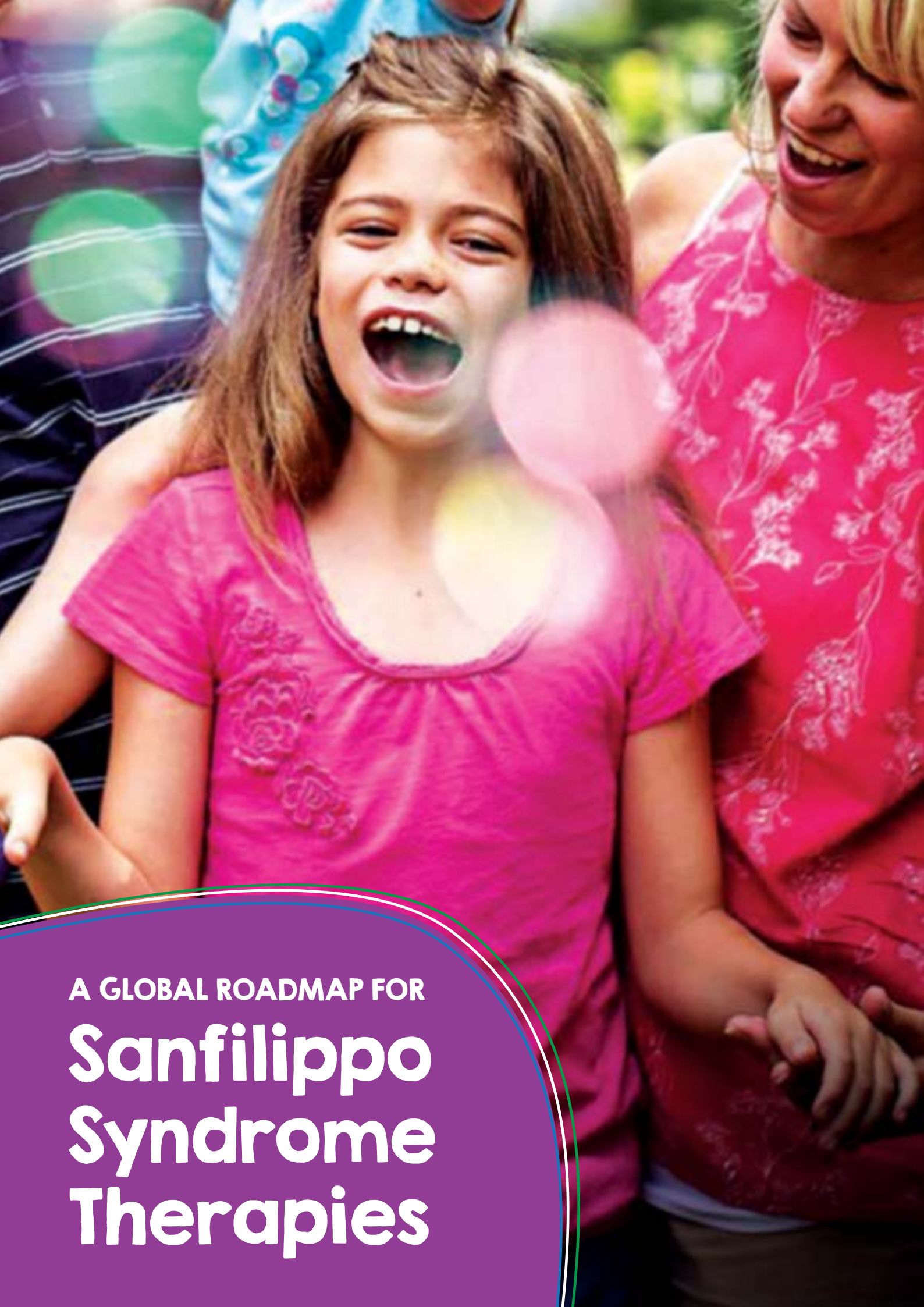

A GLOBAL ROADMAP FOR

Sanfilippo Syndrome Therapies

Eliza from USA

To be told that there is a way of treating this disease would be amazing and give so much hope which is what is needed at the time of getting this devastating news.

- Sanfilippo parent, Australia

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Cover: Abby & her family from USA

BACKGROUND

ABOUT THE ROADMAP

This Roadmap is a collection of ideas, strategies, and thought leadership collected from interviews, presentations, publications, and in collaboration with researchers, industry leaders, clinicians, and families affected by Sanfilippo. It is meant to aggregate and distill key ideas that will empower the rapid delivery of much-needed solutions for all families affected by Sanfilippo.

All forms of Sanfilippo take an immeasurable toll on the whole family.

Liam & his mum from Switzerland

About Sanfilippo syndrome

Sanfilippo syndrome, also known as mucopolysaccharidosis type III (MPS III), is a rare genetic condition, a type of childhood dementia, that causes progressive and ultimately fatal brain damage as well as other systemic manifestations.

There is no treatment or cure currently available and most individuals with Sanfilippo never reach adulthood.

In Sanfilippo, the absence or insufficiency of one of the enzymes responsible for the breakdown of heparan sulfate leads to its accumulation in cells causing dysfunction, cell damage and cell death, particularly in the brain. Children experience severe hyperactivity, disordered sleep, loss of speech, cognitive decline, seizures and loss of mobility.

In most cases, death occurs within the second decade of life. Frequent ear and respiratory infections, digestive symptoms and effects on lungs, liver, joints and heart are also experienced.

In some individuals the condition takes an attenuated form with slower progression and longer life expectancy, however, all forms of Sanfilippo take an immeasurable toll on the whole family.

Children experience severe hyperactivity, disordered sleep, loss of speech, cognitive decline, seizures and loss of mobility.

CHILDHOOD PROGRESSION

Development progression in a neuro-typical vs. a Sanfilippo child

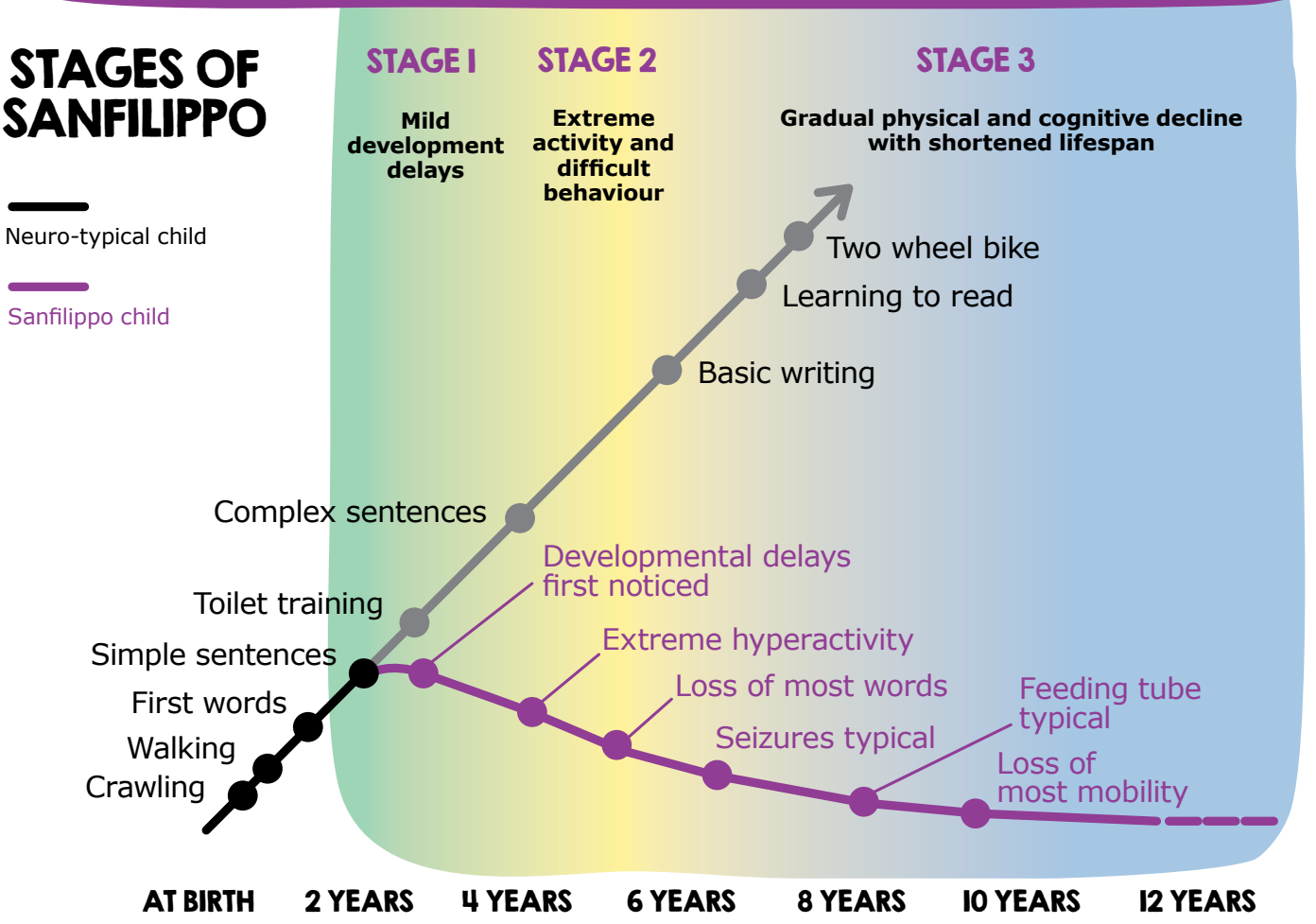


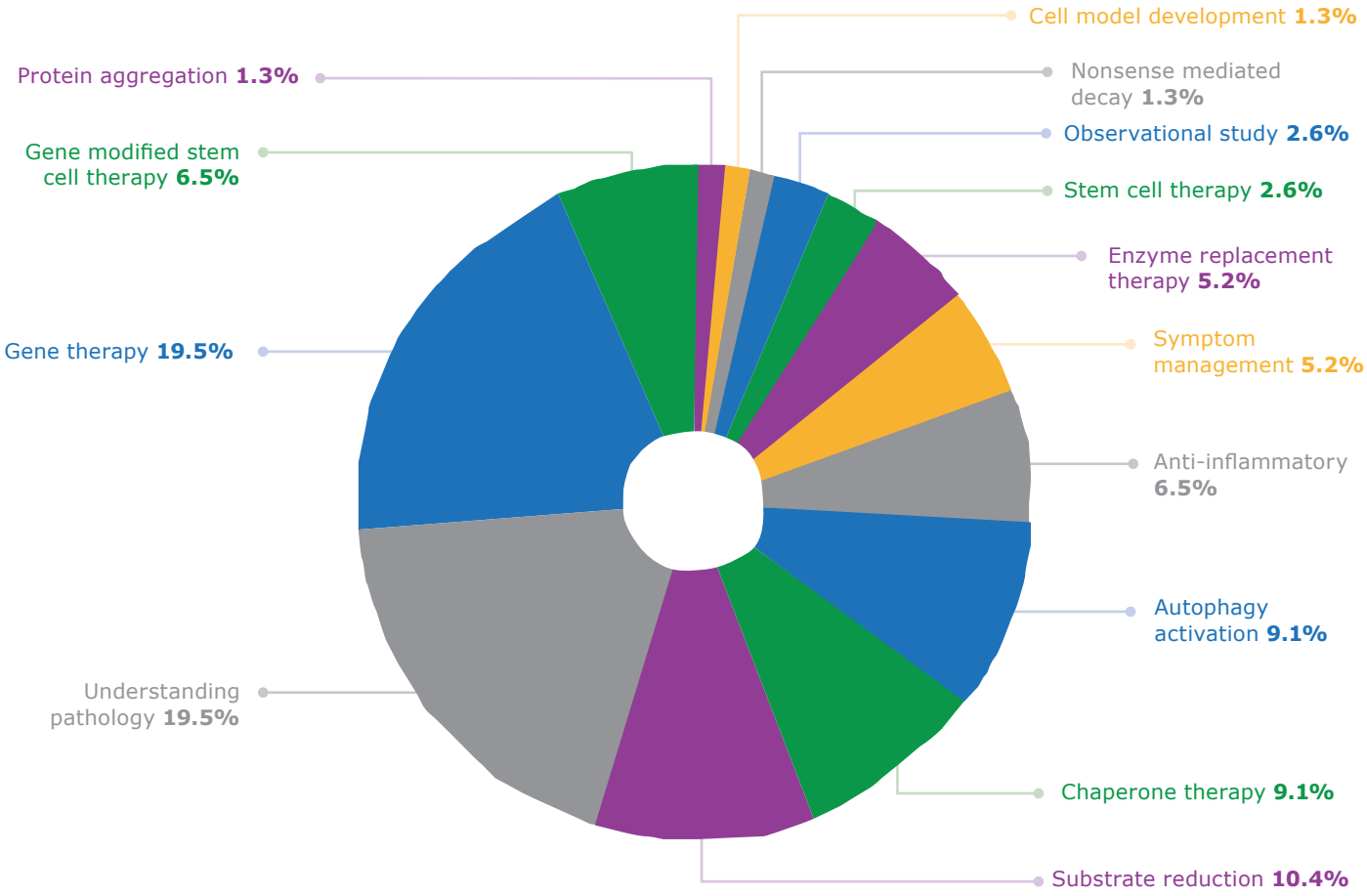
Illustration adapted from a Figure created by (c) 2019 Cure Sanfilippo Foundation, representing the rapidly progressing phenotype of Sanfilippo Type A (https://curesanfilippofoundation.org/what-is-sanfilippo).

The research landscape

Funding challenges are common to all research in the rare diseases space. However, the Sanfilippo community, largely led by family-founded not-for-profit entities, has successfully invested in a broad range of research and several therapies are now licensed by commercial or academic entities and in preclinical and clinical research phases. Scientific efforts to date have been relatively evenly distributed across many areas of research, therapy types and stages of research (basic, preclinical, clinical).

While significant focus and investment has been seen in gene and enzyme replacement strategies, several of which are now in clinical trials, there has also been a large investment in developing experimental therapies that target substrate reduction, chaperone therapies, and disease mechanisms such as inflammation and autophagy.

This has led to a growing pipeline of potential therapies that are reaching the significantly more expensive pre-clinical and clinical development phases.



Number of non-clinical research projects funded by international not-for-profit entities (e.g. Sanfilippo foundations, MPS societies) and government entities (e.g. US NIH, Canadian CIHR, Australian NHMRC)

Data from 77 research projects, current to December 2020. See Appendix II for industry and investigator-led clinical trials and natural history studies.

NOTE: *data has been collated to the best of our ability from publicly available sources from Sanfilippo organisations, MPS and related organisations on grants awarded to projects specifically looking at Sanfilippo syndrome. Additional grants may exist, including additional grants from government sources for broader projects on related conditions that may include or benefit Sanfilippo research.*

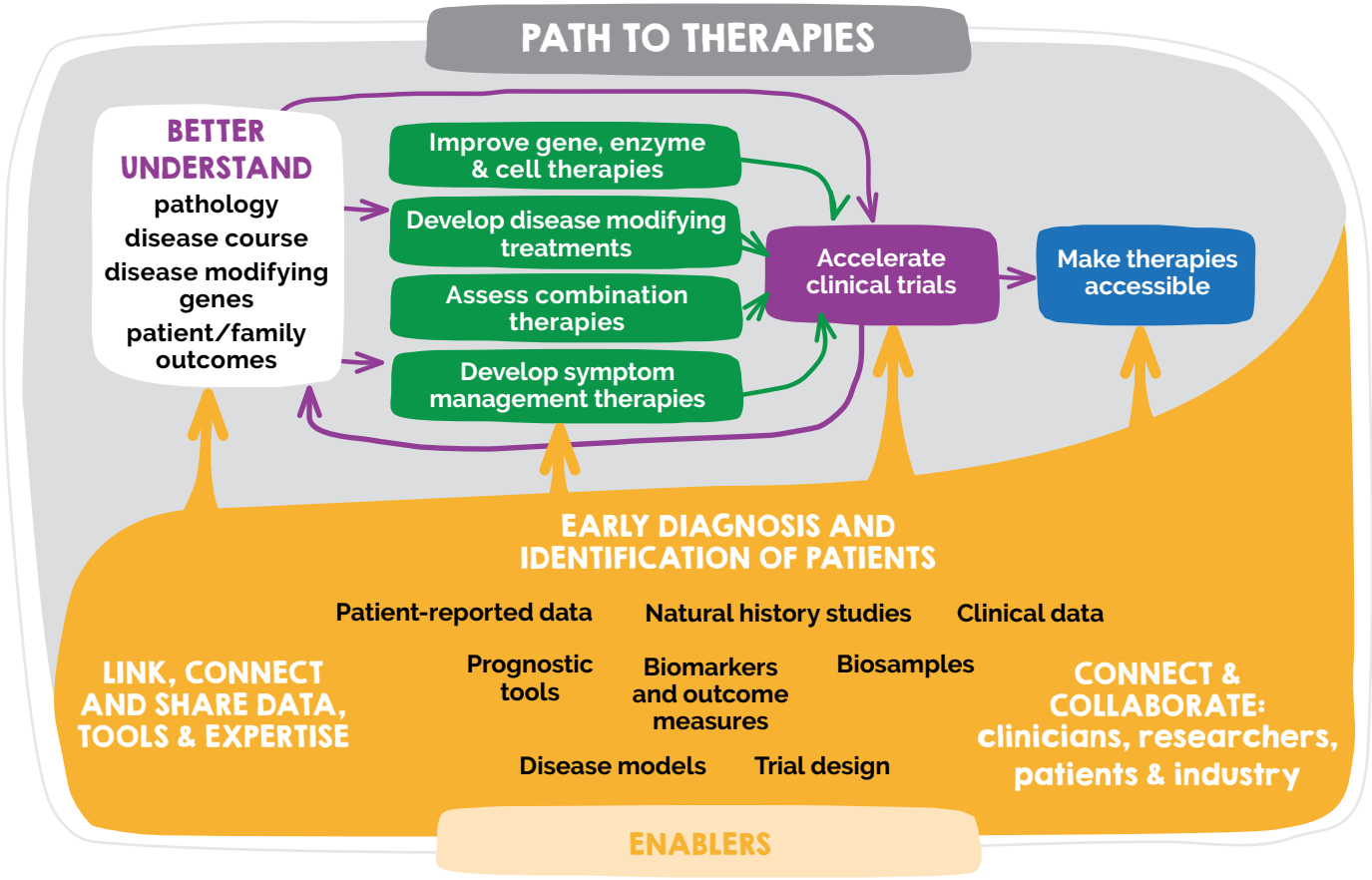
Pathway to therapies

Significant progress has been made in our understanding of the biology of Sanfilippo and several clinical trials of potential therapies have been completed or are underway.

With further focussed, coordinated and collaborative efforts, progress would be accelerated.

Through an examination of the Sanfilippo research landscape, interviews with academic, industry and clinical experts and consultation with families, we have developed a Roadmap for Sanfilippo Therapeutics that will more rapidly deliver much-needed solutions for all families affected by Sanfilippo.

For ease of organising the information, we have divided the research needs into three core elements of research focus to stop, treat and better manage Sanfilippo syndrome. The research pillars are underpinned by a set of enabling principles that can support and connect multiple aspects of laboratory and clinical research. However, we recognise that there is considerable overlap and integration of concepts between the research pillars. The enablers facilitate the flow of information and innovations between research fields, from the laboratory bench to the clinics, and vice versa, will allow clinical findings and data collection to inform the research questions and discovery processes.



Matilda from Australia

For Sanfilippo we need to understand the window of opportunity if treatments are going to be successful.

- Sanfilippo researcher, USA

STOP

Target the root cause

AIM

Children born with Sanfilippo will have enough enzyme to clear heparan sulfate from their cells - symptoms and neurodegeneration are prevented.

The blood-brain barrier is like a shield to protect the brain from toxins and infection

but it also makes it difficult to deliver vital therapies to the brain

Ellie from USA

Despite promising progress with gene therapy strategies, the approach still faces unknowns and challenges in relation to the duration of the effect and the immune response to the viruses used to deliver the therapeutic gene.

The first treatment strategies for Sanfilippo that were tried in clinical trials included un-modified bone marrow transplants with the hope of delivering enzyme via cells transplanted from unaffected individuals (Shapiro et al, 1995); genistein, a proposed substrate reduction therapy (Ghosh et al, 2021); and intrathecal delivery of enzyme replacement therapy for Sanfilippo type A (Wijburg et al, 2019). These trials proved unsuccessful in terms of neurocognitive outcomes, and for bone marrow transplants the risks are extremely high.

However, since then, encouraging progress has been made in developing further experimental therapies, particularly gene therapies (GT) and enzyme replacement therapies (ERT). These strategies are currently in trials, some of which are showing positive neurodevelopmental signs for children who have been treated at a very young age.

These include a trial of intravenous Adeno-Associated Virus (AAV) gene therapy trial for Sanfilippo type A (ClinicalTrials.gov Identifier: NCT02716246; Flanigan, 2021) and a trial of intracerebroventricular delivery of ERT for Sanfilippo type B (ClinicalTrials.gov Identifier: NCT03784287; Muschol, 2021)

Despite promising progress with gene therapy strategies, the approach still faces unknowns and challenges in relation to the duration of the effect and the immune response to the viruses used to deliver the therapeutic gene. Pre-existing immunity to gene therapy virus vectors excludes a significant proportion of children from participating in clinical trials for systemically delivered AAV gene therapies. It also precludes the re-administration of the therapy, should that be needed. The longevity of the effects of early life gene therapy treatment remains unclear and there is some evidence from studies involving mouse models of other human genetic conditions to suggest that later treatment with a second therapy after very early treatment may be beneficial (Rafi et al, 2020).

Approaches to prevent or circumvent the immune response to both gene and enzyme therapies are under investigation in Sanfilippo (e.g. Gougeon et al, 2021) and other Lysosomal Storage Disorders (LSD) and alternative carriers for delivery of therapeutic genes, such as nanoparticles and exosomes, are being explored. Collaborations across multiple disease fields will be necessary to ensure that these platform technologies can also benefit individuals with Sanfilippo.

Of note, gene-modified cell-based therapies under development do not face the same hurdles related to immunity to viral vectors and immune responses to the transgene also appear to be less of a concern (Drysdale et al, 2019). A clinical trial of autologous haematopoietic stem cell (bone marrow) transplant with ex vivo (outside the body) gene therapy is currently underway for Sanfilippo (ClinicalTrials.gov Identifier: NCT04201405) and other similar diseases, with some promising early data emerging (conference presentations). Other gene-modified stem cell therapy approaches, such as neural and mesenchymal stem cells and iPSCs (Christensen & Choy, 2017), are also in preclinical testing phases for Sanfilippo and other LSDs.

There are clearly groups of patients being left behind. MPS IIID and IIIC patients, attenuated patients and those who have already been in clinical trials or precluded from them. Focus is needed on these groups.

- Sanfilippo researcher, Australia

Approaches to prevent or circumvent the immune response to both gene and enzyme therapies are under investigation in Sanfilippo

While enzyme replacement therapies (ERT) are already approved and in use for some LSDs, an important aspect for Sanfilippo and other LSDs that have a serious impact on the brain, is the route of delivery to by-pass or cross the blood-brain barrier. This can be accomplished by direct delivery to the brain via infusions or injections into the fluid within or around the brain. This approach is showing promise in a clinical trial of ERT for Sanfilippo type B (Muschol, 2021).

Methods are also being explored to bind enzymes to carrier molecules that harness natural delivery systems across the blood-brain barrier such as insulin, immunoglobulin and transferrin receptors (e.g. Guigliani et al, 2021; Ullman et al, 2020). Gene therapy constructs have also been evaluated in which the transgene is delivered peripherally, but is engineered to enhance enzyme secretion and generate chimeric enzymes with enhanced ability to cross the blood-brain barrier (Sorrentino et al, 2013; Sorrentino et al, 2019). These strategies may be useful for Sanfilippo types A, B, and D which involve secreted enzymes. For Sanfilippo type C, which is caused by deficiency of a lysosomal membrane-bound enzyme, successful ERT will likely require additional methods to deliver the enzyme to the brain. Efforts are underway in this area.

Immune responses to the introduced enzyme can also be a problem for ERT, with neutralising antibodies potentially reducing efficacy of the treatment. This is particularly the case where no residual enzyme is produced in the individual. This is an issue common across lysosomal storage diseases and has been the subject of much research and discussion to understand and mitigate this with immune tolerance induction and other strategies (Kishnani et al, 2016).

Where patients are able to produce a form of the enzyme, but the mutation makes its structure incorrect or unstable, pharmacological chaperone therapies are a possibility. These can only be applied to certain types of mutation, hence only to a subset of Sanfilippo patients, but significant progress is being made in the laboratory. Enzyme crystal structures for types A, B (Sidhu et al, 2014; Birrane et al, 2019) and C (unpublished, private communication) have enabled rational drug design to generate new drug molecules. In silico drug identification techniques and high throughput testing strategies are being used to identify small molecules that could be repurposed for this use. Similar approaches are being used to identify drugs that can reduce the production of heparan sulfate, potentially enabling substrate reduction therapy (SRT) for Sanfilippo syndrome.

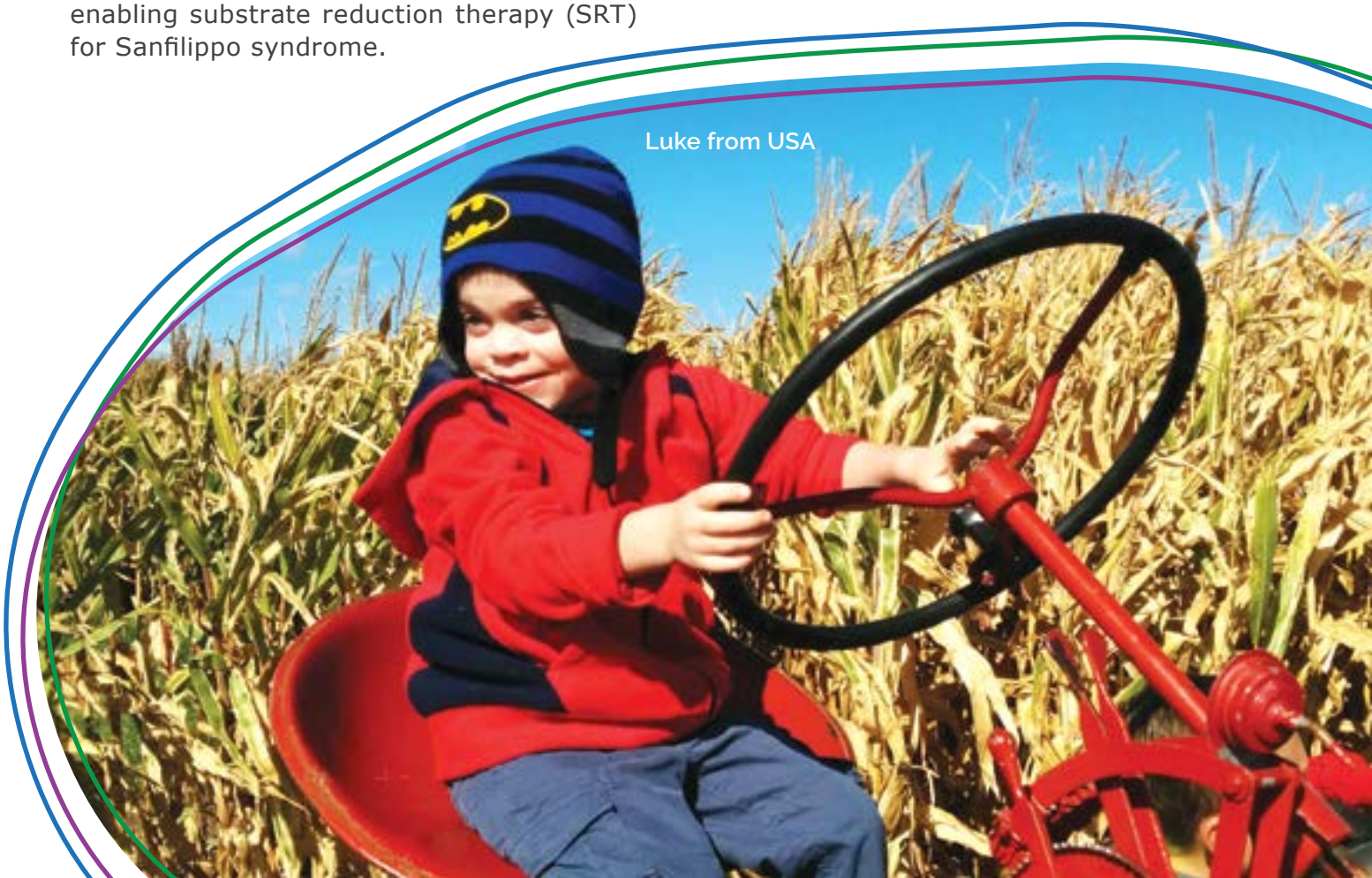
An estimated

1

in

70,000

children are born with Sanfilippo syndrome



Luke from USA

About twelve percent of the gene mutations that cause Sanfilippo syndrome are nonsense mutations that inactivate protein production with a premature stop codon. These are frequently associated with a severe disease course and have been found in all subtypes of Sanfilippo. Drugs known as nonsense readthrough drugs have been developed to help the cell ignore the stop codon and produce an active enzyme. However, other mechanisms in the cell also need to be overcome to enhance the efficacy of these drugs (Nagel-Wolfrum et al, 2016). Research is underway in this area, including in Sanfilippo syndrome.

developmental trajectory. However, the signs and symptoms of Sanfilippo generally are not recognised until children are at least two years old and, without a family history or older sibling with Sanfilippo, definitive diagnosis rarely occurs before four to six years of age. By this time there has been considerable build-up of heparan sulfate, secondary storage molecules and cell damage. Therefore, urgent advocacy is required to expedite the implementation of available newborn screening technologies (see below) so that treatments that target the root cause of Sanfilippo can be delivered as early as possible.

Urgent advocacy is required to expedite the implementation of available newborn screening technologies so that treatments that target the root cause of Sanfilippo can be delivered as early as possible.

Clinical trials of gene and enzyme therapies to date have centred on Sanfilippo types A and B. Therapies are in development for types C and D, but require more preclinical research. Further sharing and collaboration on disease models may facilitate this work.

A lack of clinical and natural history study data is also a barrier to getting clinical trials for these subtypes underway.

The early results emerging from ERT and gene therapy clinical trials suggest that patients treated at a very early age, usually less than two years old, are more likely to benefit in terms of a normalised cognitive

For those individuals who have already reached more advanced stages of disease, or for those who will still receive a later diagnosis in the future (despite introduction of newborn screening), gene and enzyme therapy strategies are unlikely to provide transformative cognitive benefit on their own, although they may provide benefit for other disease manifestations. Therefore, exploration of the potential effects of gene and enzyme replacement strategies in combination with other therapies that help clear accumulated storage molecules, or mitigate inflammation and damage, will be important to explore as a strategy to prevent or slow disease progression in more advanced disease.

KEY POINTS

- Delayed diagnosis may be a significant barrier to treatment success in terms of cognitive outcomes
- Gene and enzyme replacement therapies are challenging to deliver to the brain, potentially requiring higher doses with increased safety risks, and precluded in those with pre-existing antibodies to the vector or who develop neutralising antibodies to the enzyme
- Opportunities for therapeutic benefit with gene and enzyme therapies in individuals with more advanced disease need to be explored, perhaps through the development of combination and add-on therapies and exploration of broader efficacy endpoints
- More research is needed on small molecule therapies for chaperone and nonsense readthrough approaches
- More research and funding is needed to develop treatments for neglected subtypes and more data is needed to support clinical trials for these subtypes

RECOMMENDATIONS

- Drive research and collaboration to improve gene therapy (novel capsids, non-viral vectors, improved CNS targeting, reduce immune responses/barriers and safety)
- Drive research to further explore gene-modified cell-based therapies
- Collaborate to continue to improve ERT-delivery technologies to efficiently target the brain and reduce the need for invasive delivery approaches
- Support research into therapies for neglected subtypes (C, D and attenuated forms of all subtypes) through the collection and sharing of clinical data
- Explore combination therapies and the pre-clinical and clinical study design requirements to enable this
- Advocate for newborn screening to identify patients as early as possible

Joana from Portugal

More than just one or two therapeutic approaches are needed for individuals with these diseases, and combination therapies are likely to be highly beneficial.

- Sanfilippo researcher, Australia

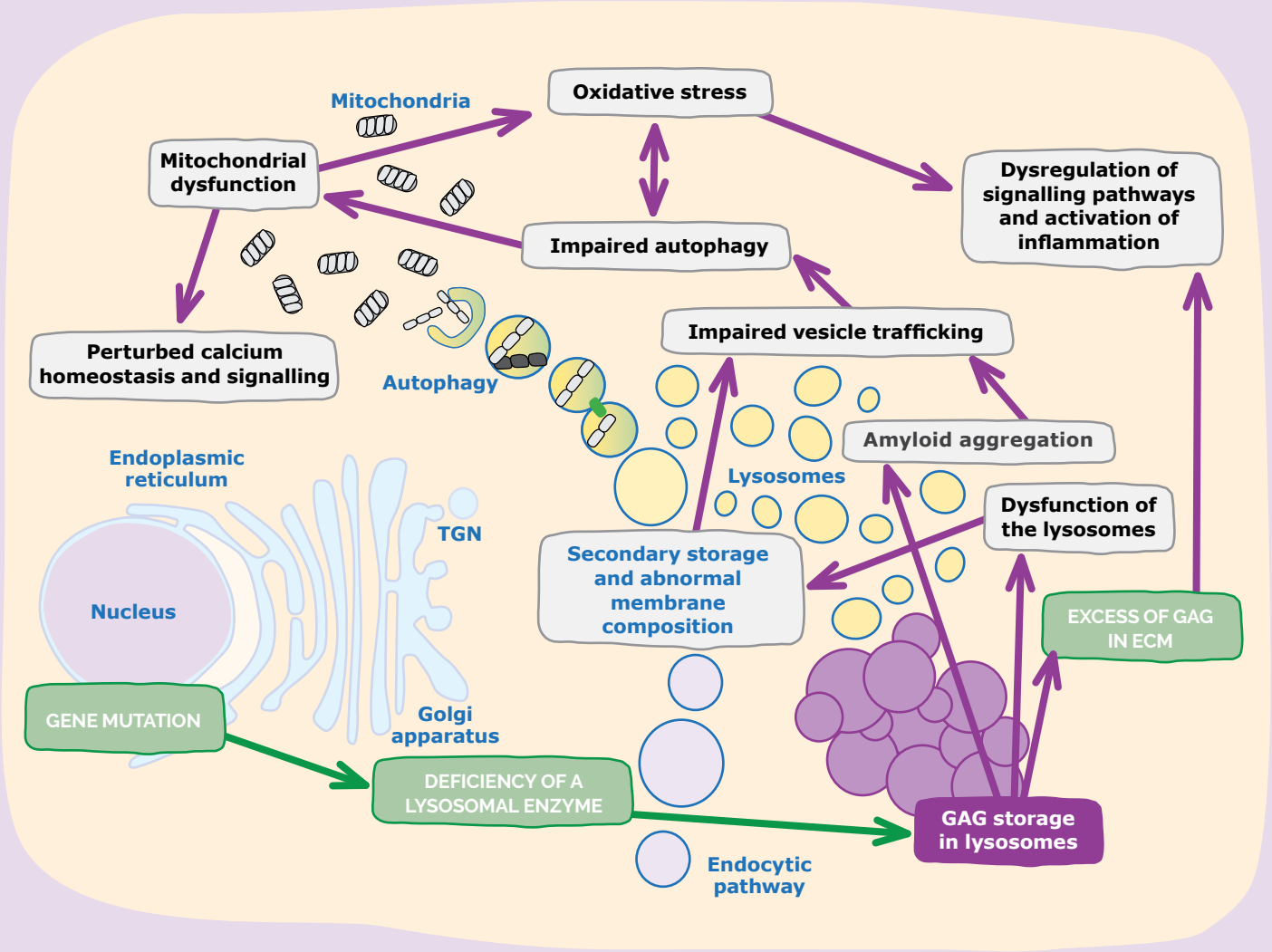
TREAT

Address the impact on the brain and body

AIM

The dysfunction and damage caused by heparan sulfate accumulating in the tissues of the brain and body are targeted - disease progression is slowed, symptoms are reduced or reversed and therapies that restore enzyme function are enhanced.

In Sanfilippo syndrome, heparan sulfate accumulates in cells in the brain and body.



'The pathogenic cascade of mucopolysaccharidoses.' Diagram from Ferracotta et al, 2020, licenced under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/

In the brain, the accumulation of heparan sulfate is accompanied by secondary accumulation of gangliosides, inflammation (astrogliosis and microgliosis) and accumulation of protein aggregates such as tau, amyloid and alpha-synuclein. Exactly how these processes lead to cell dysfunction, symptoms and ultimately cell death remains largely unclear, however, there is evidence that synaptic dysfunction, mitochondrial dysfunction, inflammation, failure of autophagy and secondary protein aggregation may all play a role (Heon-Roberts et al, 2020; Monaco & Fraldi, 2020).

Human studies show that neuronal cell death is a prominent feature of Sanfilippo, with MRI scans of individuals with Sanfilippo showing steady declines in the volume of cortical grey matter and other brain regions (Abreu et al, 2021; Barrone et al, 1999; Zafeiriou et al, 2001).

Postmortem studies show devastating neurodegeneration, but are naturally limited by access to tissues at the end stage of the disease process (Viana et al, 2020). Animal studies suggest that some of the earliest pathological processes may involve inflammation, synaptic dysfunction and mitochondrial dysfunction, with neuronal cell death occurring later in the disease process and perhaps dissociated from the symptoms typical of Sanfilippo (Heon-Roberts et al, 2020). Impaired autophagy is a prominent feature in cell and animal models (Sorrentino et al, 2013; Pshezhetsky, 2016; Ohmi et al, 2011). Some data also suggests that the disturbance in heparan sulfate processing and inflammation in the brain may also lead to some very early neurodevelopmental effects in the pre- and postnatal period (Lemonnier et al, 2011; Canals et al, 2015, Zengeler et al, 2021).

Good inroads have been made in research into neuronal dysfunction, inflammation and autophagy, including the development of potential treatments that target some of these mechanisms. However, more work is needed to understand exactly how these processes are contributing to symptoms and pathology and therefore more effectively target and improve treatment strategies.

Good inroads have been made in research into neuronal dysfunction, inflammation and autophagy, including the development of potential treatments that target some of these mechanisms.

Sadie Rae and her parents from USA

Closer liaison between animal studies and human clinical studies could yield important insights into disease mechanisms. Better understanding of the disease pathology in animals could help inform the search for better biomarkers to track disease progression in clinical trials.

Most of the neuropathological evidence to date has been derived from animal studies, with mouse models of types A, B, C and D being well-characterised and large animal models of types A, B and D also providing valuable information (see Appendix I for a list of animal models with references). Additional clarity around any possible neuropathological differences between the subtypes and the potential impact of this on disease course and treatment strategies would be beneficial.

Closer liaison between animal studies and human clinical studies could yield important insights into disease mechanisms. Better understanding of the disease pathology in animals could help inform the search for better biomarkers to track disease progression in clinical trials. Inversely, deeper examination of MRI images, biosamples collected during natural history studies and clinical trials, and postmortem samples of brain and other tissues, could help direct attention to the biological pathways and processes that are most in need of exploration in the animal models. It will also reveal much-needed biomarkers for use in clinical trials. This includes the use of genomic, metabolomic (e.g. Tebani et al, 2018) and proteomics techniques ('omics).

Considerable work is being done on strategies to reactivate autophagy flux and reduce inflammation. A clinical trial of one such anti-inflammatory approach is already underway with Anakinra (ClinicalTrials.gov Identifier: NCT04018755), a drug that blocks the action of the inflammatory molecule, interleukin-1beta. These approaches will be enhanced by deeper understanding coming from further neuropathological research.

Most consider that these approaches, which target the downstream effects of enzyme insufficiency, will not be curative alone. It is likely that they will need to be combined with strategies to prevent ongoing heparan sulfate accumulation (such as gene and enzyme replacement strategies). However, it is possible that they could help to reduce some of the symptoms

We need more work to refine outcome measures for clinical trials - keeping a child's engagement in the cognitive tests for long enough is a challenge.

- Neuropsychologist, Australia

of Sanfilippo such as hyperactivity or sleeplessness or slow neurodegeneration. Recent research into what families value in terms of therapeutic benefit shows these outcomes are also extremely important and that the hunt for therapies should not be solely focussed on complete restoration of normal cognitive development (Porter et al, 2021). In this respect, it will be important to develop and validate a broader array of outcome measures beyond neurocognitive development to assess the potential benefits of these therapies and also design methods to explore combination therapies in experimental and clinical settings.

For each of these approaches it will also be important to identify the timing of their role in the biology of the disease across the developmental pathway and disease trajectory of an individual with Sanfilippo. This will help to identify the therapeutic window for treatments that target these mechanisms and understand what gains in quality of life may still be achieved even in more advanced disease.

Jude and Isla
from Australia

In addition, patients with attenuated or slower progressing forms of disease may be more likely to benefit from some of these therapeutic strategies than those with more rapidly progressing neurologic disease. However, this research is currently limited by lack of access to animal and cell models, or tissue samples from attenuated patients. Inclusion of patients with attenuated disease in clinical trials to date has also been extremely limited. Recruiting more attenuated patients into cell-based studies and focussing research attention on attenuated mutation-specific, small-molecule drug discovery would help to address this.

Costs are a significant barrier to advance research through to clinical trials at the pace needed.

Most of these biological processes – inflammation, neurodevelopment, neuro-degeneration and repair, etc – are also likely to be influenced by the genetic background of the individual as is seen in adult neurodegenerative disorders. We know that the severity of Sanfilippo syndrome is highly variable, even within the same family. A better understanding of the genes and processes that influence disease severity in Sanfilippo will potentially help identify targets for treatment. Increasing access to human cell and tissue samples encompassing a diverse range of Sanfilippo mutations and utilising the genetic tractability of fly and fish models would be beneficial.

Another area that has not yet been investigated adequately is the role that stem cell approaches to replace damaged tissues or techniques to enhance neuroplasticity, might play in Sanfilippo. Some cell and animal studies are underway, testing the benefits of existing drug molecules to enhance neuronal function. There has been much effort in these areas for other adult and paediatric neurodegenerative diseases. Increased awareness and collaboration on strategies that target these shared mechanisms across diseases could be beneficial for patients in many rare diseases and could potentially be explored for Sanfilippo under basket trial designs with other conditions.

Additional considerations in the development of therapies, relate to the costs of preclinical development and the commercial viability of what in most cases are going to be expensive advanced therapeutics. To date, the Sanfilippo community has invested significantly in the discovery, preclinical and even clinical phases of research. The costs are a significant barrier to advance research through clinical trials at the pace needed. Clinical trials for combination therapies will also prove challenging to fund, due to lower commercial opportunities for industry. Developing innovative funding models and partnerships to fund this phase of research will be vital in a landscape where the discovery research is largely driven by funding from small family-led foundations. Additionally, connecting researchers with the necessary expertise and guidance to capitalise on discoveries and proceed to preclinical testing is essential. This can include experts in the patient community, medicinal chemistry, preclinical work-up, toxicology, accredited Good Manufacturing Practice (GMP) facilities and experienced clinical trialists. Creating connections and guidance early in the development process can help accelerate treatments along the translational pipeline and reduce trial and error and duplication.

KEY POINTS

- Knowledge is building on what processes are going wrong inside the cells and tissues of individuals with Sanfilippo, but we don't yet know which of these hold the most promise as targets for drug development to improve symptoms or slow disease progression
- We need to know more about what other genes influence disease processes and how they affect disease severity
- We don't understand enough about the timing of the disease mechanisms, exactly how and when they contribute to symptoms and therefore when would be the best time to use different treatment strategies to improve patient's quality and length of life
- Emerging evidence suggests that gene and enzyme replacement strategies will be most effective in restoring cognitive development if patients are treated when they are very young. We are yet to understand if we can combine gene and enzyme therapies with additional strategies that target the downstream effects of Sanfilippo on the brain and body to widen the treatment window.
- Broadening assessment of treatment outcomes, beyond cognitive development, in relation to these types of therapies could also identify meaningful treatment benefits for families at all stages of disease that include both neurological and peripheral effects that can impact on health and quality of life.
- The community has invested heavily in these areas of research but new funding models are needed to move these discoveries to the preclinical and clinical phases of research.

RECOMMENDATIONS

- More research is needed to better understand the neuropathology of Sanfilippo, how and when different mechanisms cause symptoms and progression, with a focus on:
  - Neuronal/synaptic dysfunction (brain cells and their connections)
  - Neurodevelopment (early development of the brain)
  - Autophagy (enhancing waste disposal to clear accumulated debris)
  - Inflammation (how does inflammation contribute to symptoms and CNS damage)
  - Accumulation of other materials (lipids and protein aggregates)
  - Mitochondrial dysfunction (failures in the energy production of cells)
  - Substrate reduction
- More research is needed to better understand the manifestations of the disease outside of the central nervous system and their impact on neurological and peripheral symptoms and quality of life
- Stimulate greater use of 'omics technologies to identify new treatment targets and pathways
- Conduct research to improve our understanding of the link between gene mutations and disease severity and discover other genes or processes that may influence severity
- Drive research to further explore regenerative approaches, including regenerative cell therapies and stimulation of neuroplasticity
- Develop guidance and connections to support and enhance drug development and pre-clinical research pipelines, including dialogue with regulatory authorities (e.g. roundtable/symposium with publication of outcomes)
- Identifying funding mechanisms and sources to bridge the valley of death between discovery research and preclinical/pre-commercial research
- Build synergies and collaboration with other adult and paediatric neurodegenerative diseases to explore common biological mechanisms and potential drugs candidates.

Julia from Switzerland

A focus on a treatment and management plan would be a huge help for Sanfilippo families with older children.

- Sanfilippo parent, Australia

MANAGE

Manage symptoms for improved quality of life

AIM

Clinicians and families living with Sanfilippo can manage the symptoms and optimise quality of life, regardless of age, stage and subtype.

The increasing number of clinical trials for Sanfilippo syndrome getting underway, some with encouraging early signs of positive treatment outcomes, has provided hope that effective treatments are within reach.

However, we still have some way to go and the first therapies to be approved are unlikely to be perfect, may not be applicable to all individuals with Sanfilippo, and may require refinements to benefit all types and stages of Sanfilippo syndrome. In the meantime, effective strategies to manage the symptoms of Sanfilippo syndrome are needed to improve quality of life for individuals with Sanfilippo and their families.

Recent work by Cure Sanfilippo Foundation and their collaborators has helped identify the priorities for families with Sanfilippo syndrome when it comes to symptom management and meaningful benefit from therapies (O'Neill et al, 2019; Porter et al, 2020; Shapiro et al, 2019). In the psychological domains these include communication and relationships, impulsive and hyperactive behavior, anxiety and distress in the child and sleep disturbances. In relation to physical health, there were high unmet needs around pain, mobility, vulnerability to illness, seizures, feeding and maintaining nutrition, digestive issues and toileting.

While the primary disabling impact of Sanfilippo is on the brain, the disease does affect a wide number of body systems including the lungs, bones and joints and the digestive system. The retina and heart can also be affected and are the predominant sites affected in late-onset/attenuated Sanfilippo

Oliver from Australia

Andrea from Spain

(Nijmeijer et al, 2019). These aspects of the disease have received relatively little attention, in comparison to central nervous system targets. Their contribution to symptoms such as pain/distress, behavioural symptoms and mobility may be significant for individual patients and their quality of life, yet remain poorly explored. For example, recent research has confirmed a high prevalence of hip osteonecrosis, particularly in individuals with more severe subtypes (Breyer et al, 2021). A better understanding of the pathology and impact of the peripheral effects of Sanfilippo may reveal objective ways to measure treatment impact in clinical trials and beyond.

The rarity of Sanfilippo and lack of awareness of the condition amongst many health and allied health practitioners means that many are not familiar with the complex care needs or best practices for managing Sanfilippo. In a project led by Sanfilippo Children's Foundation, Australia and Cure Sanfilippo Foundation, USA, clinical guidelines are currently in development. This will guide health professionals in the best-practice care and management of patients with Sanfilippo syndrome. A concerted effort will be needed to ensure that these guidelines reach as wide an audience as possible. Families will also benefit from access to a lay-friendly version of the Guidelines to assist them in communicating with health practitioners and seeking the best care and support.

In addition, families are a rich source of anecdotal and experiential information on managing symptoms and behaviours and optimising quality of life for individuals with Sanfilippo and the family. This includes their experiences with pharmacological treatments, alternative therapies and adaptive approaches. Well-designed qualitative research can tap into this expertise and help develop evidence-based advice for families and their health-care providers.

Families are also important partners in clinical research. Their priorities for their child and their experiences in participating in trials can help with the identification and development of accurate, objective, low-burden outcome measures to assess symptoms and quality of life. This will ensure that therapies that can improve symptoms and quality of life, even if they do not halt or reverse cognitive decline and disease progression, can be successfully identified in clinical trials.

Coupling this knowledge to the neurobiological discoveries underway, to biomarkers, functional imaging and other physical and biochemical tools could also help inform research into effective treatments for behavioural symptoms.

We need to understand patient and caregivers' perspectives on the disease and on potential treatment outcomes so that important aspects for the families are not missed in the development of therapies.

- Industry representative, UK

Simon from USA

KEY POINTS

- Advances in curative treatments take time, but there is an acute need to improve quality of life for families now
- Cognitive development is the primary focus of current clinical trials but families identify certain behavioural and physical symptoms as higher priorities to improve quality of life
- Lack of awareness of Sanfilippo among clinicians and allied health practitioners hinders timely diagnosis and optimal clinical management
- Families need access to the best advice and information to empower them to manage symptoms and seek the best medical care and support.
- Families are a rich source of knowledge and expertise in managing the symptoms of Sanfilippo and can help identify and design lower burden, meaningful outcome measures for clinical management and trials

RECOMMENDATIONS

- Focus research to better understand what causes the physical, behavioural symptoms and other non-cognitive neurologic symptoms that have been identified as most important to families (pain, distress, hyperactivity, impulsivity; sleep; communication; mobility; feeding and nutrition) and develop targeted interventions
- Support collaboration between families, clinicians and researchers to harness the wealth of clinical and lived experience and evidence around effective symptom management
- Develop tools and methods to collect patient/family reported outcomes with minimal burden to families, including a Sanfilippo-specific quality of life assessment tool and composite measures, to support monitoring of clinical care and use in clinical trials
- Support collaboration between clinical trialists, families and regulatory authorities to ensure trials measure treatment outcomes that have been identified as important to families with acceptable participation burden
- Develop, disseminate and regularly update Clinical Guidelines and expand clinical expertise and centres of expert care to enhance the care and clinical management of individuals with Sanfilippo
- Develop a lay-friendly version of the Clinical Guidelines and a patient pathway to empower families as advocates and partners in their child's care
- Explore the true impact of the multisystem effects of Sanfilippo and investigate treatment and management options

Haidyn from USA

Data needs to be accessible and utilised, curated and standardised.

- Sanfilippo parent, USA

ENABLE
for success

DATA
To inform discovery research, initiate trials, run effective & efficient trials, support regulatory approvals & reimbursement for treatments.

TOOLS
To test therapies, identify patients and evaluate clinical care and treatment effects in clinical trials.

COLLABORATION
To connect clinicians, researchers, industry and families and ensure clinical and laboratory research are informed by each other and by families; and the data, tools, resources and expertise are shared.

There are some common themes and tools that emerge from this examination of the landscape of discovery and development of therapeutics for Sanfilippo and were articulated in our discussions with stakeholders. These enablers can be broadly grouped into the themes of data, tools and collaboration.

Clinical, natural history data and patient/family reported data is needed to inform discovery research, initiate trials, run effective & efficient trials, and support regulatory approvals & reimbursement.

Tools such as biological samples and disease models are needed to identify and test therapies in preclinical research. Clinical trials are currently hampered by late diagnosis of patients and lack of prognostic tests to predict disease course. Additional outcome measures and biomarkers are also required that are less burdensome and invasive, are fit-for-purpose for Sanfilippo and capture data with enough relevant detail to monitor treatment effects.

All of these data and tools and the sharing of information and expertise can also be enhanced through forums and opportunities for deeper collaboration. Clinicians, researchers, industry partners, and families can be connected to ensure clinical and laboratory research inform each other and the data, tools, resources, expertise and priorities are shared to accelerate progress and minimise the burden on families and clinicians.

Peter from Australia

DATA

AIM

Data is shared and different data sources are linked to help inform discovery research, initiate trials, run effective & efficient trials, and support regulatory approvals & reimbursement.

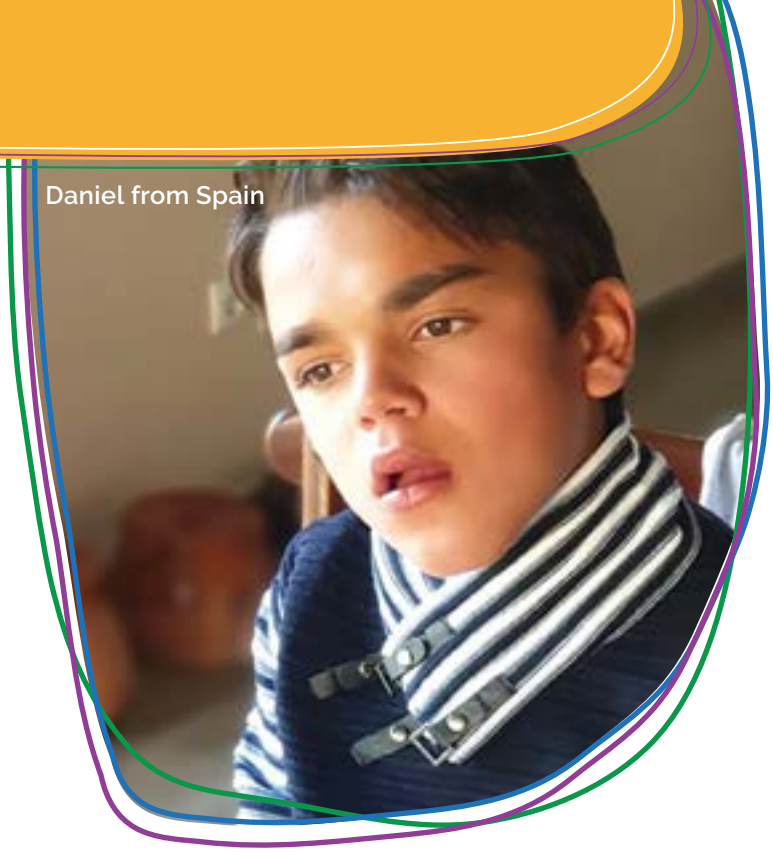
To date 18 therapies have reached the clinical trial stage, involving 14 different commercial sponsors and two academic sponsors (see appendix II). The trials have been conducted at clinical centres in at least 12 different countries. The majority of these are gene and enzyme replacement therapies for Sanfilippo types A and B.

Some have failed to show any benefit against the primary outcome measures used. This may in some cases, be due to the older age of participants enrolled in the earlier trials or selection of uninformative clinical endpoints. Preliminary results from some of the current ERT and gene therapy trials are indicating that early treatment is likely to be most beneficial in terms of restoring a more typical trajectory of neurocognitive development. Completion of more trials and analysis of additional outcome measures is needed before any conclusions can be drawn about potential benefits relating to behavioural symptoms, sleep and quality of life. It is imperative that trials are designed to include, and regulatory bodies are incorporating into decision making, the totality of data obtained during clinical trials in order to confidently understand potential treatment effects.

The burgeoning Sanfilippo trials landscape means that a significant body of clinical trial experience, expertise and data is accumulating. Even 'failed' clinical trials have accumulated important data, and can potentially provide information on disease mechanisms, natural history and trial design. It is crucial to ensure that if treatments fail, it is because the therapies are not effective, not because the trial design or tools were inadequate, patients were identified and treated too late, or uninformative outcome measures were selected.

18

therapies have reached the clinical trial stage


Daniel from Spain

In this respect more work is needed to consolidate the available natural history study data for Sanfilippo syndrome and to collect new data where it is not yet available. Considerable natural history data has been gathered on types A and B, but there is only very limited data available for types C, case report data for type D (Jansen et al, 2007) and very little for attenuated forms of each subtype. This is a significant barrier to commencing clinical trials for these types of Sanfilippo. Consolidating data from natural history studies, where feasible, and initiation of retrospective case note reviews for the more rare subtypes of Sanfilippo, will help to fill this gap.

Patients need trials and trials need patients. Registries can provide a resource of 'trial ready' patients who come with detailed information on their genetic mutation, disease course and test results. They can also provide a portal through which patient and family-reported outcome data can be gathered. In return, registries ensure that patients for whom trials are not yet available are 'on the list' and easily contacted as soon as a relevant trial becomes available. Registries can also be linked to clinical data and biosample repositories. This can facilitate further research and treatment development by allowing researchers to access biosamples, data and information about clinical outcomes, including off-label treatments.

Trials have been conducted at clinical centres in at least 12 different countries.

A number of different registries and clinical data collection entities have been established in the MPS and rare disease space, but more work is required to reduce fragmentation, ensure equitable access to the data, optimise data collection, data-linkage, and data and sample sharing. Building or collaborating on infrastructure and building capacity in this area can lay the foundation for a real-world data and evidence strategy for care, therapy development and therapy approvals.

Also crucial is the need to make it as easy as possible for families and clinicians to contribute data. Families can go to considerable efforts to contribute to research studies and registries, but currently receive little feedback or information on outcomes relating to the use of their data. Increasing communication with registry participants could enhance engagement and provide them with knowledge and hope about the progress of research.

Sharing expertise, data and hard-won experience will benefit all players and increase the likelihood of trials being able to start more rapidly, efficiently test more therapies and extend access to more children across more countries. Industry representatives interviewed in the development of the roadmap indicated a willingness to share data via a neutrally managed platform.

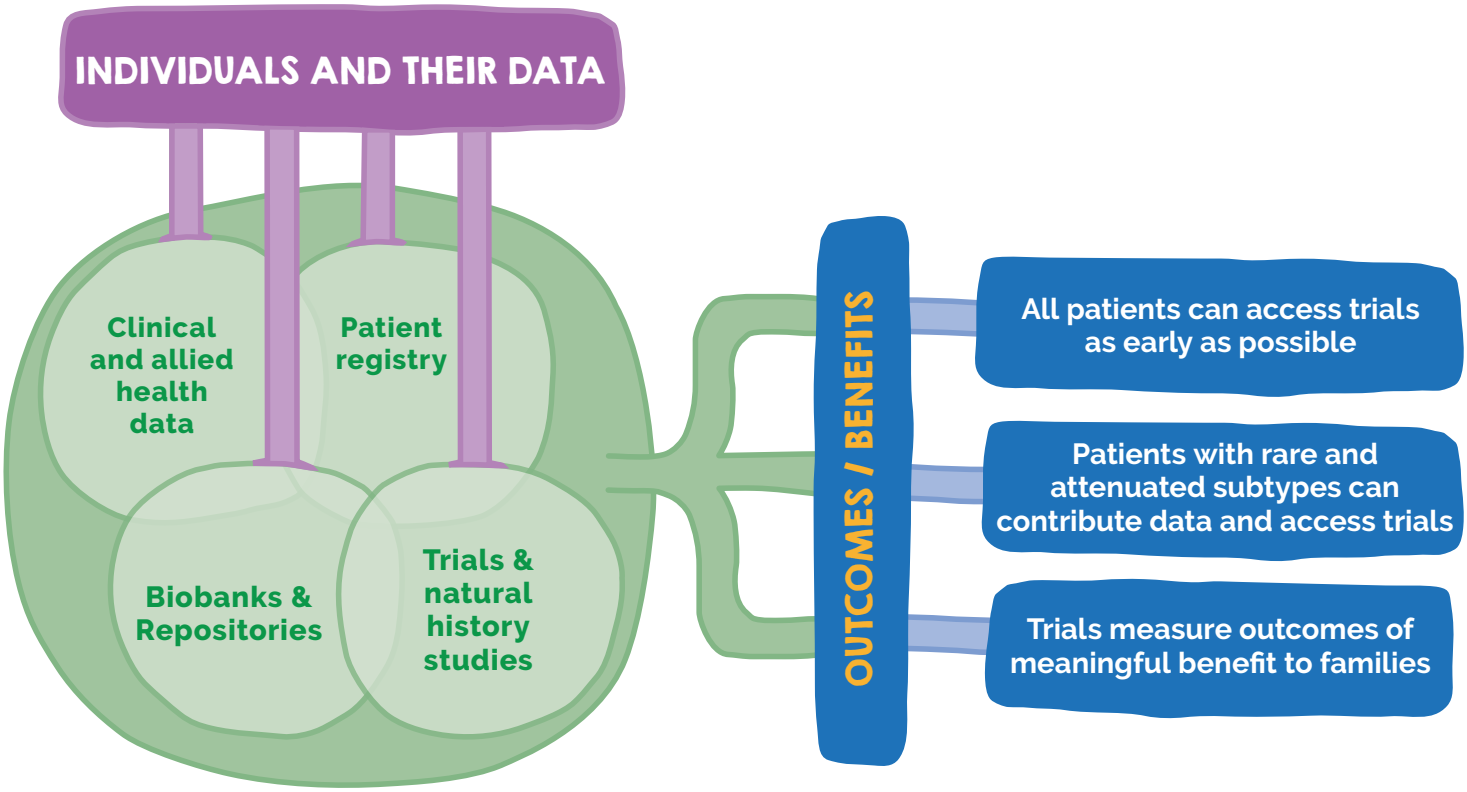
KEY POINTS

- Researchers need clinical data and biological samples from patients to better inform their hunt for treatment targets and to develop tools to support clinical research
- Clinical trialists need data about patients to plan trials and measure treatment outcomes against the natural history of the disease
- Patients need access to the right trials and treatments appropriate for them, regardless of their age, stage or subtype
- Regulators need data to approve clinical trials, licence/authorise the use of therapies and for payers to provide reimbursement for the cost of therapies

RECOMMENDATIONS

Developing and connecting the following data sources and infrastructure can support these needs:

- Consolidate existing natural history study data and expand collection for rare and attenuated subtypes
- Formalise and expand the collection of clinical data & link to biosamples and post-mortem samples as well as patient-derived data
- Patient registry - data contributed by patients and families (supports trial recruitment and collection of patient/family reported outcomes), families are informed of data uses and outcomes
- Central, independent repository & data-linkage infrastructure to pool, connect and share all sources of data
- Develop the foundation for a real-world data and evidence strategy tailored to Sanfilippo care and therapy development and approvals.



TOOLS

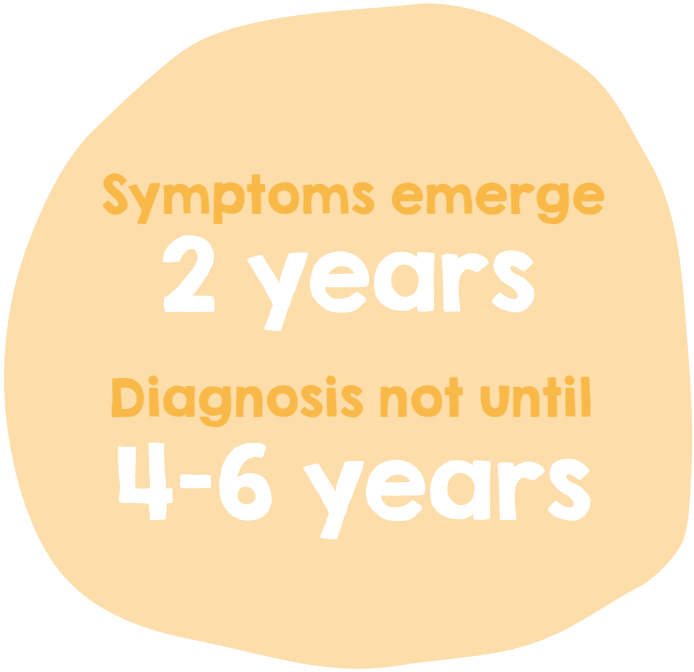
AIM

Tools are developed and shared to facilitate the development and testing of therapies, identify patients, and easily and efficiently measure treatment effects in clinical trials.

Diagnosis and Prognosis

Early treatment is likely to be most effective in providing a more typical cognitive developmental trajectory and preventing the physical and behavioural symptoms of Sanfilippo (Hassiotis et al, 2014). However, the signs and symptoms of Sanfilippo syndrome often do not come to attention until at least two years of age and a diagnosis is most commonly made between the ages of 4 and 6 years (later for those with attenuated forms of the disease). By this time developmental delay is apparent and neurodegenerative changes may already be advanced.

Technologies have been developed to detect Sanfilippo and other MPS and lysosomal storage disorders in newborn screening dried blood spots (Chien et al, 2020; Oguni et al, 2020). However, in most jurisdictions, adding a new condition to the newborn screening schedule before treatments are available is extremely challenging. A successful example of where this has been achieved is the implementation of newborn screening for Spinal Muscular Atrophy in New South Wales and Australian Capital Territory, Australia. This enabled the identification of patients, optimisation of care via specialised centres and referral to clinical trials where appropriate, in most cases in infants prior to symptom onset (Kariyawasam et al, 2020).



While the potential psychological harms of a newborn diagnosis for a condition without a treatment should not be ignored (Fletcher & Wilcken, 2012), newborn screening provides potentially significant benefits (Hayes et al, 2007; O'Leary & Maxwell, 2015).

Potential benefits of newborn screening:

- **Reduced distress caused by a lengthy diagnostic odyssey**
- **Early referral for clinical trials and therapeutic options, with greater potential for positive outcomes**
- **Enhanced recruitment for clinical trials, making trials more efficient and effective**
- **Enabling family planning considerations**
- **Potential for improved clinical management and better outcomes**

While the causative genes for all four sub-types of Sanfilippo are known, there are many different mutations identified in each gene. These mutations result in inadequate or complete absence of enzyme activity, leading to accumulation of heparan sulfate in cells and tissues. The severity of Sanfilippo can in some cases be predicted by the specific gene mutation (Valstar et al, 2010, Yogalingam & Hopwood, 2001), but not always. New gene mutations are also frequently identified in newly diagnosed individuals, meaning prognosis is challenging. Variation of disease severity also occurs with the same mutation, and even within the same family, suggesting that other genes and other factors may influence disease processes and progression. Newborn screening would likely result in diagnosis of more patients with attenuated phenotypes who may otherwise have gone undiagnosed or misdiagnosed. This will therefore also increase the need for prognostic tools to predict the disease course. Some tools such as residual enzyme activity assays (Knotterus et al, 2017) have been explored, but more are needed.

If we can achieve early diagnosis and patients are referred to clinical trials prior to symptom onset, it will become even more crucial to be able to predict disease course. This is because many trials in Sanfilippo have been single-arm, open-label in design; without placebo arms due to ethical concerns. Instead, the patients' treatment outcomes have typically been compared against an untreated disease course, determined through natural history studies, or patients are used as their own controls, comparing disease trajectory before and after treatment. This will not be possible in future studies where patients are enrolled prior to symptom onset, unless an accurate presymptomatic prognosis, or expected disease trajectory, can be determined from genetic tests, biological assays or statistical disease progression modelling.

Early diagnosis and prognosis tools coupled with early initiation of data collection on individual patients, potentially through registries, will mean that patients will be able to contribute data for natural history studies and trials. Patients will also be 'trial-ready' in terms of their genetic, biologic, prognostic and disease course information, allowing them to be identified and stratified in appropriate clinical trials.

Sandra from Spain

Disease models

Animal models, predominantly mice, exist for all four subtypes of Sanfilippo syndrome (see appendix I for a complete list and references). The model predominantly used for Sanfilippo type A research is a naturally occurring missense mutation in the mouse, however, it is not the same mutation or location as the majority of type A human mutations. Type A is unique in that it has some common missense mutations, therefore it could be feasible and useful to generate clinically relevant type A mice or other species with the most common missense mutations. The other subtypes have a large number of different mutations, making it impractical to think about generating mice with just one or two representative human mutations. As a result, the mouse models for types B and D are knockout models. Type C has both a knockout mouse and a mouse with a clinically relevant missense mutation.

The mouse models show pathology, behaviour and cognition/memory symptoms that reflect the human condition. Even where these models are knockouts or have non-human mutations, they are extremely useful for exploring the neuropathology of Sanfilippo and for testing gene and enzyme replacement and substrate reduction therapies, and therapies that target mechanisms such as inflammation and autophagy. The utility of these models can be enhanced with additional genetic tools and markers (dual markers) to help visualise cellular processes such as lysosome function. Further collaboration across diseases could help build and enhance these banks of tools to expand research capabilities in Sanfilippo.

Some therapeutic strategies such as pharmacological chaperones and treatments that improve the reading, editing and stability of some types of gene mutations (such as nonsense mutations), require the presence of the disease-causing gene mutation and/or faulty enzyme. In this respect it would be useful to have access to clinically relevant type A cell models or animal models. Some fruit fly, nematode worm and zebrafish models also exist or are in development for types A, B and C, with a mixture of knock-out and human disease gene variations (see Appendix I). These have utility for high-throughput screening for potential therapeutic molecules. Expanding the bank of these species with additional clinically relevant mutations could be a faster and more cost-effective approach than developing additional mouse models.

Sanfilippo has four subtypes A, B, C, D. Each subtype corresponds to a deficient enzyme. Types A and B are more common, C and D much rarer.

Human cell models are also an incredibly valuable resource for modelling the exact genetic mutations seen in individuals with Sanfilippo and progress has been made in developing human cell models using skin fibroblasts from patients and induced pluripotent stem cells (iPSC) and iPSC-derived neuronal cells from patients' skin samples (Benetó et al, 2020; Vallejo-Diez et al, 2018). These can provide a valuable resource for modelling the effects of mutations on cell biology and for high-throughput screening of drugs, with the potential to bring a personalised medicine approach to the development of treatments. The Sanfilippo Children's Foundation-funded 'Brain in a

Human cell models can provide a valuable resource for modelling the effects of mutations on cell biology and for high throughput screening of drugs.

Dish' project is considerably expanding this work, generating a bank of patient-derived iPSC and neuronal cells, and screening drug libraries for candidates. The use of human cell models may be particularly important for individuals with attenuated disease as there are currently no animal models with an attenuated phenotype.

Naturally occurring large animal models have been identified and studied for types A, B and D, but there is no large animal model for type C. Recent FDA guidance issued in January 2021, suggests that, while small animal models of neurodegenerative disorders are useful for the generation of proof of concept data of treatment efficacy, animals with larger brains may better extrapolate to humans for modelling dosing and administration routes. However, it is likely that this can be achieved in normal large animals without the need for disease-specific large animal models. The FDA also requires demonstration of the therapy's effects on relevant biological pathways and outcomes that reflect clinically relevant endpoints in humans. This can potentially be adequately demonstrated in small animal models, where the data is combined with data from human biological samples that demonstrate that the pathways and biomarkers are valid in the human condition.

Biological samples

Currently, biological samples, from both clinical studies and post-mortem collections, are often held by individual clinicians and researchers in clinical centres with larger numbers of patients and by clinical trial sponsors. A limited amount of post-mortem brain tissue has also been collected, most of which is housed in a USA National Institutes of Health neurodevelopmental diseases biobank, NeuroBioBank. Access to biological samples is essential for discovery researchers to explore and test theories about the biology of the disease and to test and develop potential biomarkers to be used in clinical trials. Making it easier for families to provide samples, including post-mortem, harmonising the collection of biosamples and collection protocols, creating a network of biorepositories and ensuring consent and access protocols are streamlined, could greatly enhance the discovery of treatment targets and biomarkers.

Clinical trial design

An international workshop on clinical trial design for treatments for Sanfilippo syndrome led to the publication of a set of recommendations in 2015 (Ghosh et al, 2015), and the USA Food & Drug Administration has also published guidance for industry on developing drugs for Sanfilippo syndrome. However, the Sanfilippo community (industry, advocates and clinicians) have noted many areas where the draft guidance does not reflect certain aspects of the disease or the disease specific challenges with trial design. As such, a joint advocacy/clinician commentary was submitted to the FDA docket to make these critical perspectives available to regulators.

There are also a range of different types of experimental therapies coming through the pipeline and growing recognition that combination therapies may be required,


Skye from Australia

which will require additional considerations for trial design. In addition, there are a large number of patients who, for a variety of reasons, remain ineligible for the current clinical trials. Future clinical trials may need to take into account that some patients will have received treatment in previous clinical trials. Earlier diagnosis will mean that very young pre-symptomatic patients are entering trials. As cognitive symptoms generally do not become apparent until two years of age or more, surrogate measures are likely to be required to track treatment effects on brain development. Likewise, surrogate measures will be required to identify treatment effects within reasonable clinical trial timeframes for the more slowly progressing patients with attenuated subtypes of Sanfilippo. Some therapies in development may potentially benefit patients with more advanced disease, targeting symptoms and behaviours not currently prioritised or measured in the gene and enzyme replacement therapy trials.

For these reasons there is a growing need to take an innovative approach to trial design.

It will be important to show the behavioural benefits, for example if a patient can walk again, or sit alone on the toilet, or show where they feel pain. This may sound small but can make a big difference for the quality of life of the whole family.

- Sanfilippo parent, Poland

Outcome measures

As cognitive and behavioural development are significantly affected in individuals with Sanfilippo, primary and secondary clinical outcome measures currently focus on this. Consensus recommendations have been published for the use of cognitive outcome measures for neuronopathic MPS disorders (van der Lee et al, 2017). Cognitive development is assessed using the Mullen Scales of Early Learning, Bayley Scales of Infant and Toddler Development and/or the Kaufman Assessment Battery for Children. These are used to calculate Developmental Quotient (DQ) or Age Equivalent Developmental scores as change from baseline and compared to natural history study data. The Vineland Adaptive Behaviour Scale is another important clinical outcome measure. Quality of Life instruments such as the Paediatric Quality of Life Inventory (PedsQoL) and Parent Stress Index (PSI-4) are also likely to be informative. The Sanfilippo Specific Behaviour Rating Scale is the only instrument specific to Sanfilippo syndrome and measures behaviour along a specific pattern and progression of behavioural symptoms (Shapiro et al, 2015).

These important instruments are all providing important data on treatment outcomes in Sanfilippo clinical trials. However, challenges remain, particularly in terms of neurocognitive testing which can be particularly burdensome and can take a long time to complete for children with significant behavioural symptoms. It also requires trials of 2 years or more, particularly where individuals are treated in infancy, to reliably conclude that there is an improvement or stabilisation in cognitive performance.

Objective measures for the priority symptoms for families such as hyperactivity and impulsivity, sleep, pain, mobility, gastrointestinal issues, and dysphagia, also need to be further explored and developed. A stool habits questionnaire has been developed by Cure Sanfilippo Foundation to assess gastrointestinal issues and is currently being explored in clinical trial protocols. Video analysis methods for monitoring cognition and adaptive behaviours are also in development. Exploration of passive data collection tools such as activity trackers could also be helpful for non-invasive, low-burden monitoring of hyperactivity and sleep.

Symptoms typically experienced by individuals with Sanfilippo include hyperactivity, sleep disturbance, loss of speech, dementia, seizures and loss of mobility.

Biomarkers

The primary biomarker used to demonstrate restoration of enzyme activity in the CNS in gene therapy and enzyme replacement therapy trials is heparan sulfate levels in the cerebrospinal fluid. There is also some debate as to how fully it may reflect the resolution of dysfunction and damage within the cells and may be dependent on the route of delivery and nature of the therapeutic (Jones et al, 2016; Wijburg et al, 2018).

Regardless, a reduction in CSF heparan sulfate would clearly indicate successful action upon the primary disease mechanism in some compartment of the CNS. Urine heparan sulphate and urine and CSF glycosaminoglycan (GAG) levels are also valuable biomarkers. Spleen and liver volumes are useful markers of treatment effect in the peripheral organs, but may not reflect treatment efficacy in the CNS. Segmented brain volumes as measured by MRI are also useful longitudinal measures of disease progression (Abreu et al, 2021). Several other biochemical biomarkers have been validated or evaluated in research and clinical trial settings with varying degrees of utility (Saville et al, 2019; Shapiro et al, 2016). Plasma heparan sulfate has also been shown to be predictive of disease severity, including the timing of speech and mobility loss (De Ruijter et al, 2013).

However, further non- or low-invasive biomarkers, such as imaging and fluid biochemistry (e.g. blood, saliva, urine) need to be improved and tailored to the therapeutic target to ensure that treatment effects can be identified within shorter duration trials and support regulatory approvals for new therapies.

The need for accurate surrogate outcome measures and biomarkers that do not rely solely on the expected progression of cognitive and behavioural signs and symptoms will increase as the pressure to enrol patients as young as possible increases. Some progress has been made in this field, with a range of biomarkers, but consolidating efforts in this area will be beneficial.

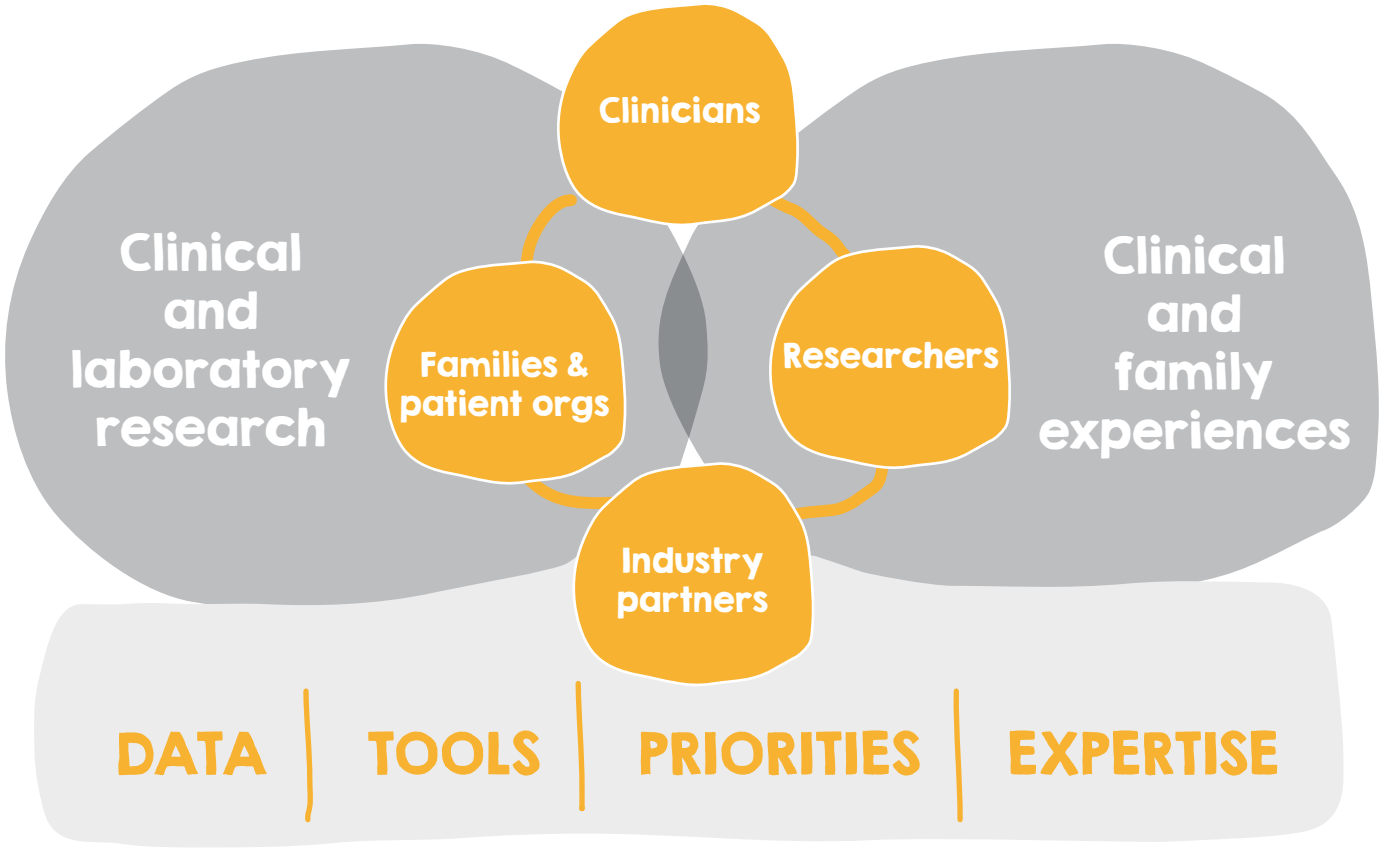
RECOMMENDATIONS

- Advocate for newborn screening for Sanfilippo and other MPS to enable earliest possible treatment. This could be done in collaboration with other LSD and MPS advocacy groups, clinicians, scientists and industry
- Develop tools to predict disease severity/prognosis (prior to the onset of symptoms) to enable stratification of patients into faster and slower progressing cohorts in clinical trials
- Consider development of clinically relevant Sanfilippo type A mouse models, or other species, with the most common human mutations, to support mutation-specific therapy development
- Support collaboration to develop appropriate disease models, with a focus on neglected subtypes, conditional knock-outs and dual reporter systems, and tools to optimise the sharing of and access to disease models
- Explore utility and feasibility of clinically relevant attenuated disease models and/or other methods to model attenuated disease.
- Support collaboration to capitalise on the availability of human cell lines and iPSC-derived neuronal cell models (e.g. a Sanfilippo neuro cell bank).
- Innovate on trial design for:
  - Combination therapies
  - Attenuated patients
  - Patients who have previously participated in trials
  - Patients with advanced disease
- Drive research to develop and validate new low-burden, non-invasive outcome measures with a focus on symptoms of high priority for families beyond cognition, including sleep, hyperactivity, impulsivity & pain, with attention to detecting slower rate of change in attenuated subtypes
- Conduct research to develop and validate biomarkers (including eyes and hearing) for use in clinical trials

COLLABORATION

AIM

Clinicians, researchers, industry partners and families are connected to ensure clinical and laboratory research, and clinical and family experiences, inform each other and the data, tools, resources, priorities and expertise are shared.



Clinical trial expertise and knowledge in Sanfilippo is accumulating and it will benefit all stakeholders if we can share this knowledge to develop guidance around likely therapeutic windows, eligibility requirements, appropriate outcome measures and biochemical, imaging or other biomarkers. All of these need to be tailored to the particular therapeutic target and all of these can be informed by data from trials that have gone before.

Facilitating the sharing of biochemical, biomarker and biosample data between clinical and laboratory researchers will help to better inform both discovery research and development of preclinical data to support clinical trial regulatory approvals.

Consistent protocols for collecting and sharing data (including protocols such as MRI, audiology, vision; biosample collection and storage; harmonised data collection; trial set-up resources) would increase the ability to use and share data.

Infrastructure and special requirements for delivering advanced treatment trials is also limiting. **Access to the appropriate facilities for delivery** of gene therapies, GMP accreditation and hospitals whose pharmacies, regulatory and ethics approvals committees are experienced in advanced therapeutics is needed. This is not unique to the Sanfilippo community and suggests there may be a case to establish centres of excellence for the delivery of treatment and trials.

Will from USA

RECOMMENDATIONS

Support collaboration within the Sanfilippo Research Community

- Platforms and networks to facilitate collaboration and sharing of resources and expertise between industry, academics, clinicians and families around tools, data & expertise
  - Biomarker development
  - Disease Models
  - Preclinical research resources and expertise
  - Clinical trial design, expertise and resources
  - Diagnosis and prevention - newborn screening, carrier screening
  - Supporting clinicians' engagement in research
  - Industry/clinician/research/family collaborations
  - Harmonised biosample and data collection
- Symposia to enhance information sharing and collaboration

Support collaboration with the wider rare disease community to achieve the goals common to us all

- Advocacy for newborn screening - for early detection and entry into trials
- Regulatory & reimbursement pathways for rare disease therapies
- Platform technologies for delivering treatments to the brain
- Advocacy for equitable access to carrier screening so that every person who chooses to, may be informed of their genetic risks of passing on serious/fatal childhood diseases

No clinical trial to date has been able to reverse established disease. This means advocating very strongly for newborn screening given that several therapeutic approaches are on the horizon.

- Sanfilippo researcher, Australia

Sanfilippo Children's Foundation

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CURE SANFILIPPO FOUNDATION

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APPENDIX 1 - ANIMAL MODELS FOR SANFILIPPO SYNDROME

SPECIES	MPS III SUBTYPE	MUTATION	REFERENCE/LOCATION
Fruit Fly (Drosophila melanogaster)	MPS IIIA	Knockdown of SGSH/ CG14291	Webber et al. 2018. University of Adelaide, SA, Australia
	MPS IIIC	Knockdown of HGSNAT/ CG6903	Paper in preparation (Hewson). University of Adelaide, SA, Aus
	MPS IIIA & B	KO and pathogenic variants	Housed at Greenwood Genetic Center, Greenwood, SC USA/ Cure Sanfilippo Foundation funded
Worm (nematode)	MPS IIIA & B	KO and pathogenic variants	In repository. Cure Sanfilippo Foundation-funded
Zebrafish	MPS IIIA	Knockout of SGSH	In preparation (Douek et al, 2021). Australian Regenerative Medicine Institute, Australia, Sanfilippo Children's Foundation & Cure Sanfilippo Foundation-funded
Zebrafish	MPS IIIA, B, C		In preparation (Lardelli), University of Adelaide, Sanfilippo Children's Foundation-funded
Mice	MPS IIIA	-MPS IIIA B6.Cg-Sgshmps3a -Missense mutation (G to A at nucleotide position 91) reduces enzymatic activity to ~3%. -D31N mutation in the SGSH protein	Bhaumik et al. 1999, Bhattacharyya et al. 2001, Crawley et al. 2006 Colony at Flinders University, Australia (Hemsley lab) and Jackson Labs (C57BL/6J). Also see Parker et al. 2020.
	MPS IIIA	MPS IIIA mice ubiquitously expressing GFP	Lau et al. 2010 University of Adelaide, SA, Australia
	MPS IIIA	MPS IIIA x YFP and MPS IIIA x GFP mice (crossed from Feng et al. 2000) - made for neuronal architecture work	YFP cross Shoubridge et al in prep. GFP cross Hemsley et al in prep. Flinders University, SA, Australia
	MPS IIIA	Conditional knockout (SgshKO) mouse with Sgsh deletion	Lau et al. 2017 University of Adelaide, SA, Australia
	MPS IIIA	MPS IIIA mice with SCNA knocked out (α-synuclein-deficient)	Soe et al. 2019
	MPS IIIA	inactivation of Sgsh in neurons (Sgshf/ fSyn1-cre+), astrocytes (Sgshf/fGFAP-cre+) or endothelia/myeloid cells (Sgshf/fTie2-cre+).	Dwyer et al. 2017
	MPS IIIA immune-deficient	RAG2/IL2R/SGSH mutant animals (cross of B6.Cg-SGSHmps3a/ PstJ and B6.129S-Rag2tm1Fwa Cd47tm1Fpl Il2rgtm1Wjl)	UC Davis/Cure Sanfilippo Foundation-funded
	MPS IIIA immune-deficient	MPSIIIAxIL1R1−/−	Parker et al. 2020. University of Manchester, Manchester, UK
	MPS IIIB	Disruption of exon 6 of Naglu (knockout)	Li et al. 1999 Available from Jackson Labs

Continued....

SPECIES	MPS III SUBTYPE	MUTATION	REFERENCE/LOCATION
Mice continued...	MPS IIIC	Constitutive knockout Hgsnat-Geo	Martins et al. 2015 Alexey Pshezhetsky, CHU St. Justine, Montreal, QC, Canada
	MPS IIIC	Targeted disruption of the HGSNAT gene	Marcó et al. 2016
	MPS IIIC	Knock in Hgsnat-P311L mouse strain with frequent human missense mutation that causes misfolding of the enzyme.	Bose et al. 2019 Alexey Pshezhetsky, CHU St. Justine, Montreal, QC, Canada
	MPS IIID	Knockout of Gns that lacks exons 2-13 of the 14 exons	Jamil et al. 2016 (dissertation) Roca et al. 2017
	MPS IIIE	Knockout of Arsg gene	Kowalewski et al. 2012
Dog (Dachshund)	MPS IIIA	3 bp deletion in both alleles	Fischer et al. 1998 Aronovich et al. 2000
Dog (Huntaway, NZ)	MPS IIIA	Adenosine insertion leading to a frameshift & premature chain termination	Jolly et al. 2000 Yogalingham et al. 2002
Dog (Schipperke)	MPS IIIB	Insertion in exon 6 consisting of a 40–70 bp poly-A and an 11 bp duplication of the exonic region preceding the poly-A	Ellinwood et al. 2003 Raj et al. 2020
Emu	MPS IIIB	2 bp deletion in exon 6 resulting in frameshift with a longer ORF	Aronovich et al. 2001
Goat	MPS IIID	Stop codon in the 5' region of the coding sequence	Thompson et al. 1992 Jones et al. 1998
Pig (White Boars)	MPS IIIB	Heterozygous disruption of NAGLU (insertion of BMPR-IB gene into exon 6). Slow growth, early death, somatic & cerebral abnormalities	Yang et al. 2018
Cow	MPS IIIB	Cows homozygous for the missense mutation E452K (c.1354G > A) - progressive ataxia, gait and balance difficulty, onset around 2 yrs	Karageorgos et al. 2007

APPENDIX 2 - CLINICAL TRIALS FOR SANFILIPPO SYNDROME

SPONSOR	INTERVENTION	MPS III SUBTYPE(S)	TESTING PHASE(S)	LOCATIONS	STATUS AS AT JUNE 2021	REFERENCE
Abeona Therapeutics Inc.	N/A	MPS IIIA and IIIB	Natural History study	US	Completed	Truxal et al, 2016; Abreu et al, 2021; Wilhelm et al, 2018; Kamata et al, 2017
	ABO-101 (AAV9-based gene therapy)	MPS IIIB (young)	Phase I/II study	US, SP, DE, FR	Active, not recruiting	NCT03315182
			Long-term follow-up study	US, DE, FR	Active, recruiting	NCT04655911
	ABO-102 (AAV9-based gene therapy)	MPS IIIA (young)	Phase I/II	US, SP, AU	Active, recruiting	NCT02716246
			Long-term follow-up study	US, SP, AU	Active, recruiting	NCT04360265
		MPS IIIA (middle & advanced)	Phase I/II study	US, SP, AU	Active, recruiting	NCT04088734
Alexion Pharmaceuticals (formerly Synageva)	N/A	MPS IIIB	Prospective MRI observational study	UK	Completed	NCT02090179
			Retrospective review study	US, BR, NL, SP, UK	Completed	NCT02293382
			Natural History study	US, BR, IT, PT, SP, UK	Terminated	NCT02293408
	SBC-103	MPS IIIB (2-12 years)	Phase I/II study	US, SP, UK	Completed	NCT02324049; Whitley et al, 2018
		MPS IIIB (>5 years)	Phase I/II study	UK	Terminated	NCT02618512
Allievex Corporation (MPSIIIB program acquired from BioMarin)	N/A	MPS IIIB	Prospective observational Study	US, AU, CO, DE, SP, TW, TR, UK	Completed	NCT02493998
			Prospective Natural History study	US, AR, AU, BR, CO, DE, SP, TW, TR	Active, not recruiting	NCT03227042
	AX 250 (formerly BMN-250)	MPS IIIB	Phase I/II study	UK, CO, DE, SP, TW, TR, UK	Completed	NCT02754076
			Phase II Treatment extension study	UK, CO, DE, SP, TW, TR, UK	Active, not recruiting	NCT03784287
Esteve; Laboratorios del Dr. Esteve, S.A.	AAV9-CAG-coh-SGSH	MPS IIIA	Phase I/II study	SP	Ongoing	2015-000359-26
Manchester University NHS Foundation Trust	High Dose Oral Genistein Aglycone	MPS IIIA, B or C	Phase III study	UK	Completed	2013-001479-18 Ghosh et al, 2021
Lysogene	SAF-301	MPS IIIA	Phase I/II study	FR	Completed	NCT01474343 Tardieu et al, 2014
			Phase I/II long-term follow-up study	FR	Completed	NCT02053064
	N/A	MPS IIIA	Prospective Natural History study	BR, FR, DE, NL, UK	Completed	NCT02746341
	LYS-SAF302 (AAVrh10-h.SGSH) gene therapy	MPS IIIA	Phase II/III study	US, FR, DE, NL, UK	Active, not recruiting	NCT03612869

Continued....

SPONSOR	INTERVENTION	MPS III SUBTYPE(S)	TESTING PHASE(S)	LOCATIONS	STATUS AS AT JUNE 2021	REFERENCE
Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	Anakinra	MPS IIIA, B, C or D	Phase II/III study	US	Active, not recruiting	NCT04018755
University of Manchester and Orchard Therapeutics	Autologous CD34+ HSS gene therapy	MPS IIIA	Phase II/III study	UK	Active, recruiting	NCT04201405
Shire (acquired by Takeda Pharmaceutical Company Limited)	N/A	MPS IIIA	Natural History study	UK	Completed	NCT01047306
		MPS IIIA and B	Observational neurobehavioural study	US	Completed	NCT01873911; Shapiro et al, 2015; Whitley et al, 2018
		MPS IIIB	Natural History study	US, DE, UK	Completed	NCT01509768
	HGT-SAN-055 Recombinant human heparan N-sulfatase (rhHNS)	MPS IIIA	Phase I/II study	NL, UK	Completed	NCT01155778
			Phase I/II study extension	NL, UK	Terminated	NCT01299727
	Recombinant human heparan N-sulfatase, HGT-1410	MPS IIIA	Phase I/II study	UK	Completed	NCT012060526
			Phase II extension study	US, FR, DE, IT, NL, SP, UK	Terminated	NCT02350816; Wijburg et al, 2018
UniQure Biopharma B.V.	rAAV2/5-hNAGLU	MPS IIIB	Phase II/III study	FR	Completed	NCT03300453 Tardieu et al, 2017

Belle from USA

Jacob from Australia

If you would like to get involved, please contact:
research@sanfilippo.org.au or **contact@curesanfilippofoundation.org**