childhood dementia Symposium 2023

REPORT

of the second Childhood Dementia Symposium 14 March 2023

childhood dementia INITIATIVE

Acknowledgements

In the spirit of reconciliation, Childhood Dementia Initiative (CDI) 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.

This report has been prepared by CDI based on the key themes that were raised at the Childhood Dementia Initiative Symposium and discussion groups held on 14 March 2023. We thank the participants for their enthusiastic and knowledgeable contribution on the day.

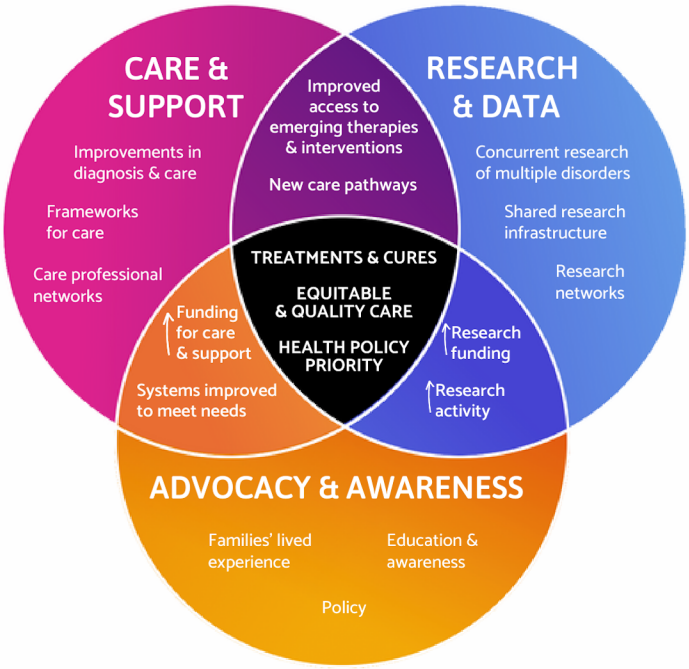
We would like to thank the CDI Scientific and Medical Advisory Committee (SMAC) - John Christodoulou, Marcel Dinger, Michelle Farrar, Kim Hemsley, Leszek Lisowski, Peter Schofield and Nicholas Smith for their input in planning the symposium. Special thanks to Tiffany Boughtwood, SMAC chair and CDI Director. Thank you also to the speakers, session chairs and discussion group scribes and facilitators and to Dr Saili Moghe in the preparation of this report.

We would also like to acknowledge and thank the symposium sponsors - Alexion, Sanofi and Biomarin, whose financial contribution made the symposium possible. All support is gratefully received and has been given without influence over the content, speakers, or attendees at the event.

It's time for change

Childhood Dementia Initiative is driving world first action for every child with dementia. We are finding better ways to research and treat childhood dementia. Through bold, innovative approaches and systemic change we are improving outcomes for children with dementia across the world. Our Framework for Systems Change (pictured here) guides our work to achieve:

- Treatments and cures for childhood dementia
- Equitable and quality care for children and families
- Recognition of childhood dementia as a health policy priority



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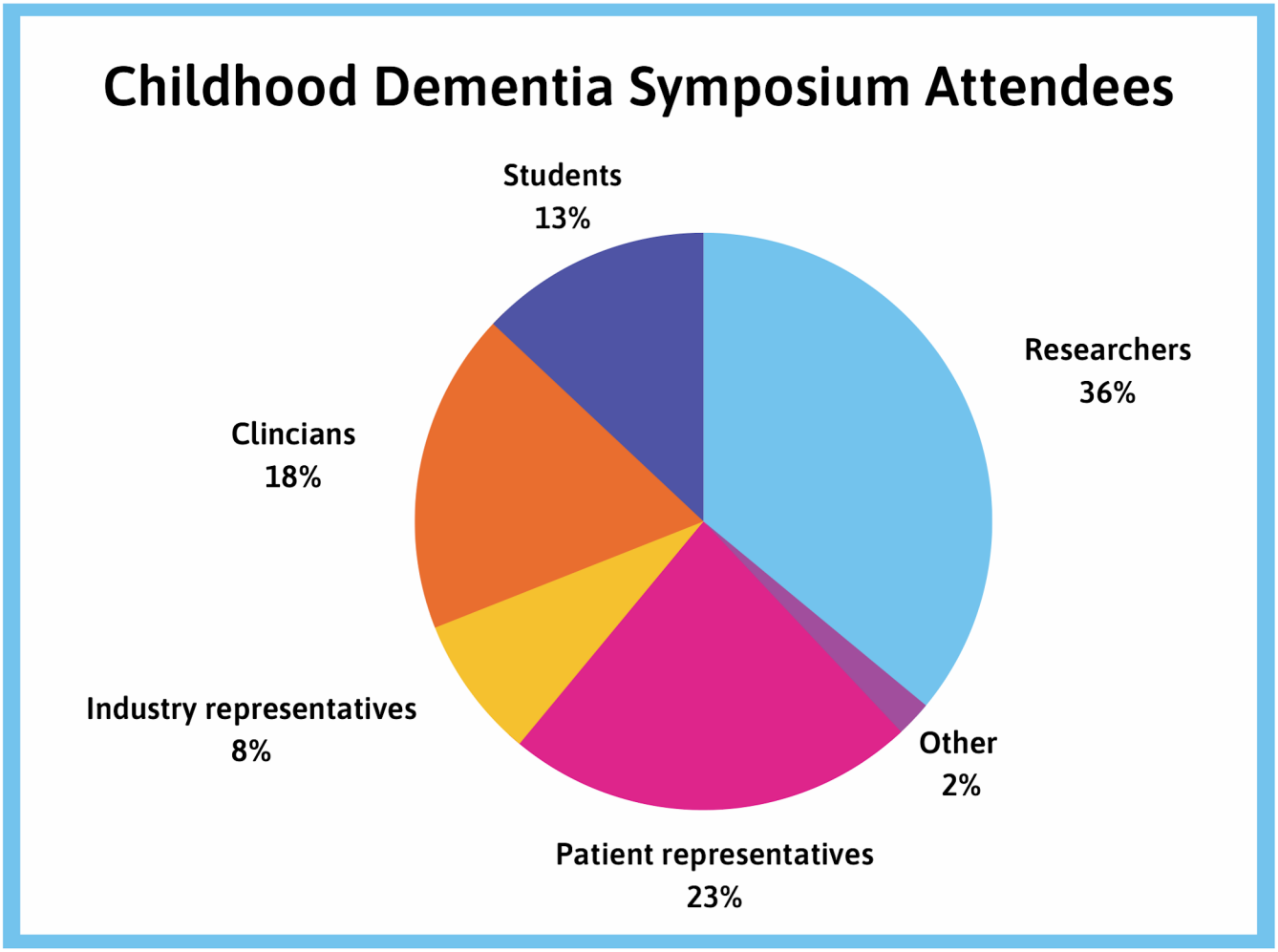
Executive Summary

Childhood Dementia Initiative (CDI) hosted the 2nd Childhood Dementia Symposium on 14 March 2023, which was attended by 100 clinicians, researchers, industry, and patient representatives, all in person in Sydney.



Three sessions of presentations inspired new ideas and provoked thoughtful discussion. Networking sessions also gave the opportunity for small groups to discuss important topics.

Key themes that emerged from the day were:

- The need for international engagement. Childhood dementia is a global problem that needs a global solution.
- Overlapping mechanisms both between childhood dementia disorders and in common with adult dementia present opportunities for therapy development.
- Research is starting that aims to identify and develop drugs for multiple childhood dementia disorders based on overlapping disease mechanisms. Basket clinical trial design and outcome measures need to be defined in readiness for trials of such drugs.
- Multimodal therapies need to be considered for the best outcome for patients.
- The family perspective and involvement in research is extremely important.

- There is a need for networks to enable more efficient clinical trials and biosample collection and sharing, including brain banking.
- Newborn screening could transform therapy development for childhood dementia and collaborative effort is needed to ensure successful implementation.

Projects that received funding from the MRFF childhood dementia funding opportunity were announced on the day of the symposium. This funding will kick start some exciting projects but more funding is needed.

The outcomes of the 2023 Childhood Dementia Symposium will help inform research strategy going forward. Importantly, new connections made between researchers, clinicians and other stakeholders will have an enduring benefit for the acceleration of research in the years to come. CDI will launch a webinar series in the second half of 2023 to capitalise on the outcomes of this symposium and allow regular knowledge sharing and networking.

Session 1: Introduction and family perspectives

The morning began with a welcome and Acknowledgement of Country from Megan Maack, CEO of Childhood Dementia Initiative and the session was expertly chaired by Tiffany Boughtwood, Managing Director of Australian Genomics and Director, Childhood Dementia Initiative.

Two bereaved mothers - Louise Jessop and Peta Murchison - shared their very personal stories of loving and caring for their child, and ultimately losing their child to childhood dementia . Their moving presentations emphasised the pressing need to find treatments for childhood dementia, increase awareness and understanding and improve care and support.

Jason Djafar from University of New South Wales spoke about the importance of understanding the common clinical phenotypes of childhood dementia disorders to measure core outcomes of treatments. He presented findings from his mixed methods study that identified clinical commonalities across the childhood dementia disorders within the cognitive, behavioural, and physical domains and identified the most frequent and most troubling symptoms. Jason also shared results that demonstrated that a large portion of families supported the use of "childhood dementia" and that families report that there are significant gaps in care and respite support.

Dr Kristina Elvidge, Head of Research at Childhood Dementia Initiative presented the results of the Childhood Dementia Burden Study which will soon be published in collaboration with leading clinicians. This scoping review and burden of illness study sought to refine definitions and understand the spectrum of childhood dementia conditions. The study also estimated the collective incidence, prevalence and life expectancy. Over 140 individual genetic conditions were identified that can be consistently defined as childhood dementia with the largest proportion of births belonging to the lysosomal disease and mitochondrial disease categories. Of concern is considerable diagnostic delay noted in many studies. Early diagnosis is not only critical for the delivery of equitable and quality care, but it also plays a key role in therapeutic development.

Megan Donnell, CEO of Childhood Dementia Initiative gave an overview of the work of the organisation, strategy, and delivery model. She outlined how childhood dementia is neglected across policy, research and care. Childhood Dementia Initiative is a world-first organisation changing the national, and global, discourse for children with dementia and their families. Calls to action from Meg's talk included:

- Help us advocate for meaningful inclusion of childhood dementia in policy such as the National Dementia Action plan that is currently under development
- Promote the CDI Family Advocates program amongst your networks so that the family voice can be heard, understood and amplified
- Engage your global networks - look for ways to collaborate internationally or simply introduce the concept of the collective consideration of the childhood dementia disorders
- Seek collaborative projects that study multiple childhood dementia disorders concurrently
- Join us in advocating for increased research funding for childhood dementia research
- If you are involved in clinical care please spread awareness amongst your clinical peers and look out for the Childhood Dementia Community of Practice to be launched later this year
- Above all, use the terminology "childhood dementia" in your everyday practice. Using this collective language will drive greater awareness and understanding

Key discussion points from the session panel discussion included:

- Whole genome sequencing will be needed to screen for all childhood dementia disorders. Current policy is to only screen for treatable conditions despite the many benefits of knowing early, including increased opportunities for involvement in clinical trials. More work is needed to understand preferences, models of consent and the best way forward to take advantage of the benefits of broad newborn screening.
- Australia can lead the world in driving awareness, advocacy, and research for childhood dementia, CDI is engaging with international organisations (e.g. Alzheimer's Disease International) to extend reach globally.
- Reflection by parents on the terminology "childhood dementia" indicated it may have been useful for better awareness, acceptance of symptoms, and providing clarity about the disorders.
- Having a Human Phenotype Ontology (HPO) term for "childhood dementia" will be beneficial for ensuring better coding of the disease within health systems, enabling a better capture of data regarding what services are needed and used for childhood dementia patients.
- The need to obtain real world evidence to quantify the health economics across the entire family (not the patient alone) was emphasised.
- Similarly, consideration of resources and services needed for the entire family were raised as important unmet needs.

Session 2: Childhood dementia disorders: the commonalities, the opportunities and what we can learn from other fields

Professors Peter Schofield and John Christodoulou shared the chairing of this session which had so much important content that it was split into two halves.

Dr. Christopher Missling from Anavex Life Sciences Corporation in the U.S shared clinical data from global studies of Blarcamasine (Anavex ® 2-73) for Alzheimer's disease, Parkinson's disease and Rett syndrome. Anavex® 2-73 is an orally available drug candidate that restores cellular homeostasis by targeting sigma-1 and muscarinic receptors. He explained that based on preclinical data, these trials could be extended to include more childhood dementia disorders. Christopher also encouraged involving regulatory bodies early in the drug development process and sees great potential in the use of the Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium to expedite the approval of therapies.

Associate Professor Anthony White from QIMR Berghofer described current efforts in his lab on repurposing approved drugs for childhood dementia using a computational approach. His lab uses brain cells, 3D microglia, and 3D neurovascular systems to determine drug responses and delivery to the brain. Access to blood samples from patients with childhood dementia disorders will enable his lab to conduct patient-specific drug screening.

Professor Sarah Spencer from RMIT University spoke about the involvement of microglia in childhood dementia. She shared unpublished findings demonstrating that unique features of microglia may make them useful as a biomarker. She explained that retinal microglia may reflect what is occurring in brain microglia, and that future work involves determining if retinal scans may be useful for early diagnosis and disease monitoring.

Professor Rick Leventer from the Royal Melbourne Hospital explained the utility of forming global networks to accelerate and monitor progress in research and advocacy of childhood dementia disorders. He emphasised the need for more natural history studies for the development of meaningful clinical trials. He provided an overview of the Ionis ION373 antisense oligonucleotide (ASO) therapy clinical trial for Alexander disease, and highlighted that the Global Leukodystrophy Initiative-Clinical Trials Network (GLIA-CTN) played a key role in securing the Royal Melbourne Hospital as one of the global trial sites.

Associate Professor Michael Lardelli from the University of Adelaide presented his research using zebrafish as a model system to understand familial Alzheimer's disease and childhood dementia disorders such as Sanfilippo syndrome. In particular the role of lysosomal acidification and iron homeostasis was highlighted as a potential common pathway to target.

The recipients of $2.7 million in research funding for childhood dementia were announced by Australia's Federal Minister for Health and Aged Care, Mark Butler on the morning of the symposium. The recipients of the 5 grants gave a short overview of their projects:

- Associate Professor Anthony Cook from the Wicking Dementia Research & Education Centre at the University of Tasmania will develop and test a new substrate reduction strategy to treat childhood dementia. In collaboration with researchers at Murdoch University in Perth they will investigate if this treatment approach can stop the build up of certain harmful substances in the brain. It will be tested in cell models of around 10 different types of childhood dementia.

- A multidisciplinary team at Sydney Children's Hospital Network, John Hunter Children's Hospital, UNSW Sydney and University of Sydney, led by Professor Michelle Farrar will develop a comprehensive biomarker panel for childhood dementia. Biomarkers are substances in bodily fluids such as blood or spinal fluid, that can be used to understand disease processes, monitor disease progression and measure the benefit of treatments.
- Dr Ya Hui Hung at The Florey in Melbourne will develop an mRNA-based gene therapy for Niemann-Pick disease type C1. This project, being conducted with collaborators at Royal Melbourne Hospital and Monash University, will serve as a blueprint to establish an mRNA-based gene therapy pipeline for other types of childhood dementia.
- Associate Professor Wendy Gold's project aims to uncover new therapeutic targets, disease drivers and biomarkers for Rett syndrome. The researchers at the University of Sydney and the Children's Medical Research Institute will use patient cell models to increase understanding of this complex disease and accelerate improved treatment options for individuals with Rett syndrome.
- Dr Nicholas Smith from University of Adelaide and the Women's and Children's Hospital, with collaborators at Flinders University and University of South Australia will develop nanoparticle technology as a platform for targeted gene-delivery for Sanfilippo syndrome. This technology has wide applicability across the childhood dementia conditions if proven successful.

Key discussion points from session panel discussion included:

- Some of the challenges of doing clinical trials for multiple childhood dementias, for example using a basket trial design, can be overcome by working with regulatory bodies from the start.
- Repurposed drugs will likely be applicable across multiple disorders. One of the challenges of testing them in clinical trials across disorders will be monitoring outcomes; a combination of assessing biomarkers as well as the clinical phenotypes such as those identified in the study by Djafar et al. can be helpful for these purposes.
- There is a precedent for using retinal scans for diagnostic purposes (e.g. diabetic retinopathy) and it could be useful as an outcome measure in childhood dementia clinical trials as is being explored for multiple sclerosis. Rapid scanning methods need to be developed for this to be practical for children.
- It was proposed that childhood dementia disorders can serve as a suitable disease group to develop Artificial Intelligence (AI) - pattern recognition in MRI scans for diagnosis.
- There was a discussion about whether having a placebo arm, as is included in the ION373 trial, may deter participants. This was not a problem with this particular trial and demand far outstriped available places. It was acknowledged that inclusion of a placebo arm is important, but for trials of disorders that rapidly progress, the necessity and ethics of including a placebo arm will need to be carefully evaluated.
- Deep sequencing experiments in disease modelling to understand pathogenesis are very valuable but the cost is still prohibitively expensive.
- There was a discussion about the role of iron deficiency in neurodegenerative diseases. More work is needed to understand this.

Session 3: Clinical and clinical trial aspects of childhood dementia

Professor Michelle Farrar from Sydney Children's Hospital and the University of NSW chaired this session and facilitated the discussion.

Dr. Kirsten Furley from Monash Children's Hospital provided a scoping review about developmental regression. She underscored that clearly defining developmental regression can assist with developing a standard of care for children. Her team is working on creating a world-first research-embedded developmental regression clinic in collaboration with CDI.

Dr. Perez-Iturralde and Dr Haase from the Children's Medical Research Institute (CMRI) presented their work on engineering transgenes, and adeno-associated viral (AAV) vectors that can be used to efficiently, safely, and specifically deliver gene therapy in pre-clinical models.

Prashant Bharadwaj from Edith Cowan University presented his research on identifying and detecting genetic variants of brain biomarkers for adult and childhood dementia. He shared information about the emergence of sensitive biomarker detection systems, such as SIMOA (Single Molecule Array) which can enable better screening and determine treatment outcomes of clinical trials.

Key discussion points from session panel discussion included:

- There is a need to streamline the pathway for gene therapies to move from preclinical to clinical trials.
- A discussion of autophagy impairment in neurodegenerative diseases indicated that autophagy dysfunction in these conditions is likely due to protein aggregation.
- Prior to developmental regression there is often a developmental plateau seen in childhood dementia, data reflecting this plateau will also be captured and assessed in the developmental regression clinic run by Dr. Furley and others.
- Children who come to the developmental regression clinic may get access to exome sequencing through flagship requests, a research biobanking option, or through Medicare if they meet certain conditions (e.g. moderate intellectual disability). The hope is that they will also get referred to clinical trials relevant to them.

Networking sessions

Symposium attendees broke into small groups to discuss topics nominated by the attendees prior to the symposium. Each participant joined two groups for about 20 minutes each. High level outcomes are summarised below.

1. Collaborations to obtain biosamples for research

- Researchers made connections with clinicians and discussions are currently ongoing to obtain samples with great enthusiasm from all involved.
- Volumes of blood obtainable from children was flagged as an issue (5ml vs 100ml from adults) however protocols may be able to be adapted.
- For some applications the samples need to be freshly collected therefore a biobank would not help. However, a clinical network with ethics in place across institutes/hospitals would accelerate research.
- For other applications, a biobank with standardised protocols would be advantageous and the more samples available for each rare disease the better.

2. Brain banking

- There is interest from researchers and families (some, not all!) and an appetite for a working group following this discussion.
- Implementation will need to be sensitive towards families, and could involve integration with clinical trials.
- Appropriate funding methods for a brainbank need to be determined.
- Work has begun post-symposium to understand the global landscape of paediatric brain banking.

3. Overlap in pathologies between adult and childhood dementia

- Main overlapping mechanisms were identified but acknowledged that multimodal therapies will be important (can't just target one disease process).
- Post mortem brains would help uncover pathology in common.
- Addition of disease mechanisms to the Knowledgebase will be helpful (this work is ongoing).
- The overlap with adult dementia can be leveraged for funding.

4. Brain Organoid Models

- This is an exciting and growing field of research and was one of the most popular discussion topics.
- Assembloid systems were discussed to include multiple brain structures to model specific phenotypes.
- The importance of including microglia in these models was raised.
- There was discussion about the precedent for using in vivo models for vascularized brain organoids.

5. How can we bring more childhood dementia clinical trials to Australia?

- Need faster trial start up times and an agile and ready workforce. Demonstrating successes in this area and promoting this broadly could be helpful.
- Clinical trial centres don't always have capacity to take on more trials, capacity building is needed which will require funding from philanthropy and hospitals/universities.
- Greater collaboration between sites is needed.
- Patient registries and expanded newborn screening would make Australia more attractive for trials.
- Work could be done to build relationships with industry and demonstrate clinical trial capabilities in Australia.

6. Industry collaboration

- Industry are keen to collaborate - don't be afraid to build relationships.
- Important for researchers to look at a range of funding sources including philanthropy, private equity and venture capitalists.
- Universities need to be better at fostering collaboration with industry and helping with navigating IP etc.
- Positive case studies of successful industry collaborations could be a good topic for our webinar series.

7. Medical research and medical innovation projects with commercial potential

- Childhood dementia is appropriate for inclusion in the proposed Dementia BioMedTech Incubator.
- Emphasising the overlap with adult dementia could help sell commercial viability, platform technologies will also be attractive.
- Researchers may need help to get their idea to the right stage - signposting to resources/partners.

8. Successful implementation of expanded newborn screening

- There is a need for workforce capacity following diagnosis of any condition(s) detected through NBS and clear clinical pathways.
- Improve equity of access to clinical pathways after a positive result, especially in regional areas.
- More research is needed into genotype/phenotype, natural history and what conditions to include.
- Ethical considerations of informed consent and ensure trust in the current system isn't jeopardised.

9. Meaningful engagement of patients and families

- Research should be communicated in plain English, not 'dumbed down'.
- Increase opportunities for bringing researchers and families together.
- Need to respect the busyness of family lives - consider childcare arrangements.
- Increase communication of research to the general public e.g. podcasts.

10. How can we promote respectful language use by researchers and clinicians?

- Greater awareness is needed regarding the time, place and appropriate participants in difficult conversations e.g. at diagnosis.
- Important not to assume that children cannot understand when they are attending medical appointments.
- Reflective practice (individual or group supervision) for clinicians and inclusion of good communication practice in tertiary education is necessary.

Feedback
from symposium attendees

Attendees who rated the content and speakers as excellent or very good:

Attendees rated the content covered as:

Attendees rated the speakers as:

“Very inspiring and collaborative feel to the day”

“[This symposium] enabled so many different research and clinical groups to come together, share, bounce ideas and forge new collaborations.”

“A great opportunity to hear a breadth of talks in the area and meet other clinician researchers”

“Hearing personal stories from the families [was a highlight for me]. This really provided much needed perspective to all clinicians and researchers in attendance to understand the gravity of childhood dementia and why there is a huge need to invest in research in this area.”

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