A GLOBAL ROADMAP FOR

Sanfilippo Syndrome Therapies

EXECUTIVE SUMMARY

Sanfilippo syndrome is a rare genetic condition, a type of childhood dementia, that causes progressive brain damage together with other impacts on the body.

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

Julia from Switzerland

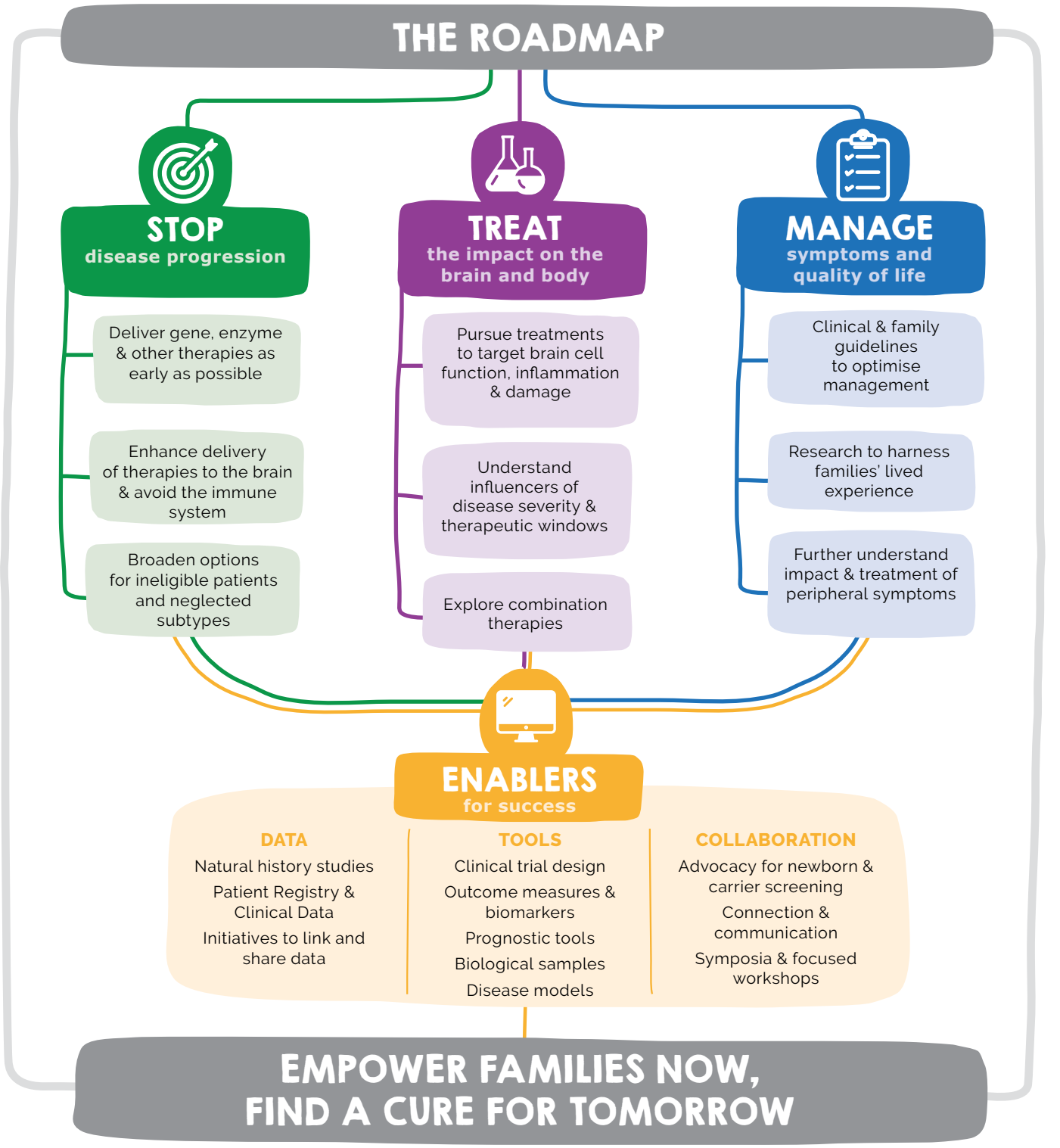
The symptoms of Sanfilippo include hyperactivity, disordered sleep, loss of speech, cognitive decline and other body symptoms. In some individuals the condition takes an attenuated form with slower progression. All forms of Sanfilippo take an immeasurable toll on the whole family.

While significant advances have been made in Sanfilippo research and clinical trials initiated, progress could be accelerated through a focussed, coordinated and collaborative approach.

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.

Front cover: Alec from Australia

The Roadmap has three interconnected pillars, underpinned by a set of enabling initiatives that support and connect multiple aspects of laboratory and clinical research.



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.

Oliver and his mum from USA

Approaches currently underway to target the lack of active enzyme include:

- **Genetic Therapies** – introduce a healthy copy of the gene, or repair the affected gene, so that enzyme is produced
- **Gene-modified Cell Therapy** – introduce cells that can produce the missing enzyme
- **Enzyme Replacement Therapy** – deliver the missing enzyme
- **Pharmacological Chaperone Therapies** – stabilise & enhance the activity of existing mutant enzyme
- **Nonsense read-through drugs** – to overcome a certain type of DNA change and allow enzyme to be produced (approx. 10% of Sanfilippo patients)

Key gaps & hurdles to address:

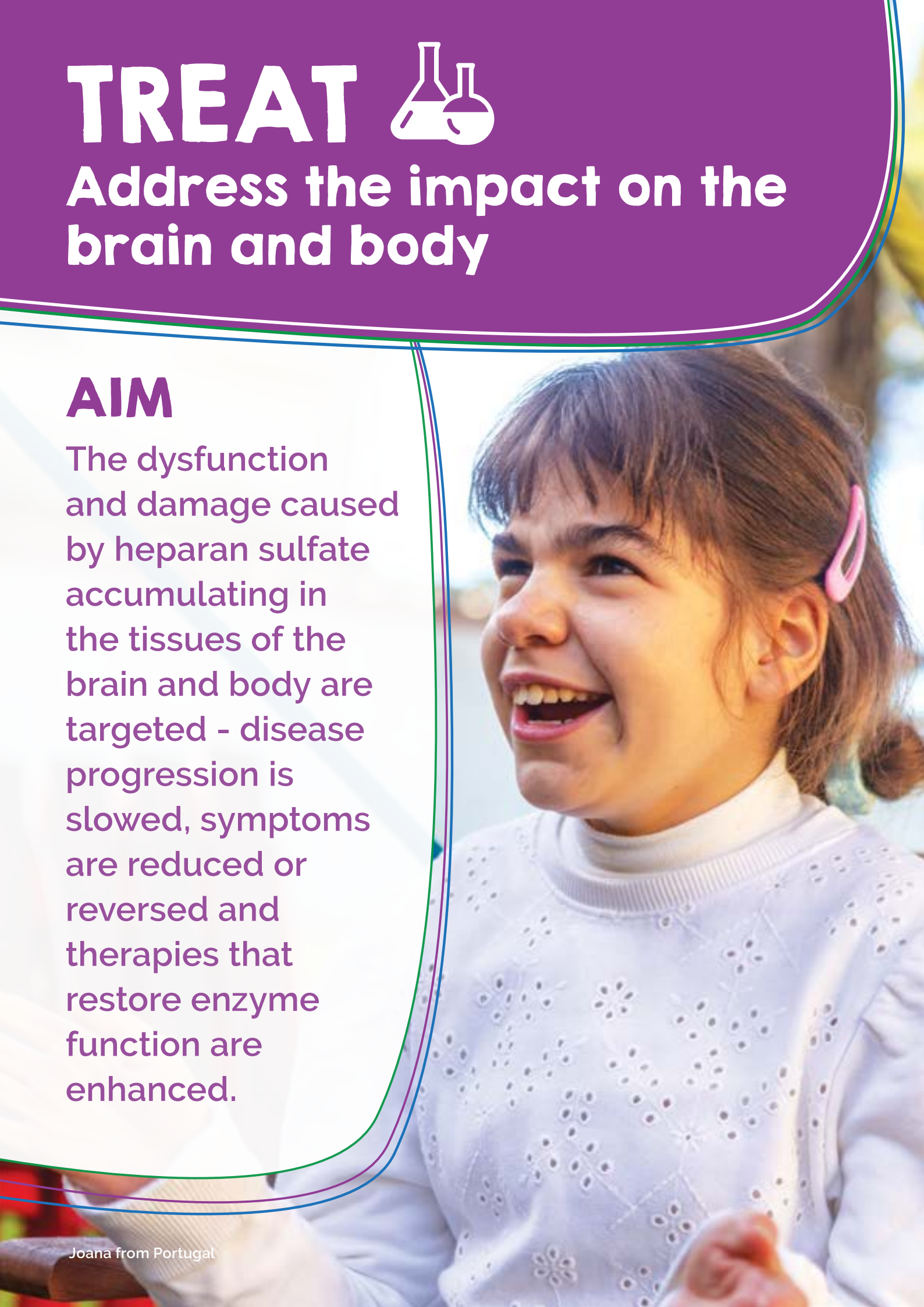
1. **Early treatment is vital** – implementation of newborn screening is needed
2. **Getting enough therapy safely into the brain** and overcoming the blood brain barrier
3. **Developing strategies** to avoid the adverse immune reactions that can compromise treatment efficacy
4. **Enhance therapies & expand treatment windows** – determine whether combination and adjunct therapies can address advanced disease and secondary impacts on the brain and body
5. **Address symptoms and complications beyond cognitive development** through deeper exploration of potential therapies
6. **Develop options for patients who are currently ineligible for clinical trials**
7. **Increase focus on treatments for neglected subtypes** (C, D & attenuated forms of all subtypes)
8. **Overcome challenges for clinical trials** including further availability of natural history data, outcome measures & biomarkers to support clinical trial design for all stages and subtypes

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.



Joana from Portugal

Treatment targets that are currently being investigated & require further exploration include:

- **Neuronal/synaptic dysfunction** (brain cells and their connections)
- **Disruption of neurodevelopment** (early development of the brain)
- **Failure of autophagy** (enhancing waste disposal to clear accumulated debris)
- **Inflammation** (how does inflammation contribute to symptoms and tissue damage)
- **Accumulation of other materials that damage tissues** (lipids and protein aggregates)
- **Mitochondrial dysfunction** (abnormalities in the energy production of cells)
- **Cell regeneration** (methods to restore damaged cells and tissues)
- **Substrate reduction** (reducing the amount of heparan sulfate that is made)

Key gaps & hurdles to address:

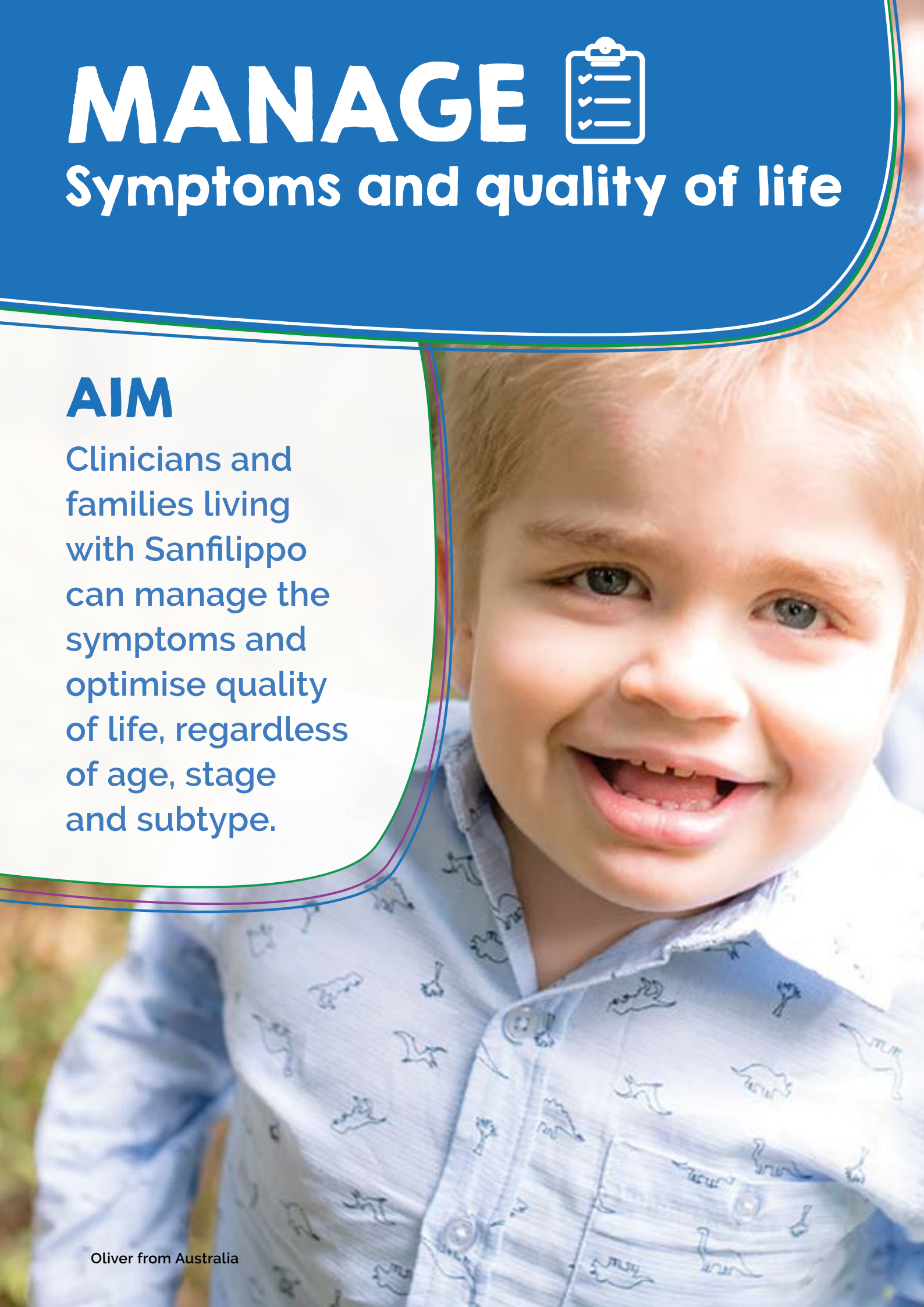
1. **Understanding the therapeutic window(s)** – acknowledging that very early treatment to target the root cause is most likely to achieve the best outcomes in terms of cognitive development, is there still an opportunity to improve quality of life or slow progression at any stage of disease or in attenuated disease, by targeting these mechanisms at the right time?
2. **Explore how patients' symptoms and quality of life can be improved by all therapy avenues** even when the CNS is not the direct target, noting that one body system does not exist in isolation of the others.
3. **Using 'omics approaches to explore disease biology** to understand other genes and factors that influence disease severity (disease modifiers), identify other pathways and drug targets to slow disease progression, and identify biomarkers
4. **Develop innovative collaboration and funding models to accelerate potential therapies into clinical trials,** allowing us to build on the strong progress that has been made in understanding the disease and support further therapies through the challenging preclinical research phase.

MANAGE

Symptoms and 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.



Oliver from Australia

Symptoms that have been identified as a priority by families and clinicians include:

- **Pain & distress**
- **Communication challenges / loss of speech**
- **Behaviours (hyperactivity / impulsivity / safety)**
- **Sleep problems**
- **Loss of mobility**
- **Eating & nutrition**
- **Gastrointestinal symptoms**

Key gaps & hurdles to address:

1. **Focus research to understand the causes of these prioritised symptoms** and develop treatments
2. **Harness the wealth of families' lived experience and clinical experience** through collaborative research to optimise symptom management and psychosocial support
3. **Empower doctors to follow best practice and empower families as advocates** for optimal disease management
   - Develop & disseminate clinical guidelines
   - Develop family-friendly clinical guidelines
4. **Further explore the impact of the disease on the body** (e.g. lungs, bones/joints, heart, retina, nutrition, and gut) and how this might affect both peripheral and neurological symptoms and quality of life and identify treatments.

ENABLERS

DATA

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

- **Consolidate natural history study data** and expand collection for rare and attenuated subtypes
- **Clinical data** – formalise and expand collection & link to biosamples and other data
- **Patient registry** – data contributed by patients and families & linked to clinical data and samples, with communication & feedback to families on uses and outcomes
- **Central, independent infrastructure for data sharing** & data-linkage to pool, connect and share all sources of data

TOOLS

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

- **Advocate for newborn screening** for Sanfilippo and related diseases
- **Develop prognostic tools** to predict disease course – important for clinical trials and particularly once newborn screening is introduced
- **Disease models** – expand and share a pool of clinically relevant animal and human cell models, including reporter systems to label cells and cell structures, to enhance discovery and drug testing
- **Biosamples** – network of biorepositories of patients biospecimens
- **Clinical trial design** innovation for:
  - combination therapies
  - patients with attenuated disease
  - patients previously treated in clinical trials
  - patients with advanced disease
- **Outcome measures and biomarkers** – discover and validate further outcome measures that detect change faster with lower burden on trial participants, including cognitive & behavioural testing, smart technology, imaging, eye, ear and fluid biomarkers, and fit-for-purpose caregiver/clinician reported outcomes
- **Innovative funding models for clinical trials** which are of low commercial interest (such as combination therapies)

COLLABORATION

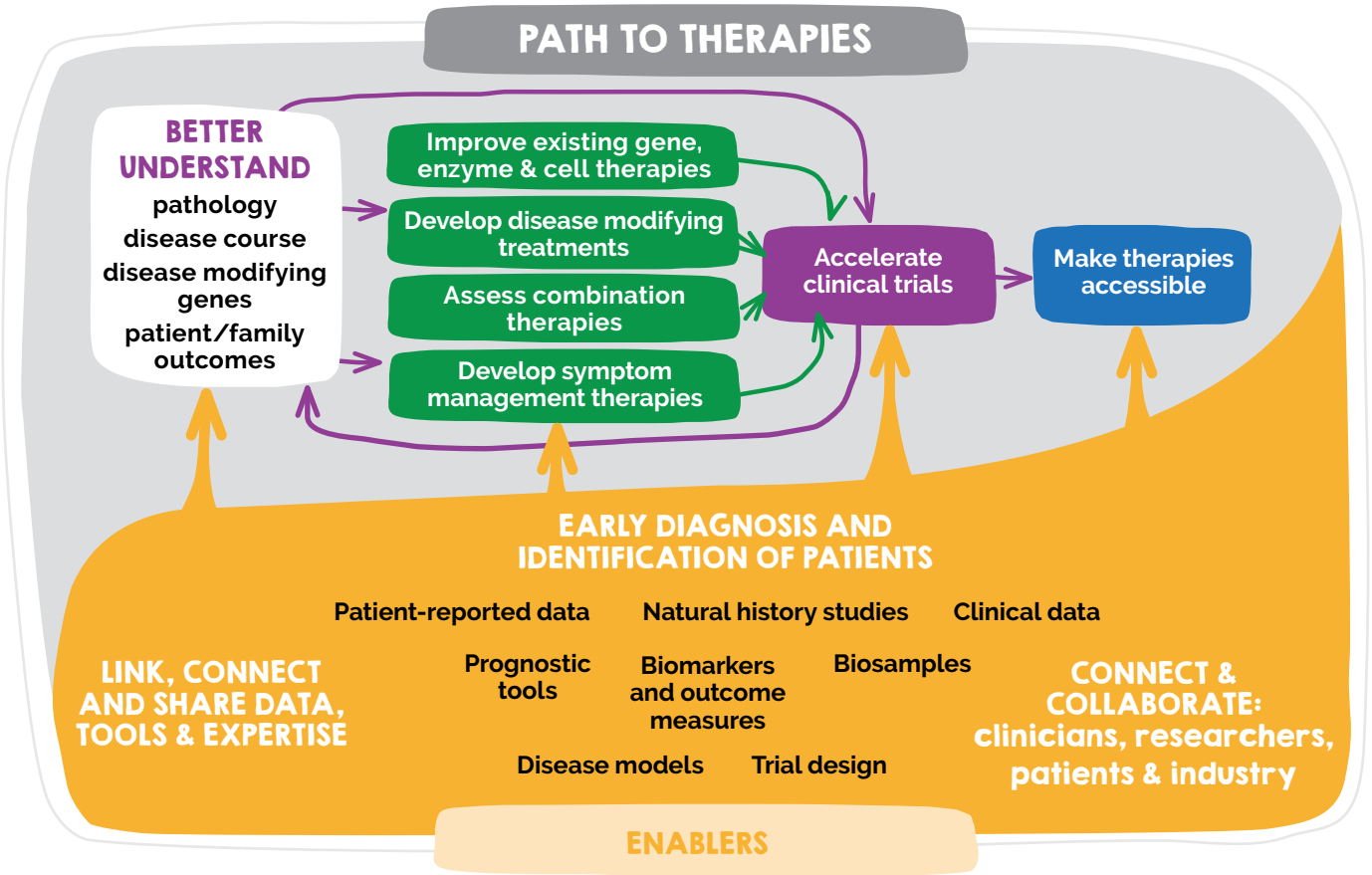
To connect clinicians, researchers, industry and families and ensure clinical and laboratory research are informed by each other and by families; and the data, tools, resources and expertise are shared

For the Sanfilippo Research Community

- **Platforms, networks and consortia** to facilitate collaboration and sharing between industry, researchers, clinicians and families around tools, data & expertise (clinical trial design, preclinical research, data, disease models, biosamples)
- **Symposia** to enhance information sharing and collaboration with all stakeholders

With the wider rare disease community to address our common challenges

- **Advocacy for newborn screening** for Sanfilippo and related diseases – for early detection and entry into trials
- **Advocacy to ensure regulatory & reimbursement pathways** for rare disease trials and therapies include consideration of families' preferences and needs
- **Development of platform technologies** for delivering treatments to the brain
- **Advocacy for equitable access to genetic carrier testing** so that every person who chooses to, may be informed of their risks of passing on serious/fatal childhood diseases



Sanfilippo Children's Foundation

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CURE SANFILIPPO FOUNDATION

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