
Annual Update
2023 - 2024
Sanfilippo
Children's Foundation

Sanfilippo Children's Foundation
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Front cover image: Featured on our front cover is the Monk family from Queensland. In 2023 their daughter, Agatha (Aggie) was diagnosed with Sanfilippo syndrome. Aggie, aged 6, lives in Brisbane with her parents Rebekah and Jason, twin sister Clementine and older brother Herschel.

About the Foundation

Sanfilippo Children's Foundation drives research for a world without Sanfilippo syndrome, a devastating type of childhood dementia with no available cure. Sanfilippo affects around 1 in 70,000 births (five births each year in Australia, and 2000 births worldwide).

Established in 2013, the Foundation has to date directed nearly $8 million into promising medical research in Australia and around the world in the hope of finding solutions for families affected by Sanfilippo.

What is Sanfilippo?

Sanfilippo syndrome is a rare, genetic form of childhood dementia causing fatal brain damage. Children are born seemingly healthy but are missing an enzyme that clears waste from their cells. Over time this waste becomes toxic and causes damage throughout the body, especially the brain. As the brain becomes progressively damaged, children experience severe hyperactivity, disordered sleep, loss of speech, cognitive decline, cardiac issues, seizures, loss of mobility, and finally death, usually before adulthood.

In the absence of treatments, families are simply told to 'take their child home and love them'. It is an unimaginably cruel disease, robbing children of the skills they've learned, their language, ability to eat, play, walk, and recognise their loved ones. Every loss is deeply grieved and the unrelenting progress of Sanfilippo takes an enormous toll on the whole family.

Life expectancy is only 12-20 years of age.

While there is currently no treatment or cure available to children diagnosed with this devastating disease, researchers around the world are working tirelessly to develop effective treatments, with several clinical trials already completed or underway. Promising therapies are within reach, but there is more work to do to get these to a point where families can access them.

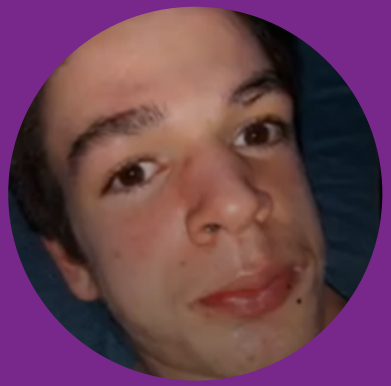
In Memoriam

Tamika Barry

In June 2023 Tamika Barry tragically lost her battle with Sanfilippo syndrome. She was only 17 years old. Beautiful Tamika passed away peacefully in Queensland surrounded by her loving parents Chris and Virginia, and siblings Cameron, Laura, Lachlan, Olivia and Bryson. Our hearts are with you all.

Thomas Mooney

In January 2024 we were heartbroken to hear Thomas passed away at the age of 23. Thomas brought so much joy to his close-knit family and was deeply loved by parents Rose and Brett, and brothers Jack and Samuel.



Dr Louise O'Keefe

In March 2024 Dr Louise O'Keefe, an outstanding and dedicated Sanfilippo and adult dementia researcher at The University of Adelaide, passed away from a terminal illness. Louise used fruit fly models to study complex human diseases, and her work has uncovered new insights and potential therapy avenues for Sanfilippo. Her legacy will endure for many years and we extend our deepest condolences to her loved ones.

Message from our CEO

It's an absolute privilege to share with you our Annual Review for the period January 2023 - June 2024.

Sanfilippo Children's Foundation reached a major milestone in September 2023 as we marked our 10th anniversary. After ten years of funding and driving research forward to find solutions to the devastating childhood dementia, Sanfilippo syndrome, we were very proud to launch our impact report - A decade of difference for Sanfilippo syndrome. This report highlights the remarkable progress, achievements and gains made through the work of the Foundation, including:

- Directing more than $7.5 million to over 40 promising research projects and initiatives
- Bringing the first clinical trial for Sanfilippo to Australia
- Securing $2 million in Australian Government funding to establish the 'Brain in a Dish' drug discovery platform
- Launching the internationally-endorsed Global Roadmap for Sanfilippo Syndrome Therapies
- Publishing the first-ever global consensus clinical care guidelines for Sanfilippo syndrome
- Establishing the International Sanfilippo Syndrome Alliance with 11 founding members from ten countries
- Seed funding the establishment of the Childhood Dementia Initiative.

Gains in the field of Sanfilippo research have been made possible thanks to the unwavering support of our donors, families and sponsors, and the commitment of researchers, clinicians and patient organisations around the world who are all striving to solve Sanfilippo. But these gains will never be enough until we find a cure.

We stand on the cusp of a new era of hope for the Sanfilippo community. Compared with 10 years ago the landscape is almost unrecognisable. Unprecedented scientific advances, increases in knowledge about the pathology and progression of Sanfilippo, multiple drug development programs underway around the world and promising results from clinical trials, and genuine collaboration across a connected international community is pushing us closer and closer to solutions and opening up opportunities we have only dreamed about for our families.

Message from our CEO

But there remains much more to be done to ensure treatments make it into the hands of families. Time and time again rare disease drug development programs have failed to progress to regulatory approval, but there is genuine hope for Sanfilippo programs with the US Food and Drug Administration (FDA) recently accepting heparan sulfate as a reasonable surrogate endpoint for neuronopathic types of MPS, including MPS III (Sanfilippo). This major development for the entire sector brings hope of access to Accelerated Approval Pathways in the US for Sanfilippo syndrome therapies as early as 2025.

A tragic paradox is children are simply not diagnosed early enough in most cases to benefit from emerging treatments, and this must change. Screening programs hold promise for unlocking pathways for earlier diagnosis. Reproductive carrier screening in Australia is slowly evolving, and it is our hope that one day all prospective parents will have the choice to take part in national screening to give them information about their likelihood of having a child with a genetic condition like Sanfilippo syndrome. The Australian Government has also committed to expanding the National Newborn Screening Program to encompass many more conditions where early diagnosis can benefit the child. Midway through this year our hopes were dealt a blow with the Australian Government's announcement that MPS III would not be referred to Australia's Medical Services Advisory Committee for formal assessment to be included in Australia's National Newborn Screening Program. Continued advocacy is needed to ensure Sanfilippo syndrome makes it onto the list of screened conditions as soon as possible.

On behalf of our team, board and families, a huge thank you to everyone who has generously supported the work of the Foundation. Many of you have been with us since inception and we are beyond grateful to each and every one of you. We hope this report gives you insight into the tangible difference you are helping to make as we strive every day to find solutions for our families and these precious children. We also acknowledge the Barry and Mooney families who have faced such unbearable loss and heartbreak, and dedicate this report to Tamika and Thommy.

Kerren Hosking
CEO

A Year in Review

- Launch of our ten year impact report - A decade of difference for Sanfilippo research.
- 10 new research projects commenced, representing a total commitment of $755,847 from Sanfilippo Children's Foundation and our international co-funding partners.
- 13 research projects were completed with another four ongoing.
- Our flagship research project - Brain in a Dish (BIAD) - secured an additional $730,000 from the Australian Government's Medical Research Future Fund. The total commitment is now over $3.2 million.
- The initial screen of drugs already in market using the BIAD platform was completed with promising results, bringing hope effective treatments may be identified for Sanfilippo.
- Steps for Skye reached a fundraising total of over $100,000 since it began four years ago.
- Our Solving Sanfilippo Symposium, bringing together more than 150 researchers, clinicians and families in person and online, was held in May 2023 and May 2024.
- World Sanfilippo Awareness Day included for the first time a light up campaign with over 30 Australian landmarks turning purple to help raise awareness of Sanfilippo.
- We launched the International Sanfilippo Syndrome Alliance (ISSA) with eleven founding members from ten countries.
- The Reagan-Udall Foundation for the FDA held a public workshop on qualifying biomarkers using heparan sulfate as the case study thanks to strong advocacy from the Sanfilippo community. This has helped drive acceptance of heparan sulfate as a biomarker for Sanfilippo which will hopefully open the door to regulatory approval of promising therapies.

Our Families

Sanfilippo is one of the most devastating diagnoses a family can receive. To be told your child will progressively decline as the disease takes hold, and will likely only survive into their teens is unimaginably heartbreaking.

Time and time again we witness the incredible strength, resilience and hope of the families battling Sanfilippo. Threaded throughout is joy and love. Joy - sometimes about the tiniest of things - but joy nonetheless and boundless love for their precious children.

In March 2024, we hosted our first ever Sanfilippo Family Retreat in partnership with the University of Newcastle's SNUG Program and the Steve Waugh Foundation. This residential retreat—specially designed for families who have a child/ren with a rare disease—brought together seven families to connect with each other, create wonderful memories as a family, and combat the isolation that is ever-present for families battling such a rare disease. For many it was their first time meeting another family in the same situation which was a lifechanging experience and the bonds that have formed will be lifelong. A heartfelt thanks to the ASX Refinitiv Foundation for supporting the 2024 Sanfilippo Family Retreat.

Despite the enormous challenges of living day to day with Sanfilippo, many families take part in fundraising and community events, raise awareness for Sanfilippo syndrome, and advocate on behalf of the entire Sanfilippo community. It is a huge deal speaking publicly about things that are so deeply personal and emotional, but our families have bravely shared their stories on TV, in newspapers, on podcasts, and even in front of politicians to raise awareness of Sanfilippo syndrome and childhood dementia more broadly, and the devastating impact this has on families.

Sarah Beattie-Stevens, mum to six year old Callum, shared her powerful and raw insights into life with Sanfilippo at the 2024 Solving Sanfilippo Symposium. We are very grateful she has allowed us to share her words with you here.

SNUG Family Retreat, March 2024

Living with Sanfilippo: a mum's perspective

Living with Sanfilippo syndrome can make your world really, really small. Small in a lot of ways you might expect and small in so many other ways that you could never imagine. For most people a diagnosis is freedom. A diagnosis can open up a world of opportunity and hope. A Sanfilippo diagnosis offers none of these things.

When it comes to discussing the next steps, options, treatments or supports, we as parents often are offered nothing but a shrug of the shoulders, shaking of heads. And a sad look across the doctors' faces as they tell us to go home and love and enjoy our children with whatever time we have left.

If you ever imagined what it's like to have your world close in on you or this big wide world to become smaller than you ever imagined, this is how it happens. You receive a Sanfilippo diagnosis for your child.

When your child has a terminal illness, everything stops. Just like those first few days with a newborn, you take your child home to love and care for them, but you're also forced to process this devastating news. Unlike the newborn stage, the world doesn't feel full of opportunity. It doesn't feel big and endless and welcoming. It closes down, shuts you in, and at every turn reminds you that your child's life is not the norm. It's challenging and it's limited.

Parents of children with Sanfilippo are some of the strongest that I've ever known. Not even a terminal diagnosis will stop us from making sure that our children fill their short lives with adventure and excitement. But other Sanfilippo parents will understand the mental anguish we experience before we even leave the house to do anything or go anywhere. Sometimes it just makes things too hard. There is literally nowhere in the public domain that is dignified, safe or clean, where you can change the nappy of a large child who needs to be properly cleaned up.

You have to have eyes and hands on your child literally every second you are out because they have no fear and no concept of danger. You can't hold a conversation, enjoy a meal, or even finish a coffee because you're constantly keeping your child engaged or grabbing them so they don't run into traffic.

Without their speech, they can't tell you what they're feeling or what they need. As their mobility regresses, they fall, trip and bump themselves constantly. There's the deep sadness of watching your child at the playground playing alone. And then there's the emotional toll of having to explain Sanfilippo syndrome to confused strangers.

There's the heaviness and persistent stress of waking up and falling asleep every night knowing that your child will lose everything, including their life, to a relentless and incurable disease.

Life with a child with Sanfilippo can become increasingly and overwhelmingly impossible. And so when your world becomes smaller and smaller, it almost doesn't matter anymore. At home, nobody looks at your child with questions in their eyes. Nobody pulls back when your child grabs them unexpectedly.

Nobody looks at you with pity and shakes their head when you have to explain that your child has a form of childhood dementia.

Living with Sanfilippo: a mum's perspective (continued)

Last year at the Solving Sanfilippo Symposium I met Professor Cedric Bardy, an international leader in the field of human neural stem cells whose team is part of the Sanfilippo Children's Foundation's incredible 'Brain in a Dish' project.

We were getting to know each other and he asked about Callum. I told him how difficult it was day to day. Feeling so alone and like nobody understood what our family was going through. How difficult it was that family and friends had become distant. How sometimes I felt resentful that other people were able to continue their lives and not be constantly burdened by Sanfilippo. How small our world had become in the years since Callum's diagnosis.

He said to me, "I know how difficult it is to have to think about Sanfilippo every day. And I want you to know that I think about it every day too."

For the first time since Callum's diagnosis, I felt like our world began to open up again. Looking around the room it hit me that all of the scientists, the academics, the medical professionals, and the team from the Sanfilippo Children's Foundation gathered together - were thinking about Sanfilippo every single day, just like I am.

This realisation gave me genuine hope for our children and a sense of overwhelming gratitude for all of the incredible people who are making it their life's work to contribute to finding a cure. For the people who are passionate about their science that I might never understand, but that might one day lead to treatments and even a cure for Sanfilippo children.

The world that had felt so closed for Callum, the world that had felt unforgiving and inaccessible and unwelcoming was suddenly so much brighter and filled with so much more hope with the knowledge that this brilliant community of people was dedicating their lives to saving Callum's. I no longer felt alone knowing there are people striving to open up the world for my son and all other Sanfilippo children, fighting with me and for us all.

Knowing this gives all of our families so much hope. Hope for treatment and hope for a cure. Hope for a future for our children. Hope that their world will be as bright and full of opportunity as it would have been if we were never living with Sanfilippo.

Community support

Steps for Skye, in honour of Skye Robson, aged 14

Beach2Beach

- Sanfilippo Children's Foundation was a benefiting charity once again in 2023 for the annual Beach2Beach Charity Fun Run; a fantastic day of fitness and fundraising on Sydney's northern beaches. It was great to see families and friends as well as the community turn out in support on a sunny August day and enjoy the event with their loved ones. A huge thank you to the Rotary Clubs on the Northern Beaches who put on this wonderful event and have been long term supporters of the Sanfilippo Children's Foundation.

5KDM

- The 5km a Day in May campaign online challenge ran in 2023 and 2024. Hundreds of people signed up to the event online and pledged their commitment to walking, running or jogging 5km every day during the month of May - increasing their fitness while fundraising for us.

Steps for Skye

- Steps for Skye was started in 2020 by two amazing carers for Skye Robson who lives with Sanfilippo. Skye's carers, Teghan and Bree, have hosted this fantastic initiative for four years and generate great support from across their community. The event challenges people to cover an impressive 15,000 steps every day during the month of August. This year Steps for Skye hit the $100k mark for fundraising which is an amazing milestone achievement

Comedy for a Cause

- On a cold Sydney night in June people gathered at the Randwick Club to enjoy a comedy night with a difference, helping to support the Sanfilippo Children's Foundation. The hilarious line up of Cam Knight, Sean Woodland, Bruce Griffiths and Mat Wakefield had us all in stitches. A huge thank you to everyone who came and special mention to the Randwick Club for generously hosting the event.

World Sanfilippo Awareness Day 2023

- World Sanfilippo Awareness Day is held each year on 16 November to raise awareness of Sanfilippo and honour individuals around the world living with Sanfilippo syndrome today, and those who have passed away. It also recognises and honours the families of these precious children. For the first time we held a light up campaign with landmarks around Australia, with over 30 lit up purple to mark the occasion and help spread awareness. Families and supporters hosted 'Sprinkles for Sanfilippo' morning teas at schools, workplaces and community centres, and we are immensely grateful to the community for getting involved and helping to raise much needed awareness and funding.

Our Research

A number of promising research projects were assessed by our clinical and scientific experts and selected for funding through the Sanfilippo Children's Foundation competitive grant round.

Between January 2023 and June 2024, seven new research projects were directly funded, top-up scholarships were granted to two promising Australian PhD candidates studying Sanfilippo in their PhD projects, and we co-funded an additional project with the Brain Foundation.

Translational Projects

Combination of HSCP transplantation and cathepsin B inhibitors for treatment of Sanfilippo disease. AUD 212,000

Sanfilippo Children's Foundation and Cure Sanfilippo Foundation awarded a Translational Grant to Professor Alexey Pshezhetsky at the Centre Hospitalier Universitaire Sainte-Justine, University of Montreal. Professor Pshezhetsky and his team will explore if an amyloid-blocking therapy combined with bone marrow transplantation (haematopoietic stem cell transplant) can prevent the development of progressive brain disease in mice with Sanfilippo types A, B and C. Both therapies are used in the clinic or approved for clinical trials for other conditions, so the results have the potential to provide a relatively swift impact for people with Sanfilippo.

Screening of potential therapeutics affecting lysosomal acidification in a fruit fly model of Sanfilippo. AUD 20,000
Sanfilippo Children's Foundation, Associação Sanfilippo Portugal, Sanfilippo Barcelona, and Sanfilippo Sud awarded an Incubator Grant to Associate Professor Michael Lardelli at The University of Adelaide. The project aims to investigate the extent to which the pH (acidity) of the lysosome is affected in Sanfilippo using a fruit fly model of the disease. These findings may indicate whether targeting lysosomal acidity is useful for treating Sanfilippo.

Swift in vitro evaluation of disease-modifying drugs for attenuated forms of Sanfilippo. AUD 121,500
Sanfilippo Children's Foundation and Cure Sanfilippo Foundation (USA) awarded an Incubator Grant to Professor Kim Hemsley at Flinders University, Adelaide. The team will transform skin cells collected from patients with attenuated forms of Sanfilippo into cells similar to those found in the eye - this new process takes just over two weeks. They will use the model to test potential drug candidates that could be further explored for use in patients. The project may discover new therapies suitable for people with attenuated forms of Sanfilippo, who currently have fewer clinical trial options.

Boosting lysosomal function and targeting neuroinflammation using a small compound for the treatment of Sanfilippo syndrome. AUD 100,000
Sanfilippo Children's Foundation and Fondation Sanfilippo Suisse awarded an Incubator Grant to Dr Johannes Schlachetzki at the University of California San Diego. The team will investigate the small molecule drug C381 in a mouse model of Sanfilippo syndrome. If C381 shows promise in this study, it opens up a potential new therapy option for Sanfilippo.

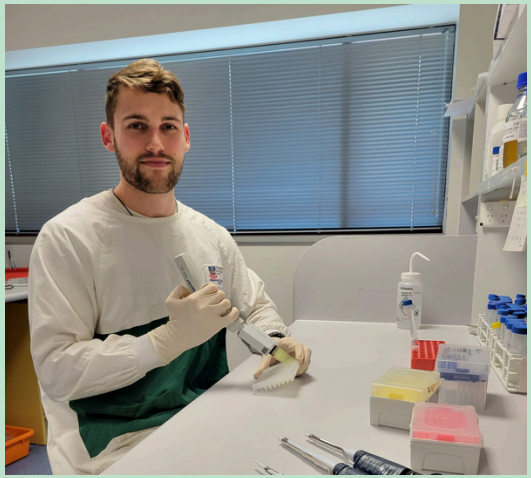
Development of iminosugar-based pharmacological chaperones for Sanfilippo type B. AUD 70,600
Sanfilippo Children's Foundation and Fundacja Sanfilippo (Poland) awarded an Incubator Grant to Professor Yves Bleriot at the University of Poitiers in France. Professor Bleriot and his team will continue their development of potential chaperone drugs that target the enzyme NAGLU. Candidates optimised in this project will go on for further testing in the hope of developing chaperones for people affected by Sanfilippo type B.

Repurposing immunomodulatory drugs for the treatment of recurrent lung infections in a pathogen-challenged Sanfilippo type A mouse lung model. AUD 90,880
Sanfilippo Children's Foundation and Sanfilippo Fighters (Italy) awarded an Incubator Grant to Dr Emma Parkinson-Lawrence at the University of South Australia. Dr Parkinson-Lawrence and her team will study the effects of a fungal challenge in the lungs of a Sanfilippo mouse model and test if the drug azithromycin can improve outcomes. Azithromycin is commonly prescribed by doctors for lung conditions such as cystic fibrosis and severe asthma, so any promising findings in this study may help to fast-track clinical impact for people with Sanfilippo.

Generation of a novel preclinical animal model of Sanfilippo syndrome. AUD 100,000
Sanfilippo Children's Foundation and Fondation Sanfilippo Suisse awarded an Incubator Grant to Professor Kim Hemsley at Flinders University. Professor Hemsley and Dr Adeline Lau aim to generate and characterise a new mouse model of Sanfilippo type A. The model will be instrumental in progressing the development of chaperone drugs for people with a common sulfamidase gene variant called R245H.

Single nuclei RNA-seq to compare the effects of mutations implicated in familial Alzheimer's disease and Sanfilippo syndrome childhood dementia.
AUD 19,300
Sanfilippo Children's Foundation provided additional co-funding support to Dr Karissa Barthelson, at Flinders University, who was awarded a grant via the Brain Foundation's 2023 competitive grants round. Dr Barthelson and her colleagues will investigate similarities and differences between two forms of dementia: early-onset familial Alzheimer's disease (EOfAD) and Sanfilippo. They will study which genes are turned on and off in different types of brain cells in zebrafish models of EOfAD and Sanfilippo type B, which may shed light on potential therapies for these and other neurodegenerative diseases.

PhD top-up scholarship to Ewan Gerken.
AUD 6,667
Sanfilippo Children's Foundation awarded a supplementary scholarship to Ewan Gerken, who is undertaking a PhD on Sanfilippo and early-onset Alzheimer's disease at The University of Adelaide under the guidance of Associate Professor Michael Lardelli. Ewan will utilise a new zebrafish model of Sanfilippo created in the laboratory. His project focuses on the common molecular changes in Sanfilippo and early-onset Alzheimer's to better understand how these diseases affect cells. His project may identify new mechanisms of Sanfilippo that can be targeted therapeutically.



PhD top-up scholarship to Ella McDonald.
AUD 15,000
Sanfilippo Children's Foundation awarded a supplementary scholarship to Ella McDonald, who is undertaking a PhD on Sanfilippo syndrome at Flinders University under the guidance of Professor Cedric Bardy and working alongside the Brain in a Dish team. The top-up scholarship will support Ella to undertake training and travel for conferences and collaboration during her PhD. Ella's project will focus on screening 60 drugs to see if any can be repurposed for Sanfilippo. As the drugs have been previously approved for other conditions, any promising candidates could reach a clinical trial with patients with Sanfilippo faster.

Completed Research Projects

A total of 13 funded projects were completed in the past year, with many overcoming COVID-19-related delays. These include five Translational projects, six Incubator projects, and two PhD top-up scholarships.

Translational Projects involve pre-clinical or clinical research that has potential to move from the laboratory to the clinic to improve outcomes in patients.

Incubator Projects are one or two year studies investigating bright new ideas with the potential to generate results that may attract larger scale funding.

Targeting the immune system as a treatment approach

The project led by Professor Kim Hemsley (Flinders University) and Associate Professor Marten Snel (SAHMRI) aimed to target parts of the immune system in the brain to see if neurodegeneration in Sanfilippo can be prevented. With their colleague Dr Adeline Lau, they studied two drugs known to reduce brain inflammation using a mouse model of Sanfilippo type A.

One drug led to improvements in motor function and potential reductions in anxiety, with analysis of the mouse brain tissue indicating reduced inflammation in the brain. Initial data for a second drug showed reduced liver and spleen sizes in mice with Sanfilippo. The team are continuing their studies on both drugs for Sanfilippo.

Evaluation of substrate reduction candidates for six Mucopolysaccharidoses

Professor Andreas Schulze (The Hospital for Sick Children, Toronto) received a grant from the Sanfilippo Children's Foundation and Cure Sanfilippo Foundation in 2020. The grant provided follow-on funding for the team to explore potential substrate reduction drug candidates for Sanfilippo originally identified in a successful Translational grant awarded in 2016, also co-funded by the Foundations.

In this project, they also developed a new protocol to assess how well drug candidates can inhibit NDST1, an enzyme that helps to make heparan sulfate, and published the protocol for other researchers in the field. They used this protocol and other experiments to confirm one of their candidates can inhibit NDST1. The team will undertake further experiments for the rest of the originally identified candidates and some new candidates and, based on the final results, will determine the top drug candidates to explore further.

Insight into the role of heparan sulfate and dopamine as disease modifiers in Mucopolysaccharidosis type IIIA

Dr Elvira De Leonibus (Telethon Institute of Genetics and Medicine, Italy) received extension funding from Cure Sanfilippo Foundation (USA), Sanfilippo Fighters (Italy), and Sanfilippo Children's Foundation in 2021. The team, which included post-doctoral scientist Dr Maria De Risi, tested two drugs that act differently on the dopamine system, to see which can best address behavioural symptoms in Sanfilippo without adverse side effects. They also investigated how the altered metabolism of heparan sulfate affects brain development in Sanfilippo.

The team is working on a manuscript to share results with the research community. Their data advances the field with a greater understanding of the impacts of heparan sulfate structure and function. The work in this project may also assist in developing a clinical trial to investigate drugs that can best target the behavioural symptoms in Sanfilippo.

Evaluating potential drug therapies for Sanfilippo

Sanfilippo Children's Foundation and Fondation Sanfilippo Suisse awarded funds to Dr Adeline Lau and Professor Kim Hemsley (Flinders University) and Professor Vito Ferro (The University of Queensland).

The team used a Sanfilippo Type A mouse model to test potential substrate reduction drug candidates for Sanfilippo in combination with gene therapy. While no statistically significant improvement in behaviour was observed during these experiments, there were encouraging signs of a positive treatment effect on liver size and body weight. Their work to develop drug therapies for Sanfilippo is ongoing, and their initial results will assist in drug candidate optimisation and inform future preclinical studies.

Strengthening the rationale for the use of the "molecular tweezer" CLR01 in the treatment of Sanfilippo syndrome

Associate Professor Alessandro Fraldi and his team completed their 2020 Translational grant co-funded by Sanfilippo Children's Foundation, Cure Sanfilippo Foundation (USA), Associação Sanfilippo Portugal, Sanfilippo Barcelona and Sanfilippo Sud. They confirmed the drug candidate CLR01 can prevent the formation of abnormal clumps of proteins that contribute to brain disease in Sanfilippo. However, CLR01 was only effective in young mice with Sanfilippo and did not benefit mice with advanced disease. CLR01 combined with gene therapy improved outcomes in a Sanfilippo type A mouse model. The team also performed initial tests with CLR01 in mouse models of Sanfilippo types B and C and confirmed the drug candidate could be used for multiple forms of Sanfilippo.

A/Prof Fraldi and his collaborators, including Prof Gal Bitan and Prof Thomas Schrader, continue their work on the molecule CLR01 in the treatment of Sanfilippo and explore the potential for testing in a clinical trial. The team is working on publishing their findings in a scientific journal to share the results with the wider scientific community.

Investigating potential stem cell therapy for Sanfilippo Type B

A/Prof Coy Heldermon and his colleagues have completed their Incubator grant awarded from the Sanfilippo Children's Foundation and Cure Sanfilippo Foundation.

Using a Sanfilippo type B mouse model, the team evaluated two different types of stem cells to see if they have the potential to treat Sanfilippo. Their findings indicate that neural stem cells may last longer in the brain, and that multiple injections of neuronal stem cells may be most effective in delivering this type of stem cell therapy. They plan to continue their work on stem cells for Sanfilippo towards getting data to ultimately start a clinical trial for patients.

Development of nanoparticle drug delivery for Sanfilippo

Dr Maria Francisca Coutinho and her colleagues have completed their Incubator grant awarded in 2019 from the Sanfilippo Children's Foundation. The project aimed to develop a substrate reduction therapy for Sanfilippo by silencing genes that make heparan sulfate.

The team used two different gene-silencing approaches to target two different genes involved in heparan sulfate production, and they determined the approaches and the target gene that produced the best results. They also developed a new cell model derived from the stem cells found in the pulp of fallen baby teeth collected and sent in by parents around the world. The new model will be used to test their substrate reduction therapy approach for people with Sanfilippo.

Targeting Autophagy in Sanfilippo Syndrome

Dr Louise O'Keefe (The University of Adelaide) received an Incubator grant from Fondation Sanfilippo Suisse and the Sanfilippo Children's Foundation to investigate autophagy, the cell's recycling process.

In part of the project, fruit flies with genetic changes causing either Sanfilippo type A or C were fed two drugs known to increase autophagy activity in cells. Preliminary tests with one of the drugs in Sanfilippo type A and C indicated improvements in autophagy inside cells of fly larvae, and improvements in physical activity and neuronal function in young adult flies.

The project has produced important data that will inform future work on the potential of autophagy-targeting therapies in Sanfilippo. Dr O'Keefe's collaborators plan to explore the promising drug in cell and animal models, and the work will be published to share results with the Sanfilippo community.

Development and Testing of Sanfilippo Types A, B and C Zebrafish

Associate Professor Michael Lardelli and his team have completed his Incubator grant awarded in 2020 from the Sanfilippo Children's Foundation. They created three new zebrafish models of Sanfilippo, one each for types A, B, and C. The researchers compared these model fish to unaffected zebrafish using behavioural and gene activity tests.

Their data revealed important clues about differences in particular brain cell types and important metabolic pathways in the brain. The team continue to explore their results with additional funding, including an Incubator grant awarded to A/Prof Lardelli, co-funded by Sanfilippo Children's Foundation, Associação Sanfilippo Portugal, Sanfilippo Barcelona, and Sanfilippo Sud, and a PhD top-up scholarship awarded to Ewan Gerken.

Investigating the role of neuraminidase 1 in Sanfilippo

Professor Alexey Pshezhetsky and his team have completed their Incubator project investigating whether a secondary deficiency of the enzyme 'neuraminidase 1' (NEU1) contributes to the effects of Sanfilippo in the brain.

Previously, the team had identified a NEU1 deficiency in the brain of a Sanfilippo type C mouse model. In this project, they further investigated the levels of NEU1 and other proteins in brain tissue from mouse models of Sanfilippo types A, B and C and other similar MPS diseases. They identified important metabolic processes that are affected in the lysosomes, how the NEU1 deficiency arises in Sanfilippo and how this leads to an unhelpful increase in sialic acid-coated proteins. Their results indicate that NEU1 deficiency may indeed contribute to the brain pathology seen in Sanfilippo and related conditions and that targeting this deficiency with treatments could be beneficial.

The project was funded by Sanfilippo Children's Foundation, Fundacja Sanfilippo (Poland), Sanfilippo Initiative (Germany), Associação Sanfilippo Portugal, Sanfilippo Barcelona, and Sanfilippo Sud.

Targeting Purinergic Signalling in the Brain to Reduce Inflammation in Sanfilippo

Professor Kim Hemsley (Flinders University), Professor Vito Ferro (The University of Queensland), and Dr Louise O'Keefe and Dr Sher Li Tan (The University of Adelaide) have completed their project supported by an Incubator Grant from the Sanfilippo Children's Foundation awarded in 2020.

Through the use of mouse and fly models of Sanfilippo type A, the team showed that a type of signalling, called 'purinergic signalling', plays a role in Sanfilippo. This is a pathway that can be targeted with medicines and with further research it may provide a potential treatment avenue for Sanfilippo syndrome.

Identification and validation of non-invasively-sourced biomarkers of central nervous system disease in Sanfilippo

In 2020, Leanne Winner received a top-up scholarship from Sanfilippo Children's Foundation for her PhD project at Flinders University. During her PhD, Leanne aimed to identify and validate accessible biomarkers for Sanfilippo. Using data collected from experiments with a mouse model of Sanfilippo and blood serum samples from patients with Sanfilippo types A, B, and C, Leanne identified two biomarker candidates.

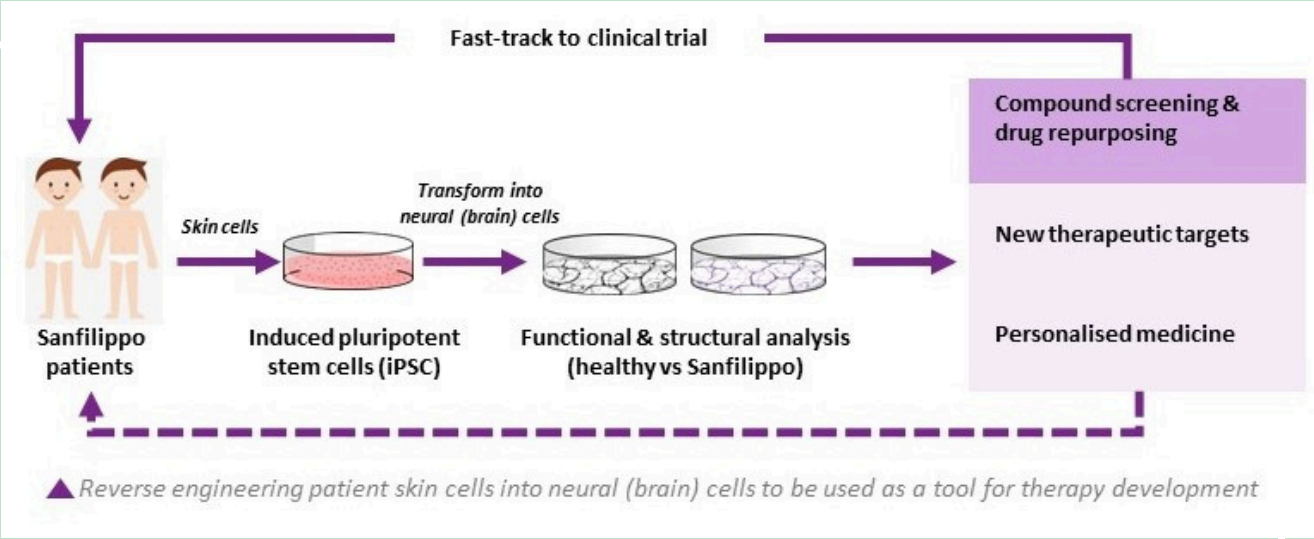
Leanne's PhD project was performed under the guidance of Professor Kim Hemsley (Flinders University), Associate Professor Mary-Louise Rogers (Flinders University), and Associate Professor Marten Snel (SAHMRI).

Are there any long-term effects of being a Sanfilippo carrier?

In 2020, the Sanfilippo Children's Foundation provided a supplementary PhD top-up scholarship to Nazzmer Nazri, who undertook his PhD project at The University of Adelaide under the mentorship and guidance of Professor Kim Hemsley (Flinders University) and Dr Nicholas Smith (Women's and Children's Hospital, Adelaide).

Nazzmer's PhD research project was to look at the potential impact of being a Sanfilippo carrier; that is, having only one copy of a particular gene variant associated with Sanfilippo. He assessed Sanfilippo type A carrier mice and found that the structure of a particular type of neuron was not changed in these mice, but protein levels in a few specific biological pathways were dysregulated in their cerebral cortex. More studies are needed to further explore the results. As the experiments were performed in a mouse model, the results from this study need to be interpreted with caution for translatability to human carriers of Sanfilippo-causing gene variants.

Brain in a Dish Update



Originally established in 2019 through a $2 million MRFF grant to the Sanfilippo Children's Foundation and a $500,000 contribution from the Foundation, the Brain in a Dish (BIAD) platform has developed a panel of cells donated by children with Sanfilippo that have been grown into neurons in the laboratory. The neurons have been deeply characterised to reveal the detailed differences in structure and function of Sanfilippo neurons compared to neurons grown from the cells of healthy children.

In 2023, the Sanfilippo Brain in a Dish research team was awarded a further $730,000, two-year grant from the Australian Government's Medical Research Future Fund Stem Cell Therapies Mission. This grant allows the team to continue this important flagship project to screen and validate drugs that may help improve the symptoms of Sanfilippo syndrome. The top candidate drugs will be further tested in cells to determine their mechanism of action, before being validated as potential therapies in a mouse model of Sanfilippo syndrome. The team is working on manuscripts to share results with the wider Sanfilippo research community.

The team has also expanded the collection of cells for use in Sanfilippo research with the collection of cells from patients with attenuated forms of Sanfilippo, creating an important resource for ongoing research.

The team includes Dr Nicholas Smith (Women's and Children's Hospital, Adelaide), Professor Kim Hemsley (Flinders University, Adelaide), Professor Cedric Bardy (South Australian Health and Medical Research Institute (SAHMRI) and Flinders University), Professor Mark Hutchinson (The University of Adelaide), Dr Chris Bye (The Florey, Melbourne), Dr Zarina Greenberg (SAHMRI), and Dr Lisa Melton (Sanfilippo Children's Foundation). Dr Cara O'Neill (Cure Sanfilippo Foundation, USA) and the Childhood Dementia Initiative also provide significant input to the project.

Connection and Collaboration

International collaboration

A major step forward for the Sanfilippo community was achieved with the formal establishment of the International Sanfilippo Syndrome Alliance (ISSA), a global network to unite and represent the Sanfilippo syndrome patient community worldwide. With 11 founding member organisations from ten countries across the globe, ISSA aims to connect families, accelerate research, and raise awareness about this devastating genetic condition. By fostering collaboration among patient organisations, researchers, and medical professionals, ISSA drives advancements in diagnosis, clinical care, and drug development, ultimately striving to find solutions for this rare, progressive childhood dementia. Together, the alliance advocates for better outcomes for individuals living with Sanfilippo syndrome and their families, ensuring no one is left behind, regardless of where they live.

Sanfilippo Children's Foundation is the Secretariat for ISSA and we are very proud of the close bonds we have and the willingness of our international partners to work together to achieve collective impact for our families as quickly as possible.

Members of the International Sanfilippo Syndrome Alliance continue to collaboratively drive implementation of the Global Roadmap for Sanfilippo Syndrome Therapies. A priority for ISSA is exploring the needs and possibilities for the collection of clinical and patient data to facilitate research and understanding of the disease and its impact on families and to support advocacy for Sanfilippo. SCF led a patient registry feasibility study in 2024 on behalf of ISSA and the recommendations from this will help shape global efforts to leverage data more effectively to inform research, development of treatments and clinical innovations. ISSA is also prioritising other initiatives, guided by the Roadmap, to fast-track therapy development and improve care and quality of life for people impacted by Sanfilippo. With much of this groundwork laid in 2023 and the first half of 2024, these activities will gather significant momentum in 2025 and beyond.

Our team represents the International Sanfilippo Syndrome Alliance as a member of the Global LSD Collaborative, a consortium of international alliances working in lysosomal storage diseases, including Sanfilippo, Fabry, Niemann Pick, Pompe, Gaucher and MPS disorders. This important collaborative initiative ensures global cooperation on issues related to people affected by these rare conditions, and unites our voices to influence policy, research priorities, support from industry and governments, and regulatory reforms to improve outcomes for our families.

Connecting researchers, clinicians and families

Our annual Solving Sanfilippo Symposium continues to bring together families, researchers and clinicians to discuss Sanfilippo and how to solve it. The event has grown since the first gathering of 30 people in early 2020, with 70 people attending in 2023 and nearly 90 in 2024. In both years, the Symposium has been held in person at the South Australian Health and Medical Research Institute and online. The many parents and carers in attendance helped ground these scientific discussions in the realities of living with a diagnosis of Sanfilippo. For families, the opportunity to connect with each other and with researchers was warmly welcomed. Researchers also greatly appreciated the opportunity to connect directly with families and also with other researchers and clinicians, with many confirming that they had made new connections and possible collaborations. A special thank you to the CommBank Staff Foundation and Ultragenyx whose support made it possible to bring everyone together.

WORLDSymposiums

After two years of remote online attendance, members of our team attended the 2023 and 2024 WORLDSymposium in the USA. This is the largest annual international gathering of researchers, clinicians, industry and patient advocates with a focus on lysosomal storage diseases, including Sanfilippo. The team were able to hear updates on basic, translational and clinical research in the field and make important direct connections with international researchers, clinicians and patient organisation colleagues. In 2024, our team helped to launch the newly formed International Sanfilippo Syndrome Alliance with a booth in the conference expo that attracted substantial interest and productive conversations.

Australian Lysosomal Disease Summit

The inaugural Lysosomal Disease Summit was held in Melbourne in October 2023 and was organised by Fabry Australia with lots of engagement with other patient organisations, including Sanfilippo Children's Foundation. The summit provided a wonderful forum for a diverse network of researchers, clinicians, patient advocates and industry representatives to discuss the latest developments in research and clinical care for lysosomal storage diseases. Our team presented on the development of the Consensus Guidelines for Sanfilippo Syndrome Clinical Care, which was a great opportunity to spread the word about this important resource and promote earlier diagnosis and best-practice clinical care for individuals with Sanfilippo.

International Symposium on MPS and Related Diseases

In April 2024, our team joined other members of the International Sanfilippo Syndrome Alliance (ISSA) at the 17th International Symposium on MPS and Related Diseases in Würzburg, Germany. ISSA convened a side meeting of stakeholders with an interest in Sanfilippo syndrome. Many families, clinicians, researchers and industry professionals were introduced to the work of ISSA to date, ISSA's driving principles, and the Global Roadmap for Sanfilippo Syndrome Therapies. The initial findings of ISSA's scoping project to determine the feasibility of establishing a research platform to collect clinical and patient data were also presented.

Improving care for individuals with Sanfilippo

The Consensus Guidelines for Sanfilippo Syndrome Clinical Care has been helping to improve the care of people with Sanfilippo since publication in October 2022.

The Sanfilippo community worldwide has heard from families who have used the Guidelines, for example, to assist with insurance and funding of supports, or to reinstate educational supports, aides and physical therapists for their child or children. While initially released in English, the guidelines have been translated into Italian and Portuguese, and further translations (including French, Russian and Spanish) are underway so more people around the world will have access to this vital resource.

Clinical Trials - the highs and lows

It is an exciting and important time in the clinical trial landscape for Sanfilippo, with several new trials underway and the release of promising results from completed or ongoing trials. The period was also marked by significant advocacy from the global Sanfilippo community to recognise heparan sulfate levels in the cerebrospinal fluid as a biomarker for Sanfilippo and other neuronopathic forms of MPS to support accelerated approvals of drug candidates.

These are all promising steps forward in the search for therapies for Sanfilippo and we hope we will see rapid progress in approval of treatments. We will continue to advocate for therapies and other solutions for Sanfilippo, including with our international partner organisations in the International Sanfilippo Syndrome Alliance and for those affected by rarer subtypes of Sanfilippo who currently have fewer trial options.

September	JCR Pharmaceuticals announced their partnership with Medipal Holdings to progress the development of an enzyme replacement therapy for Sanfilippo type B, JR-446, with hopes for a future clinical trial.
October	JCR Pharmaceuticals commenced their phase I/II clinical trial of the enzyme replacement therapy, JR-441, in patients with Sanfilippo type A, with the first patient dosed in Germany.
December	Denali Therapeutics commenced screening potential patients for their phase I/II clinical trial of an enzyme replacement therapy, DNL126, for Sanfilippo type A. The trial began in early 2024 with sites in the USA.
January	Kyowa Kirin completed its acquisition of Orchard Therapeutics and the therapy OTL-201, providing hope for further investigation into this stem-cell-mediated gene therapy for people with Sanfilippo type A.
February	The Reagan-Udall Foundation for the FDA held a workshop exploring biomarkers in rare genetic diseases using heparan sulfate in neuronopathic MPS diseases as a case study for a biomarker to support accelerated approval.
March	The FDA met with Allievex and encouraged them to file for accelerated approval of their enzyme replacement therapy AX 250. While Allievex was unable to raise the necessary capital required or be acquired at the time, they have continued their passionate advocacy to progress therapies for Sanfilippo.

Clinical Trials - the highs and lows

June	The USA's Food and Drug Administration (FDA) selected Denali Therapeutic's DNL126 for the START pilot program, which aims to increase a company's communications with the FDA to help improve the efficiency of a drug development program for rare disease.
June	GC Biopharma and their partner Novel Pharma received an FDA FastTrack designation for their jointly developed enzyme replacement therapy for Sanfilippo type A, GC1130A, that will be delivered directly into the cerebrospinal fluid of the brain. FastTrack designation helps to get new therapies into clinical trials faster, with faster review times by the FDA.
June	Ultragenyx was given the green light to apply to the FDA for Accelerated Approval for its gene therapy treatment, UX111, for Sanfilippo syndrome type A, following acceptance from the FDA that levels of heparan sulfate in the cerebrospinal fluid could be used as a biomarker to support a future application. Outcomes of this application are not expected until later in 2025/6.
June	Results from the phase I/II clinical trial of the anti-inflammatory drug anakinra in multiple Sanfilippo subtypes were published. Results indicate that anakinra used in the study was safe, improved behavioural and functional outcomes in participants, and reduced parental stress.

A Decade of Difference - Marking our 10th anniversary

In September 2023—the ten-year anniversary of the foundation—we took the opportunity to reflect on our efforts over the past decade in driving research and collaboration with the launch of our ten-year Impact Report. This evaluation of our research funding and driving activities demonstrates that we have made an enormous contribution both in Australia and globally, but it is also clear that collaboration is at the heart of everything we do. Solving Sanfilippo needs the collective knowledge and efforts of the entire international Sanfilippo community and our work has sought to facilitate and capitalise on these collaborative opportunities. We have a vibrant, diverse and expanding research community, the pool of research tools and resources is growing as a result of our funding, and there are many promising therapeutic candidates in development.

Thanks to our friends at the ASX we were able to launch the impact report with a morning tea event, attended by families and supporters and live streamed on our Youtube channel. Our founder, Megan Maack, fulfilled a lifelong ambition by getting to ring the ASX bell.

We held our inaugural Decadence Ball black tie event at Doltone House Hyde Park, Sydney in October 2023. Over 200 people attended and we were privileged to have the event hosted by Australian journalist Tracey Spicer AM. It was a very special and spectacular evening, with many people learning about Sanfilippo syndrome for the first time. Guests were deeply moved by the personal family stories and the passion of Dr Michel Tchan, member of the foundation's Research Advisory Committee, to find solutions to Sanfilippo.

Thank you to our supporters

A huge thank you to the following trusts, foundations and companies for their ongoing support of our research and to those who wish to remain anonymous:

- ASX Refinitiv Charity Foundation
- Ultragenyx
- Count Family Foundation
- HTR Group Pty Ltd
- Ha-Ke-Na Foundation
- Duveck Foundation
- Australian Equity Trustees
- CommBank Staff Foundation
- Cook Medical

We acknowledge our appreciation to the following individuals and organisations for providing professional services:

- Sparke Helmore
- Bentleys NSW
- Jane-Anne Gray, PWC

We would particularly like to acknowledge Jane Anne Gray of PwC who since the inception of the Foundation until her retirement in late 2023 provided crucial pro bono legal services.

We would also like to thank our Board of Directors and Research Advisory Committee for the time, knowledge and expertise they so generously give to our organisation. All members participate in a completely voluntary capacity.

Kyuss, aged 12

Thank you to our supporters

Stars for Sanfilippo

A huge thank you to our wonderful regular givers who donate an amount each month to support the work of the foundation. Some of these amazing people have been contributing to our cause since the very beginning, and every donation means so much to us. Thank you for your generosity and commitment to helping our families!

Crafting with kindness

We would like to say a very special thank you to Heather Parkinson from Adelaide—mum to an amazing Sanfilippo researcher, Emma Parkinson-Lawrence, and quilter extraordinaire. Heather created absolutely beautiful quilts for so many of our families around Australia. The kids and families just love them, and the many hours of work and love that goes into every stitch is so appreciated.

Our People

Our team is made up of passionate people committed to driving research towards a world free of Sanfilippo Syndrome.

They bring a collective wealth of energy, enthusiasm and expertise to our cause.

Our Board

We are immensely grateful to our pro bono board of directors for their strategic leadership and guidance over the past 18 months. We are privileged to have such depth of skills, expertise, lived experience and genuine commitment to cause, and clarity of vision and purpose to guide us as we drive research for a world without Sanfilippo.

Board of directors:

- Dr Alison Butt, Chair
- Mark Arnold
- Angeline Veeneman
- Megan Maack
- Dr Lynn Weekes AM
- Dominic Tilden
- Nicole Stanners

We would like to express our deepest gratitude to Angeline Veeneman who stepped down as director as of 30 June 2024. Angeline has been part of the board since we started, and her vision, leadership and unwavering dedication has been nothing short of extraordinary. She was instrumental in supporting and encouraging Megan Maack as she set up the Sanfilippo Children's Foundation, and has brought immense passion and kindness across her long years of voluntary service. Thank you Angeline.

Our Research Advisory Committee

Thank you to the members of our Research Advisory Committee who volunteer their valuable clinical and scientific expertise to guide our research strategy, funding decisions and research priorities.

Members of the Research Advisory Committee during the past 18 months are:

- Prof Ian Alexander - 2016 - 2023 (Chair from 2017 - 2023)
- Dr Michel Tchan - 2016 - present
- Dr Nick Smith - 2016 - present
- Prof Kim Hemsley - 2017 - present
- Prof Sarah Spencer - 2020 - present
- A/Prof Karin Borges - 2020 - 2023
- Dr Heidi Peters - 2023 temporary additional member
- Prof Trent Woodruff - 2023 assisted in the review of selected EOI applications

In particular, we would like to thank Professor Ian Alexander, a world-renowned expert in gene therapy, for all of his contributions to the Scientific Advisory Board since its inception. We also thank Associate Professor Karin Borges, a neuroscientist researching epilepsy and brain metabolism, for her contributions.

To help us drive research with the most impact for families, we also rely on families around Australia and New Zealand for their reviews and feedback. Thank you to all of our families who have participated in our grant round's Family Consultation Panel and the Solving Sanfilippo Symposium Planning Committee.

THANK YOU

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