no childhood dementia specific registry exists in Australia (or anywhere in the world). A few individual childhood dementia conditions have patient registries in Australia, but those that exist are often underfunded. Supplementary Table 1 lists known patient registries in Australia that may contain data about children with dementia.

Ideally, comprehensive global data collection to understand childhood dementia is needed, as the rare and ultra-rare nature of the underlying conditions means that no single country or region has enough cases to build a complete picture of disease progression, treatment efficacy, and patient outcomes.

"My child [with an ultra rare form of childhood dementia] was offered a bone marrow transplant and there was very little information available, even from overseas, about the likely outcome for them. It certainly hasn't been curative and nobody is collecting data about how they have responded to the treatment either, so that information will not be available to parents who come after us."
- Parent of a child with dementia

3.4 Health system data analysis

Health system data analysis can provide a comprehensive view of the incidence and prevalence of childhood dementia within a region relatively quickly, while offering insights into affected children's characteristics and their journey through the healthcare system.

Population studies where medical records were retrospectively examined have been conducted in Norway and Sweden to give data on incidence, cause and age of diagnosis.[12,13] These two studies used the terminology "progressive childhood encephalopathy" rather than childhood dementia but the definitions are similar (Supplementary Table 3).

In west Sweden, 76 children with progressive encephalopathies were identified in the study area during 1970-1985, yielding a live birth prevalence of 58 per 100,000.[13] In Norway, 84 individuals were documented between 1985 and 2003, corresponding to an incidence rate of 60 per 100,000 births.[12] These higher incidence rates, compared to other studies, may be attributed to two factors: comprehensive case identification through the study methodology, and the inclusion of potentially treatable conditions that were excluded from other studies.

Retrospective analysis of data in the health system, including incidence, prevalence, life expectancy and health service usage by the childhood dementia cohort, and indeed all rare diseases, is currently hampered by the lack of reliable rare disease coding. It is known that under-representation of rare diseases in hospital healthcare coding systems leads to a paucity of rare disease epidemiological data required for healthcare planning.[14] Childhood dementia is a pertinent example of this.

Australian health systems (and most health systems globally) currently use the World Health Organisation's International Classification of Diseases ICD-10 classification. However, ICD-10 has only 500 of over 6000 rare diseases represented, with only 250 having an ICD-10 code mapping exactly to one rare disease by a specific code.[14,15]

There are only 11 ICD-10 codes that could identify childhood dementia patients in the health system (Supplementary Table 2). We can be reasonably certain that most of the patients labelled with these codes have a childhood dementia disorder. These codes only represent 30 of the 145 childhood dementia disorders, therefore, only 20% of childhood dementia disorders have a specific ICD-10 code, accounting for only a third of childhood dementia births. The rest of the childhood dementia disorders are grouped together with other rare diseases that do not cause childhood dementia, meaning that it is near impossible to identify these

children in health system records. For example ICD-10 code E76.2 - 'Other mucopolysaccharidoses (MPS)', includes MPS types III, IV, VI and VII, while only types III and VII cause childhood dementia. MPS types IV and VI can also be life limiting but do not affect cognitive function, they affect other systems, including skeletal, cardiac, and respiratory systems.

Examples of when this has been a problem include:

- Experts have told us that there is no data available about health care use, for example palliative care, for childhood dementia for planning purposes available
- The Australian Institute of Health and Welfare (AIHW) can not accurately include data about childhood dementia in their "Dementia in Australia" reporting (as described below).

The AIHW included childhood dementia in "Dementia in Australia" reporting for the first time in 2024 using mortality and NDIS data.[16] In analysing deaths, they used 18 ICD-10 codes, with 5 codes restricted to deaths below age 30 to exclude other conditions in these categories that typically have longer life expectancies. Using this method, it is estimated that less than 50% of childhood dementia cases have a usable code in this context. Between 2013 and 2022, 372 childhood dementia deaths were found in the mortality database using these codes. Disease modelling[1] estimates around 850 deaths over that period.

NDIS data was only available for two childhood dementia conditions - Juvenile Huntington's disease and Rett syndrome. The analysis found 1,100 approved NDIS plans for people living with Rett syndrome. There were 80 approved plans for people living with Juvenile Huntington's disease (aged 20 or younger). Disease modelling estimates that in Australia there are 834 people living with Rett syndrome and 35 with juvenile Huntington's disease[1] which indicates that the disease modelling[1] may be an underestimate of childhood dementia prevalence.

An alternative to ICD codes is the ORPHAcodes rare disease nomenclature, curated by Orphanet. It is designed to capture all rare disease diagnoses and contains information on over 6000 unique rare diseases. ORPHAcodes are recognised as the most appropriate coding system for rare diseases in Europe, and globally by the International Rare Disease Research Consortium.[17] Implementation of ORPHAcodes into European health systems has been underway for several years. Work has begun in some systems in Australia e.g. Rare Care Centre, WA, to add ORPHAcodes to medical records, but more work is needed to make this widespread. In collaboration with Orphanet, there are increasing efforts to incorporate rare disease classifications into ICD, and align with other health information systems such as SNOWMED.

Australia is still using ICD-10 codes despite ICD-11 coming into effect on 1 January, 2022. 72 countries around the world have commenced the implementation process for ICD-11. ICD-11 includes codes for 5500 rare diseases. ICD-11 will still have a specific code for only a minority (approximately 40%) of rare diseases. ICD-11, therefore, will be an incremental improvement but not the solution for health system coding of rare diseases.

"Better rare diseases coding is the number one priority for improving health systems, as without it they are running blind to the biggest costs in the health system and health related costs in other systems, and therefore missing the best ways to intervene to improve health and well-being and sustain health systems."
- Prof. Gareth Baynam, Medical Director, Rare Care Centre, WA

In addition to the lack of rare disease coding, there is no national patient record data system in the Australian health system. Children with dementia see many different health professionals and each use their own hospital or practice data system. This fragmentation across different healthcare providers and their separate data systems impedes comprehensive analysis of children with dementia, especially at the national level. The fragmented health data systems also place additional burden and stress on families, because the onus is on parents to share information between health professionals. This also creates risks around medication management and continuity of care.

"I'm holding all of the information and it's the history and the clinical information and the medications. It's all in my head and on my Google Drive. And we participate in a clinical trial outside of the state so there's a big chunk of her history in another state."
- Parent of a child with dementia on the challenges of information sharing between medical professionals.

An interim solution to gather real world data about childhood dementia could be to analyse patient records from selected hospitals in Australia, or countries or regions with more centralised health systems, such as the UK, New Zealand or Scandinavia. This analysis would provide concrete evidence of epidemiology, healthcare utilisation and associated costs and help identify gaps in current care delivery and opportunities for improvement. This will enable better planning of clinical services and resource allocation. However, caution should be exercised when extrapolating this data to other regions due to demographic and ethnic variations.

4. Conclusions and recommendations

After analysing the current landscape of childhood dementia data collection in Australia, several key challenges and opportunities have emerged. These findings highlight both the significant gaps in our current data systems and the potential paths forward for improving our understanding and management of childhood dementia.

The current state of childhood dementia data collection in Australia faces several significant challenges:

- There is no comprehensive data collection system specifically designed for childhood dementia, making it difficult to understand the full scope of the condition and its impact on families.
- Health system coding is inadequate, and health records are fragmented across different providers and systems.
- Existing data collections (surveillance studies, patient registries, and health system data) each have significant limitations in terms of completeness, relevance and accessibility.

The lack of comprehensive data hampers multiple aspects of childhood dementia clinical management, including:

- Health and support service planning.
- Development of clinical best practices.
- Clinical trial planning and recruitment.
- Assessment of treatment effectiveness.

Table 1 summarises desired outcomes from childhood dementia data, types of data needed and possible solutions. To address these challenges and improve the availability and quality of childhood dementia data, we propose the following key recommendations:

1. **Establish a national clinical quality patient data registry,** that:

- Combines elements of a clinical quality registry with patient/parent entry capacity
- Is securely and sustainably funded with dedicated resources for data collection and analysis.
- Leverages existing (limited) patient registries both nationally and internationally.
- Minimises burden on clinicians and families through the use of data linkage and artificial intelligence.
- Ensures access to data for all relevant stakeholders while adhering to high privacy standards.

2. **Unlock data about childhood dementia in the health system,** through:

- Joining advocacy efforts to improve rare disease coding in Australian health systems, for example through adoption of ORPHAcodes, transition to ICD-11 and other initiatives. This will enable better identification and tracking of childhood dementia cases.
- Developing interim solutions for identifying childhood dementia cases within current systems including analysis of patient records from selected hospitals, countries or regions.
- Consideration of surveillance studies to capture newly diagnosed cases and support research studies to fill specific knowledge gaps such as health economics.

Implementation of these recommendations will require coordination between multiple stakeholders, including federal and state health departments, healthcare providers and institutions, patient advocacy organisations, research institutions, technology providers, and funding bodies.

With support from the Department of Health, Childhood Dementia Initiative will begin work in 2025 to investigate data solutions, examining the feasibility, costs, and timelines of different options to determine the most effective approach for driving progress in this area.

TABLE 1: Summary of data needs and potential solutions for childhood dementia

Desired outcome	Data needed	Potential data sources	Advantages	Challenges
Health and support services have the capacity to meet the needs of families.	Incidence and prevalence, health services utilised.	Retrospective review of health records in one or more hospitals/regions	Potential for fast, relatively inexpensive, comprehensive data extraction. Data from diagnostic laboratories, death records etc. could be incorporated.	Inadequate coding system makes it difficult to find patient records. Extrapolation of data might not be relevant to all settings. Historical data might not be relevant to modern settings.
		Patient registry	Data collected is tailored to aims of the registry and prospectively monitors into the future.	Difficult to enrol all patients in registry and will require resourcing
		Surveillance studies	Detailed information on newly diagnosed and also undiagnosed patients suspected to have a childhood dementia condition. Could be a useful recruitment tool	Only a snapshot at diagnosis. Relies on clinicians reporting back to the surveillance unit so won't get data for the entire patient population.

			to a patient registry.	
		Disease modelling	Relatively low effort.	Relies on accurate incidence and life expectancy data which isn't available for all types of childhood dementia. Only able to estimate incidence, prevalence, average life expectancy and some health economic parameters. Not real-world data.
Improved clinical best practice and evidence-based disease management protocols	Detailed longitudinal data	Patient registry, ideally a clinical quality registry	High quality data to compare and monitor changes to clinical care over time and in different hospitals.	Significant resources needed to enter and curate data. Costly and will take time to gather enough data for analysis.
		Research studies comparing different interventions	Focused and direct comparison of interventions. Can include qualitative elements including preferences of patients and families.	Narrow scope focused on certain interventions. Limited time scale.

		Development of clinical consensus guidelines	Relatively low effort and fast: based on clinical experience and opinion.	High quality evidence for best practice may be limited and opinion of experts may be conflicted.
Increased opportunities for clinical trial participation	Basic patient demographics and diagnosis information to enable clinical trial planning and recruitment	Patient registry	Relevant data quickly accessible and consent to be contacted for research in place.	Difficult to enrol all patients in the registry and will require resourcing.
		Ad hoc contact to individual hospitals/clinicians	No set-up required, data obtained up-to- date.	Burden on clinicians to answer enquiries, time consuming to obtain data, may not capture all patients. Pharma companies/CROs may not contact the most appropriate clinicians.
Contribute to global clinical trial readiness e.g. natural history, clinical trial protocols, clinically relevant	Detailed longitudinal data including clinical measures, patient preferences &	Patient registry, ideally linked to patient samples	Rich data, easily accessible. Particularly important for ultra-rare disorders where natural history data, outcome measures etc. does not exist.	Resources needed to enter and curate data. Costly and will take time to gather enough data for analysis.

outcome measures, biomarkers	priorities			
Emerging treatments are approved and reimbursed through real world assessment of clinical effectiveness and cost-effectiveness	Detailed longitudinal data, patient reported outcome measures	Patient registry	Can include both clinical measures and patient reported outcomes useful for health technology assessment (HTA). Pharma companies may contribute funding.	Resources needed to enter and curate data.

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Appendix

SUPPLEMENTARY TABLE 1: Patient registries that are likely to contain data about individuals with childhood dementia disorders in Australia

Patient registry	Childhood dementia conditions included	% of CD incidence	Comments
AussieRett	Rett syndrome	16%	
Australian Leukodystrophy and White Matter Disorders Registry	Multiple including: X-linked adrenoleukodystrophy, metachromatic leukodystrophy, vanishing white matter disease, Aicardi-Goutières Syndrome, Canavan Disease, Pelizaeus Merzbacher Disease	24%	Most of the conditions included in the registry cause childhood dementia
Australian Mitochondrial Disease Foundation Patient Registry	At least 12 clinical categories including Leigh syndrome, Alpers-Huttenlocher syndrome, MCHS, MEMSA, MEGDEL, Pearson syndrome,	20%	Broader than childhood dementia, approximately 10% of people with primary mitochondrial disease have

	congenital lactic acidosis, Kearns-Sayre syndrome, MELAS, MERRF, NARP, MNGIE		childhood-onset dementia.
Genomics of Rare Disease Registry	All	100%	Broader than childhood dementia - all rare diseases. This is a new registry with limited enrollment so far
International Collaborative Gaucher Group Gaucher Registry	Gaucher disease types 2 & 3	<1%	Broader than childhood dementia (includes Gaucher disease type 1 which does not cause CD)
International MECP2 Duplication Database (MDBase)	MECP2 duplication syndrome	1.9%	
International Niemann-Pick Disease Registry	Nieman-Pick disease types A and C	2.8%	First Australian site opened in Melbourne in 2024
Map-HD Registry	Juvenile Huntington's disease	1.4%	Broader than childhood dementia

Note: Some patient organisations also have informal contact databases.

SUPPLEMENTARY TABLE 2: ICD-10-AM codes that could be used to identify childhood dementia patients

Disorder	% of incidence	ICD-10-AM code	Code description	Comments
GM2 Gangliosidosis (Sandhoff Disease)	0.6%	E750	GM2 gangliosidosis	Very rarely can have onset in adulthood
GM2 Gangliosidosis (Tay Sachs Disease)	1%			
GM2 Gangliosidosis - AB Variant	unknown			
GM1 Gangliosidosis (Type 1)	0.8%	E751	Other gangliosidosis	Very rarely can have onset in adulthood
GM1 Gangliosidosis (Type 2)	0.4%			
Mucolipidosis Type IV	0.01%			
Neuronal Ceroid Lipofuscinoses (NCLs or Batten Disease) including CLN1, CLN2, CLN3,	3.4%	E754	Neuronal ceroid lipofuscinosis	There are 14 subtypes of NCL, three very rare subtypes are adult onset

CLN5, CLN6, CLN7, CLN8, CLN10, CLN12, CLN14				(CLN 4, 11, 13)
MPS I (Hurler Syndrome)	2.1%	E760	Mucopolysaccharidosis, type I	Includes Hurler-Scheie and Scheie forms that do not cause childhood dementia (one-third of MPS 1 diagnoses)
MPS II (Hunter Syndrome)	1.7%	E761	Mucopolysaccharidosis, type II	Includes attenuated form which does not cause childhood dementia (one-third of MPS II diagnoses)
Alpha-mannosidosis	0.2%	E771	Defects in glycoprotein degradation	Almost all glycoprotein degradation disorders cause childhood dementia except sialidosis type 1 which is very rare.
alpha-N-acetylgalactosaminidase Deficiency (Schindler Disease Type I)	unknown			
Aspartylglucosaminuria (AGU)	0.5%			
Beta-mannosidosis	unknown			

Fucosidosis (Type I and II)	0.09%			
Galactosialidosis (Cathepsin A Mutation)	0.1%			
Mucolipidosis Type I (Sialidosis type 2)	0.06%			
Rett Syndrome	16.1%	F842	Rett syndrome	
Ataxia telangiectasia	2.9%	G113	Cerebellar ataxia with defective DNA repair	Not all patients experience childhood dementia
Pantothenate kinase-associated neurodegeneration (PKAN)	0.6%	G230	Pigmentary pallidal degeneration	Onset can occur in early adulthood in some cases.
Cockayne syndrome/Xeroderma pigmentosum-Cockayne syndrome	0.8%	Q8711	Cockayne syndrome	
Zellweger Spectrum Disorder	3.5%	Q8783	Zellweger syndrome	
TOTAL	**35%**			

SUPPLEMENTARY TABLE 3: Childhood dementia epidemiological study definitions and characteristics

Study	Terminology	Brief inclusion criteria (see publication for detail)	Population	Study type	Incidence	Number of patients/Number of disorders
Elvidge et al., 2023[1]	Childhood dementia	Primary monogenic childhood dementia disorders defined as progressive neurocognitive decline, typically presenting before 18 years of age. Excluding progressive acquired disorders and primary epileptic encephalopathies. Treatable disorders were considered separately. Data for modelling only available for 70 of 145 conditions.	International	Disease modelling	34.5 per 100,000 live births	n/a 145 disorders
Verity et al.,	Progressive	Any child (under 16y of age at onset of	UK	Surveillance	10 per	2255 children

2021[6]	Intellectual and Neurological Deterioration (PIND)	symptoms) who fulfills all of the following three criteria: Progressive deterioration for more than 3mo; Loss of already attained intellectual or developmental abilities; and Development of abnormal neurological signs. Including seizure disorders if associated with progressive deterioration and those yet to receive a specific diagnosis. Included a small number of infectious causes: variant Creutzfeldt-Jakob disease (vCJD, 6 cases) and Subacute Sclerosing Panencephalitis (SSPE, 13 cases). Study reported under-ascertainment of Rett syndrome cases.			100,000 live births	notified between 1997 and 2019 220 disorders
Nunn et al., 2002[5]	Childhood dementia	Childhood dementia defined as any child (under 15 years) who suffers from	Australia	Surveillance	Cumulative two-year	214 children notified between May

		an illness fulfilling the following criteria: 1. Multiple losses of already attained development skills. 2. Duration of illness greater than 3 months. 3. Skill loss most likely due to CNS dysfunction. 4. Evidence of generalised (not focal) brain dysfunction. Included infectious causes such as SSPE (5 cases).			prevalence for children under 15 years was 5.6 per 100,000 (incidence not reported).	1993-June 1995 63 disorders
Stromme et al., 2007[12]	Progressive childhood encephalopathy	Children presenting with signs of progressive CNS disease associated with impairment of cognitive functioning between 0 and 15 years of age. Rett syndrome excluded. Included 2 cases of HIV encephalopathy and some conditions that were considered treatable and excluded in some other	Norway	Retrospective health system data analysis	60 per 100,000 live births	84 during during the 18-year period 1985-2003 28 disorders

		studies e.g. urea cycle disorders. PKU was excluded as it is detected by newborn screening.				
Uvebrant et al., 1992 [13]	Progressive childhood encephalopathy	Presence of signs and symptoms of a deteriorating brain impairment. Included treatable conditions such as phenylketonuria (PKU) (full article inaccessible, so detail is lacking).	Western Sweden	Retrospective health system data analysis	58 per 100,000 live births	76 during the 16-year period 1970-85