Report of the Inaugural Challenging Childhood Dementia Symposium

March 2022

childhood dementia INITIATIVE

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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 Challenging Childhood Dementia Initiative Symposium and workshops held on 1 March 2022. 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 CDI Strategic Advisor Barrie Littlefield who skilfully facilitated the workshops.

We would also like to acknowledge and thank the symposium sponsors - Sanofi, Alexion and Illumina, 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.

ABOUT CHILDHOOD DEMENTIA INITIATIVE

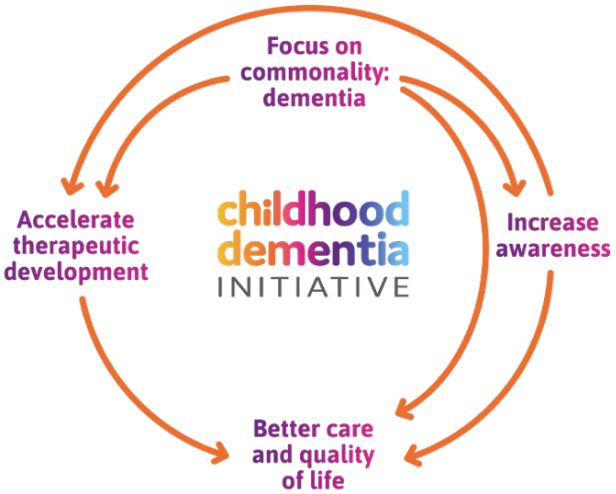
Approximately one young Australian dies with childhood dementia every four days, their short lives defined by pain and suffering, and no one knows about it.

There are 70+ rare genetic disorders that result in childhood dementia. These include conditions such as Sanfilippo syndrome, Batten disease, metachromatic leukodystrophy, Niemann-Pick disease, Rett syndrome and some of the mitochondrial disorders.

Childhood Dementia Initiative (CDI) is driving world first action to reframe the way experts, systems and policy makers view and respond to these diseases; focussing on the commonality (dementia) rather than the underlying genetic cause.

Our collective approach will address the lack of awareness, fragmented and insufficient research, poor quality of life and limited access to appropriate care and support.

To find out more about our work or make a donation www.childhooddementia.org



EXECUTIVE SUMMARY

On 1 March 2022, 75 clinicians, researchers, industry, and patient representatives gathered for the inaugural Challenging Childhood Dementia Symposium - the first meeting of its kind.

The morning symposium featured presentations on research into genetic therapies, disease models and drug discovery. There was an emphasis on the importance of early diagnosis and treatment and leveraging the learnings for one type of childhood dementia for others. Lively Q&A followed each session, and the experiences shared by families grounded and enriched discussion.

Two facilitated workshops conducted in the afternoon defined the priorities to accelerate the development of new treatments and increase the number of clinical trials for childhood dementia.

KEY RECOMMENDATIONS FROM THE SYMPOSIUM

- Research is needed to identify common mechanisms that could be targeted across multiple childhood dementia disorders;
- Increase collaboration and knowledge sharing across disciplines, diseases and institutions;
- Establish a platform to collect patient longitudinal data linked to samples in a biobank;
- Increase links with adult neurodegeneration research; and
- Achieve a nationally coordinated approach to childhood dementia clinical trials with a central point of contact for trial sponsors and streamlined feasibility, governance and ethics.

KEY RECOMMENDATIONS FOR FUNDERS

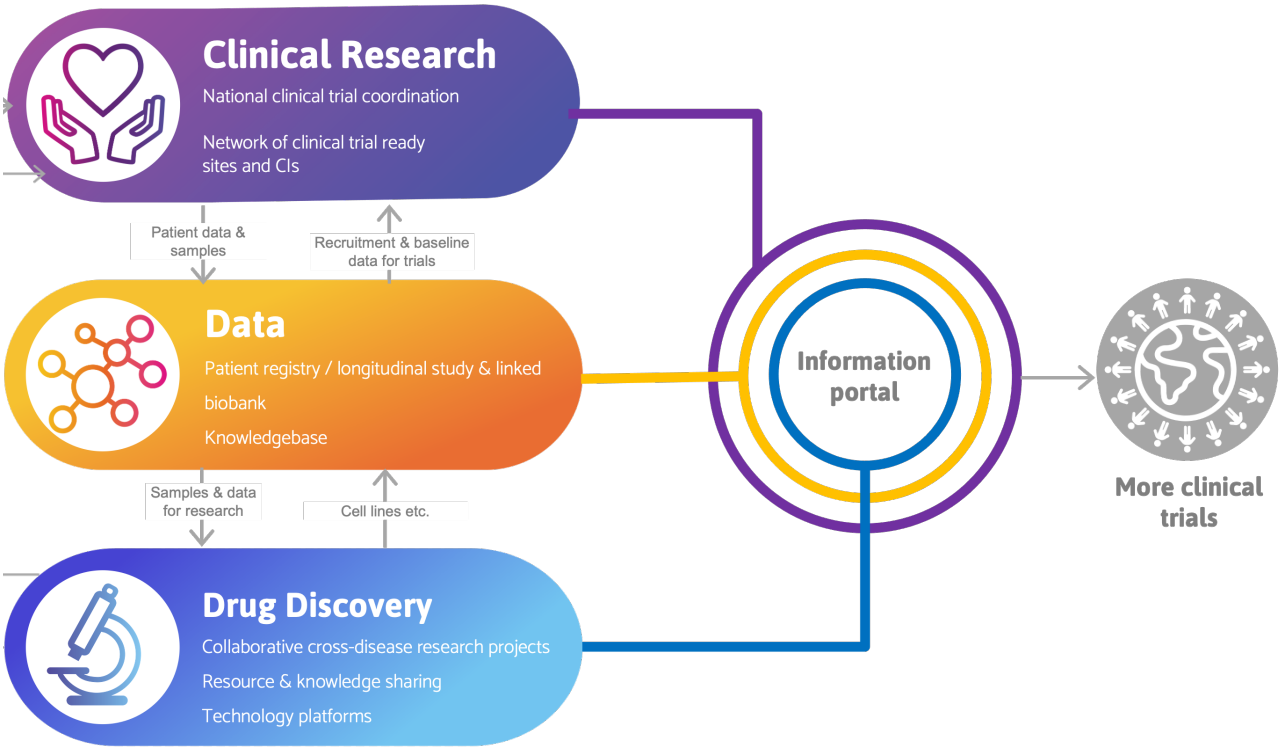
- A cohesive, coordinated approach to research funding is needed to tackle the scale and scope of childhood dementia unmet need;
- Collaborations across patient organisations to fund research that addresses multiple types of childhood dementia.

KEY RECOMMENDATIONS FOR POLICY MAKERS

- Early diagnosis through an equitable expanded newborn screening program is essential, not only for timely access to approved therapies but also to increase the success rate of clinical trials of experimental treatments;
- Streamlined ethics and regulatory processes are needed, as recommended by the Inquiry into approval processes for new drugs and novel medical technologies in Australia[1]; and
- More incentives for pharmaceutical companies to conduct trials in Australia.

[1] Commonwealth of Australia, The New Frontier - Delivering better health for all Australians. Inquiry into approval processes for new drugs and novel medical technologies in Australia, House of Representatives Standing Committee on Health, Aged Care and Sport. https://www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Report.

A major outcome of the day was strong support for the formation of a Childhood Dementia Research Consortium to address the key recommendations above. This consortium will include both drug discovery and clinical research with collaboration between scientists and clinicians being integral to success. One possible configuration is outlined in the diagram below.



A Childhood Dementia Research Consortium would bring together a national multi-disciplinary team: including researchers, clinicians and diagnosticians who once competed for research funding to collaborate, share resources, and break down silos - resulting in greater efficiencies and acceleration of therapy development.

National, streamlined clinical trial coordination will establish Australia as a leader in the childhood dementia field. Leveraging existing resources, transparency, strong governance, partnership with industry and the patient voice will be key guiding principles.

Beyond research into new therapeutics - the focus of this symposium - research into standards of care and best practice management for improving quality of life was raised and cannot be ignored. This is a pillar of the Childhood Dementia Initiative's strategy and will be a topic of future meetings.

Childhood Dementia Initiative will facilitate the formation of this ambitious consortium described above, bringing key stakeholders together, including families directly affected by childhood dementia, to collaboratively make this vision a reality and transform the childhood dementia research space in Australia.

1. INTRODUCTION

Childhood Dementia Initiative hosted the inaugural Challenging Childhood Dementia Symposium on 1 March 2022, which was attended by 75 clinicians, researchers, industry, and patient representatives. Most participants joined the in-person symposium and workshops, with additional online participation. There was a definite buzz in the air as people connected and shared ideas face-to-face for the first time in a very long time.

The morning started with a welcome and Acknowledgement of Country from Tiffany Boughtwood (Managing Director, Australian Genomics and Director, Childhood Dementia Initiative). **A video message from the Honourable Greg Hunt MP**, Federal Minister for Health and Aged Care was then played which emphasised the lack of treatments for childhood dementia as "one of our great national tasks and we can be a world leader". Minister Hunt then announced a new **$3 million MRFF competitive grant round** to focus on treatments and therapies for childhood dementia.

Two mothers gave their perspective on two different forms of childhood dementia. **Renee** told us of the diagnosis of all three of her children with Niemann Pick disease type C and **Niki** spoke about her teenage daughter's battle with Lafora disease. These powerful presentations were heart-breaking and reminded everyone of the urgency of the problem.

Megan Donnell, CEO of Childhood Dementia Initiative gave an overview of the work of the organisation, strategy, and delivery model.

2. EARLY DIAGNOSIS AND INTERVENTION

Dr Nicholas Smith from Women's and Children's Health Network, South Australia spoke about the window of opportunity for childhood dementia treatment. He presented preliminary results from the Abeona AAV9 gene therapy clinical trial for Sanfilippo syndrome type A (MPS IIIA) which showed that early treatment when patients are minimally symptomatic is essential for treatment success. Nick highlighted the need for earlier diagnosis and more research to understand and extend the therapeutic window.

Dr Nadia Mitchell, Lincoln University, New Zealand presented remotely on her research to develop an AAV9 gene therapy using a sheep model of CLN5 with promising results in both the eyes and brains of the sheep. Neurogene is now sponsoring the gene therapy and a clinical trial has recently started recruitment.

Assistant Professor Jinkuk Kim, KAIST, South Korea presented his research on fast tracked development of antisense oligonucleotide (ASO) therapies for individual patients with Batten disease (CLN7) and ataxia telangiectasia. The FDA's amenability to waiving regulatory requirements was discussed, as well as the importance of early treatment. This approach could be applicable to 10-15% of patients with rare autosomal recessive CNS diseases (2-3 million patients worldwide).

QUESTIONS AND DISCUSSION:

- Investment in screening programs (molecular and biochemical newborn screening) is needed in parallel with therapy development rather than waiting for treatments to be available;
- AAV manufacturing capabilities are limiting for gene therapy research;
- Communication with families involved in patient customised therapies is critical, and in fact, the families are often highly involved and are the driving force;
- It is remarkable that the FDA waived 4 of the regulatory requirements for ASO, this was helped by the nusinersen precedent and the unique situation and family involvement;
- Advantages of ASO over gene therapy - cell type tropism is less specific for ASOs, avoids risk of over expression which could be problematic for some genes and ASO manufacturing is easier and cheaper. However, ASO therapy requires regular intrathecal administration.

3. RESEARCH FUNDING PANEL

PANEL MEMBERS: Dr Lisa Melton (Sanfilippo Children's Foundation), Dr Ineka Whiteman (Batten Disease Support and Research Association Australia and Mito Foundation), Dr Kaele Stokes (Dementia Australia) and Dr Saraid Billiards - remote (Australian Government Department of Health).

Research funders discussed and responded to questions on funding for childhood dementia research.

KEY POINTS:

- Small grants are great for getting new bright ideas off the ground, but larger integrated program grants are really needed to tackle the size and scale of the problem;
- Small, rare disease funders can add a lot of value by facilitating collaborations between researchers, collaboratively building proposals with researchers and incorporating family input;
- Elevating the voices of lived experience is important in research funding;
- Translation into practice is slow which is a challenge;
- Priority driven nature of MRFF is an advantage, but there is still not enough funds for all the needs and good applications. Timing of opening of applications to submission is challenging;
- MRFF Missions aim to have an integrated and collaborative approach to a priority area. Evaluation is key to making sure outcomes are being achieved;
- Need to fund capacity building (people) as well as projects;
- The dilemma of funding research locally or internationally was discussed. It was agreed that a balance of funding the best research internationally and building capacity for research and trials in Australia to benefit Australian patients is needed;
- We need to consider ways that organisations focused on one type of childhood dementia can assess and collaborate to fund projects that address multiple types of childhood dementia;
- Researchers should be bold in devising research proposals and ground proposals in the impact for families;
- Research into standards of care and best practice management for improving quality of life is also important;
- For government funding it is helpful to get alignment from the sector (through forums such as this) on what is needed and approach funders with a united voice and common goal.

4. EXTENDING RESEARCH ON ONE DISORDER TO MULTIPLE

Associate Professor Anthony Cook, University of Tasmania gave a presentation titled *"Breaking Down Batten Disease - iPSC modelling of a childhood dementia"*. Tony's team has created and characterised a neuronal cell model from a patient with CLN3 which will be used to test emerging therapies. They are planning to expand - creating a panel of isogenic iPSC lines of a range of types of childhood dementia using CRISPR/Cas editing that will be sharable internationally. These cell lines will be used to compare the biology of these disorders and test therapies.

Dr Ya Hui Hung, Florey Institute of Neuroscience and Mental Health, gave a presentation titled *"mRNA: a new weapon to fight rare genetic diseases"*. Ya Hui has been working to develop an mRNA therapy for Niemann-Pick disease type C1. The next step will be to test in an animal model and overcome the challenge of delivering mRNA to the brain. There is much interest in this area after the success of mRNA COVID-19 vaccines.

Professor Matthew Gentry, University of Kentucky, gave a remote presentation which described the collaborative effort by the Lafora Epilepsy Cure Initiative consortium to understand Lafora disease and develop therapies, which was enabled by an NIH grant to bring former competitors together. Therapies now in development include ASO, an antibody-enzyme fusion, small molecules, drug repurposing and gene therapy. His talk then focused on the antibody-enzyme fusion (VAL-0417) which has been successfully tested in a disease model. Preclinical safety and pharmacokinetic studies are now underway in preparation for clinical trials.

QUESTIONS AND DISCUSSION:

- Applicability of the antibody fusion platform to other childhood dementia disorders was discussed;
- Childhood dementia researchers should consider collaborations to apply for larger pots of money;
- mRNA broad applicability emphasised;
- Partnering with industry is needed to take therapies to trial (Lafora Epilepsy Cure Initiative has partnered with 3 companies).

5. WORKSHOP - ADDRESSING THE BARRIERS TO DEVELOPING NEW TREATMENTS

A two-step process was taken in this workshop, initially brainstorming for barriers and then each group focused on addressing certain barriers.

5.1 BARRIERS IDENTIFIED

Infrastructure and funding

- Lack of sustainable funding; funding models are restrictive and short term (projects are designed to fit funding requirements rather than for the most impactful outcome);
- Funding models are competitive rather than collaborative;
- Limitations to resourcing of personnel and infrastructure;
- Finding and validating suitable disease models; and
- Lack of harmonised and standardised data - molecular, genetic, and phenotypic (including natural history and genotype/phenotype correlations).

Research and clinical

- Late diagnosis;
- Lack of awareness of this group of disorders;
- Insufficient understanding of disease mechanisms and those that could be targeted across childhood dementia disorders;
- Diversity of causes and pathomechanisms will be a challenge - there will not be a silver bullet for all, but multiple approaches needed;
- Institutional silos - lack of collaboration and knowledge sharing; and
- Insufficient collaboration between clinicians, patients, and scientists - data from the clinic should inform basic research.

5.2 SOLUTION: CHILDHOOD DEMENTIA RESEARCH CONSORTIUM

Discussion conveyed strong support for a nationally coordinated approach - a securely funded consortium with the following features:

- Common resources such as disease models, cell lines, brain bank and biobank linked to clinical data with age matched controls with agreed SOPs (see also workshop 2 below);
- National multidisciplinary teams that overcome silos, replaces competition with collaboration and reduces duplication;
- Closer working relationships between patients, clinicians, scientists and industry;
- Integration of research into clinical care; and
- Strengthened links with adult neurodegeneration research.

Key priorities for the consortium:

- Platform technologies that can be utilised across disorders such as high-throughput drug screening/drug repurposing and gene therapy; and
- Research to understand disease pathogenesis and identify treatment targets common to multiple types of childhood dementia such as neuroinflammation.

6. WORKSHOP - INCREASING THE NUMBER OF TRIALS FOR CHILDHOOD DEMENTIA IN AUSTRALIA

6.1 SOLUTIONS BRAINSTORM

This workshop jumped straight to solutions and the consensus was for a clinical trial network or an arm of the Childhood Dementia Research Consortium with the following key features:

- Centralised operations and coordination of trials to provide a single point of contact for pharma, streamlined ethics and governance support and review of trials for scientific merit, feasibility and impact;
- Identify multiple clinical trial ready sites and CIs. Develop thought leadership that showcases the talent in Australia to run trials and connect these leaders with global trial sponsors;
- Develop a transformative enabling platform to collect natural history data/longitudinal data into a patient registry and collect samples for deposition in a biobank. This will establish a baseline for clinical trial readiness (consider MRFF Research Data Infrastructure initiative). This will require funding of annual/biennial review of all patients for data and sample collection. As a minimum we need a patient registry so we know where patients are.
- Link into international registries and networks and build relationships with pharma and international trials; and
- Information portal - all the information and resources of the consortium/clinical trial network in one place

6.2 PRINCIPLES

- Patients/families involved in trial design;
- Transparency, accountability and strong governance model;
- Leverage existing clinical trial centres, research collaborations and centres of excellence to maximise impact;
- Consult pharma on what they need from a childhood dementia clinical trial network;
- Start small with solid foundations, governance and infrastructure and demonstrate scalability; and
- Consider opportunities beyond government funding.

6.3 OTHER IDEAS FOR CONSIDERATION

- Consider patient registry vs clinical quality registry;
- Learn from and/collaborate with relevant exemplars;
- Funding for research nurses, admin, clinicians' research time;
- Standardised outcome measures toolkit - opportunity to harmonise internationally;
- Innovative trial designs;
- Upskilling e.g. training for clinicians in gene therapy and ensure the regulatory and hospital/ health services are up to speed to handle biologicals;
- Financial assistance/gap funding for patients travelling overseas for trials;
- Ensure equity of access with telehealth and hub and spoke trials - elements done locally with central coordination;
- Policy and governance around compassionate access;
- Gene therapy vector manufacturing in Australia; and
- Funded think tank to develop innovative strategies.

7. POLICY ISSUES

There were a number of policy issues that were raised throughout the day to be addressed with Government:

- Expanded Newborn Screening with national consistency;
- Functional National Ethics Approval Framework/centralised HREC ;
- Incentives for pharma to do trials in Australia - more tax breaks, subsidies, fund trial infrastructure;
- Novel reimbursement models for new drugs e.g. risk sharing;
- Better partnerships between federal and state funding to hospitals; and
- Speed up regulatory pathways for new drugs e.g. Accumulus.

SYMPOSIUM QUOTES

"I have been telling everyone how great the day was and how inspiring it was to see excellent research, hear from strong loving families, glean fresh insight from research funding providers, and just be positive and excited that organisations like CDI exist and are fighting for childhood dementia families."

"There is an opportunity for CDI to lead a national vision for collaboration and break down the silos."

"I am motivated by the collective determination and enthusiasm to raise knowledge and awareness of all the conditions that can present with childhood dementia."

"I was inspired by family stories of childhood dementia - being laboratory-based it is great to connect with people actually experiencing the diseases we study."

"The workshops were the highlight for me, I really enjoyed the diversity of the group (industry, clinicians, researchers, and patient representatives) and the passion to drive change for childhood dementia."

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