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ORIGINAL ARTICLE

An Australian standard of care for Niemann–Pick disease type C

Michel Tchan [1], Nicholas Smith [2,3], Heidi Peters [4], Ellie Van Velsen [5], Catherine Marraffa [6], Carolyn Ellaway [7,8], Katrina Cruz [9], Shekeeb S. Mohammad [10], Maina Kava [11,12], Joy Yaplito-Lee [13], Shanti Balasubramaniam [7], Yusof Rahman [1], Brendon Boot [14], Ashley Bush [15,16], Felicity Munro [17], Leniza Hamoy [4], Ya Hui Hung [16], Philippa Johnston [5], Deanna Carpino [5], Molly Williams [18], Sharmila Kiss [4], Rebecca Quin [4], Ingrid Sutherland [19] and Mark Walterfang [20]

[1]Genetic Medicine, Westmead Hospital, [7]Genetic Metabolic Disorders Service, Sydney Children's Hospital Network, [8]Sydney Medical School, and [10]Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, and [14]Skin2Neuron Pty Ltd, Sydney, New South Wales, [2]Discipline of Paediatrics, University of Adelaide, Women's and Children's Hospital, and [3]Department of Neurology and Clinical Neurophysiology, Women's and Children's Health Network, Adelaide, South Australia, [4]Metabolic Medicine, [13]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, and [18]Victorian Paediatric Palliative Care Program, The Royal Children's Hospital, Departments of [6]Developmental Medicine, and [19]Neurodevelopment and Disability, The Royal Children's Hospital Melbourne, [9]Speech Pathology, NeuroRehab Allied Health Network, [15]Melbourne Dementia Research Centre, University of Melbourne, [16]The Florey Institute of Neuroscience and Mental Health, and [20]Neuropsychiatry Centre, Royal Melbourne Hospital, Melbourne, [5]Australian NPC Disease Foundation Inc., Benalla, [17]Exercise Physiology, Flexout Health, Wangaratta, Victoria, and [11]Department of Neurology and Metabolic Medicine, Perth Children's Hospital, and [12]School of Paediatrics and Child Health, Medical School, University of Western Australia, Perth, Western Australia, Australia

Key words
Niemann–Pick disease type C, delivery of healthcare, patient care team, standard of care, clinical decision-making.

Correspondence
Ellie Van Velsen, Australian NPC Disease Foundation Inc., 3 Waller Street, Benalla, Vic. 3672, Australia.
Email: projects@npcd.org.au

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Abstract

Background: Niemann–Pick disease type C (NP-C) is the fifth most prevalent lysosomal disorder in Australia. Diagnostic delay is common, impacted by disease heterogeneity, limited awareness within clinical gateway services and exclusion from state-based newborn screening programmes. A formal diagnosis, once established, places a substantial burden on the whole family, the negative impact of which is far-reaching. A clear understanding of diagnostic pathways and management objectives in NP-C is critical for optimal care.
Aims: To develop an Australian standard of care for individuals diagnosed with NP-C and their families, reflecting international best practice and tailored to the Australian healthcare system.
Methods: The Australian NPC Disease Foundation Inc. convened a national, multidisciplinary collaboration including NP-C treating clinicians, allied health professionals and a community advisory group. Using an iterative consensus approach, published international guidance statements were reviewed, ratified, excluded or modified to align with the Australian context.
Results: Consensus outputs included a diagnostic algorithm, a multidisciplinary care framework and management-centred management statements. The collaborative process resulted in a unified Australian standard of care for NP-C. This framework incorporates the carer perspective, emphasises shared decision-making and situates NP-C within the broader context of 'childhood dementias.' Consensus statements provide practical, evidence-aligned guidance on early recognition, diagnostic referral pathways and multidisciplinary management throughout disease progression.
Conclusions: This initiative represents the first Australia-specific standard of care for NP-C. It is hoped that adoption of the framework will lead to improved experiences for Australians living with NP-C and their carers as they navigate the healthcare setting.

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Introduction

Lysosomal disorders are rare, progressive diseases that arise from inherited deficiencies in enzymes and adjunct proteins complicit in the lysosomal catabolism of macromolecules. Niemann–Pick disease type C (NP-C) is the fifth most prevalent lysosomal disorder in Australia (1 in 112 000 live births).[1] In the absence of a national register, the number of current diagnosed cases in Australia is estimated by clinical services as between 25 and 33, although this is widely considered an underestimate, with many cases likely undetermined or in some cases misdiagnosed. This highly heterogeneous, autosomal recessive, neurodegenerative disorder arises from biallelic variants in either the *NPC1* (95% of cases) or *NPC2* genes.[2] Due to the implicated gene, NP-C is further classified as type C1 (NP-C1) or type C2 (NP-C2). The resulting loss of function of NPC1 and/or NPC2 proteins impairs lipid trafficking, resulting in the intracellular accumulation of cholesterol and related lipids with consequent cellular and organ damage.[3] Clinical presentations are dominated by neurocognitive regression across a heterogeneous spectrum of disease onset and severity, and cases of childhood onset are best explained under the umbrella of '*childhood dementias*'.[4] Diagnostic delay in NP-C is common,[1]; in part reflecting the protean and often undifferentiated clinical features of the disease, and impacted by a lack of awareness within clinical gateway services[5] and current exclusion from state-based newborn screening programmes.[6]

Effective and optimal patient outcomes necessitate access to specialist multidisciplinary team (MDT) care, placing considerable societal, administrative and financial burden on the individual diagnosed with NP-C, their family and carers.[7] A clear understanding of the diagnostic pathways and management objectives in NP-C is critical in supporting clinician and health services and empowers individuals with NP-C and their families in their pursuit of best practice management, across all stages of their disease.

In response to community request, the Australian NPC Disease Foundation Inc. (ANPDF) initiated a nationwide consensus project to define an Australian standard of care for NP-C. Building on international guidelines,[8] this document aims to provide Australian-specific guidance to improve identification, diagnosis and management, and to improve patient and carer experience through more timely diagnosis and coordinated management.

Materials and methods

This project was funded entirely by the ANPDF through community charitable donations. An ANPDF-appointed project coordinator established three core groups of collaborators – a lead team (four NP-C treating clinicians and three ANPDF committee members), a medical advisory group (30 clinicians/allied health professionals experienced in the management and care of patients with NP-C across the lifespan) and a community advisory group (six parents of patients). The project coordinator extracted 39 guidance statements from the 2018 international guideline[8] into a series of five online surveys. Between July and November 2024 these surveys were sent electronically to all collaborators, inviting them to indicate the level to which they agreed with the guidance statements, provide commentary to support their responses and raise comments if they felt that areas were missing. Voting responses (strongly agree, agree, neutral, disagree, strongly disagree, not my area of expertise) and feedback were collated. Clinicians in the lead team presented the survey responses to the medical advisory group and the project coordinator presented them to the community advisory group over the course of five virtual meetings (August–December 2024). Attendees provided further feedback, and, within the scope of their respective areas of expertise, discussed current management practices and experiences. The aim of each meeting was to determine the ongoing utility of 2018 guidance statements within the Australian context. After each meeting, updated or adapted statements, tables and figures were produced, drawing on contemporary published literature, clinical acumen and affected families' lived experiences. In a final online meeting, the lead team reviewed and discussed each of the revised statements to ensure clinical relevancy to the Australian healthcare environment. As this work draws on clinical acumen and published literature, ethics approval was not sought.

Results

Through this extensive, iterative review process, the original 39 guidance statements were ratified, excluded or amended, as appropriate to the Australian healthcare setting. Consensus was reached on 22 revised statements (Table 1), a diagnostic algorithm (Fig. 1) and an MDT framework (Fig. 2). Changes from existing diagnostic algorithms[8,9] included the removal of references to the filipin test, which is no longer the diagnostic assay of choice, and addition of a simplified pathway for individuals with a known family history of NP-C.

Discussion

Clinical presentation: heterogeneity and overlap in clinical characteristics

NP-C is characterised by a wide spectrum of phenotypes with varying degrees of systemic and neurological involvement (Fig. 3).[8,10,11] While there is no consensus on

Table 1 NP-C: standard-of-care guidance statements

Domain	Guidance statement
Clinical suspicion and differential diagnosis	In the first 2 years of life, history of prolonged neonatal jaundice, hepatosplenomegaly and/or developmental delay should raise the possibility of NP-C.
	From childhood to adolescence, neurological disease manifestations can be subtle and progressive. NP-C should be considered in the appropriate clinical context, taking into account other age-appropriate neurodegenerative disorders (see Fig. 3).
	Adults presenting with an atypical psychotic disorder or a progressive neurological syndrome before age 40[9] should be tested for NP-C.
	Objective evaluation of eye movements may assist with a differential diagnosis of NP-C in patients with degenerative ataxia with no clear aetiological background (see Table 3).
	Brain MRI mostly shows nonspecific abnormalities.[79] MRI can be used for differential diagnosis, but should not be a primary diagnostic modality.
Confirming the diagnosis	Assessment of biomarkers should be considered as a first-line test to screen for NP-C. Further confirmatory molecular genetic testing is necessary to establish a definitive diagnosis of NP-C (see Fig. 1).
	When a diagnosis of NP-C is suspected, refer to a metabolic geneticist/neurologist, genetic counsellor and/or team experienced with NP-C.
Management principles	Individuals with NP-C should, wherever possible, be referred to a centre with expertise in the care of this condition.
	Individuals with NP-C exhibit multisystem disease manifestations. Optimal care requires multidisciplinary support encompassing clinical, disability and allied health systems (see Fig. 2).
	NP-C is a progressive condition, and individuals with NP-C require ongoing follow-up (see Table 4).
	The individual with NP-C and/or their carer should be recognised as integral members of the health team (see Fig. 2):
	Carers, including parents or guardians, play a critical role in the coordination and continuity of care.
	Treatment goals should be established at diagnosis, reviewed regularly and aimed at improving or maintaining the physical and psychosocial well-being of individuals with NP-C and their families.
	Special considerations:
	Genetic considerations:
	After an individual has been diagnosed with NP-C there is a potential for genetic implications in other family members.
	NP-C pre-symptomatic genetic testing is best managed on a case-by-case basis and risks/benefits discussed in the context of formal counselling from a suitably qualified individual.
	All individuals with NP-C identified pre-symptomatically should be referred to appropriate specialist centres for monitoring.
	Pregnancy planning:
	Reproductive options should be discussed with at-risk couples, and include the option of natural conception with prenatal testing for NP-C or IVF with PGT.
	This requires careful counselling by maternal foetal medicine specialists, clinical geneticists and NP-C specialists.
	Transition planning:
	Most children with late-infantile and juvenile-onset NP-C are expected to reach adolescence and or adulthood with complex medical and psychosocial needs.
	There is a need to establish equitable nationally agreed models and guidelines for life-stage transition programmes.
	Palliative care:
	Specialist centre care providers, general practitioner/paediatrician and specialist palliative care services should develop close working links to optimise quality of life for individuals and families with NP-C throughout the lifespan.
Symptom assessment and management	The specific supportive procedures and therapies that an individual with NP-C requires should be determined based on their current needs in collaboration with the core medical team.
	Assessment and management, when clinically indicated, should encompass all potential areas of disease impact (see Table 4):
	Interval medical history and physical examination
	Neurologic symptoms
	Mobility – a structured and personalised rehabilitation programme may prolong mobility and transfer ability
	Spasticity
	Development/cognitive function
	Nutrition and feeding/swallowing – instruction in dietary modification and compensatory postures may be beneficial for individuals with dysphagia
	Respiratory function
	Speech, language and communication
	Hearing

Table 1 *Continued*

Domain	Guidance statement
	Neurogenic bladder dysfunction
	Sleep hygiene
	Mental health
	Emotional and social well-being
	Carer support needs
Disease-modifying and other future therapies	Clinicians should discuss access to and eligibility for therapies in all individuals diagnosed with NP-C (see Table 5).
	Evidence-based start/stop criteria should be used to guide appropriateness of treatment in NP-C.
	Future treatments:
	Clinicians should be aware of future clinical therapies and emerging health technologies.
	Clinicians should discuss potential treatment eligibility and access with individuals with NP-C.
	Clinical trials:
	For many individuals with NP-C, participation in a clinical trial may be the only way to access disease-modifying treatment.
	Clinicians should be aware of available clinical trial options and discuss and refer for participation where appropriate.

IVF, *in vitro* fertilisation; MRI, magnetic resonance imaging; Niemann–Pick disease type C; PGT, pre-implantation genetic testing.

clinical diagnostic criteria, an accurate history and clinical examination should be undertaken to elicit clinical symptoms and signs. Clinical findings are typically grouped by age of onset, but there can be considerable overlap between groups representing a clinical continuum.[2]

Perinatal: manifests primarily as liver disease presenting with fetal ascites/hydrops, prolonged cholestatic jaundice, hepatosplenomegaly and in some cases acute liver failure, with or without pulmonary disease.
Early infantile (<2 years): neurological manifestations include hypotonia and developmental delay in motor milestones. Hepatosplenomegaly and/or prolonged jaundice are almost invariably noted.
Late infantile (2 to <6 years): a history of neonatal cholestasis may be the earliest presentation. Vertical supranuclear saccade palsy (VSSP) or vertical supranuclear gaze palsy (VSGP) is typically present but is often unrecognised. The first symptoms may be gelastic cataplexy (sometimes associated with narcolepsy) or sensory deafness. Speech and language difficulties, fine motor impairments, clumsiness (motor incoordination) and gait disturbance are usually present. Epilepsy may evolve as the disease progresses. Visceromegaly can be noted but is not present in all cases.
Juvenile (6–15 years): manifests with cognitive impairment (lagging behind peers in school, language and learning difficulties), childhood dementia with a loss of previously acquired skills, psychiatric problems (aggression, new- onset behavioural changes), coordination problems (clumsiness, frequent falls, progressive ataxia and dystonia) and seizures. VSGP is almost invariably present and may present before other symptoms.
Adolescent/adult (>15 years): cognitive impairment (early-onset dementia) invariably occurs and tends to present with higher rates of psychiatric illness co-existing with or often preceding neurological manifestations (particularly ataxia, coordination problems and clumsiness). Diagnostic delay is common but is minimised if the characteristic VSGP is identified.

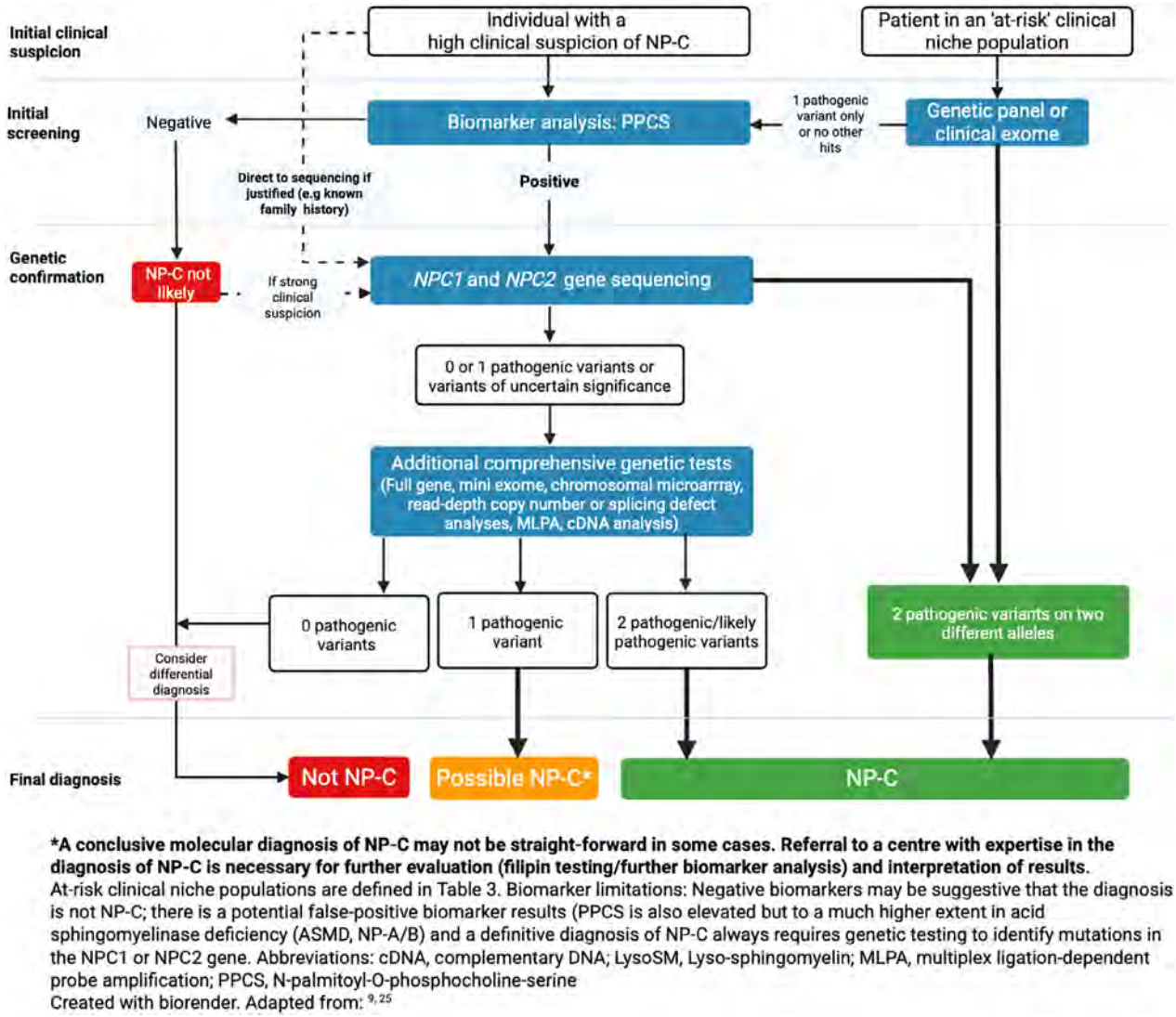
International registry experience reports that late infantile onset is the most common (26.4%), followed by early infantile (24.2%), juvenile (23.0%) and adult (20.8%), with perinatal (5.6%) the least common presentation.[12] Recent data suggest that adolescent/adult-onset NP-C may account for up to 50% of all NP-C diagnoses within the Australian population (Personal communication, M Fuller 2025).

Practical implications: The ANPDF website (https://www.npcd.org.au) provides individuals and families concerned about NP-C with accessible information, practical support and connection with the broader support community.

Differential diagnosis: what signs and symptoms raise clinical suspicion of NP-C?

Given its rarity and broad phenotype, NP-C may be overlooked and requires a high index of suspicion. Core age-related clinical signs and symptoms (Table 2) should prompt initial clinical suspicion.[2] Clinical at-risk groups and red-flag features (Table 3)[9] include visceromegaly and prolonged neonatal jaundice in neonates,[13] childhood dementia,[14] developmental delay and hypotonia in infants[13] and VSSP/VSGP at any age. Failure to reach expected developmental milestones may present as the first opportunity to assess neurological abnormality.

Practical implications: The challenges in identifying rare diseases highlight the need for awareness and education across all healthcare providers, including primary care



***A conclusive molecular diagnosis of NP-C may not be straight-forward in some cases. Referral to a centre with expertise in the diagnosis of NP-C is necessary for further evaluation (filipin testing/further biomarker analysis) and interpretation of results.**
At-risk clinical niche populations are defined in Table 3. Biomarker limitations: Negative biomarkers may be suggestive that the diagnosis is not NP-C; there is a potential false-positive biomarker results (PPCS is also elevated but to a much higher extent in acid sphingomyelinase deficiency (ASMD, NP-A/B) and a definitive diagnosis of NP-C always requires genetic testing to identify mutations in the NPC1 or NPC2 gene. Abbreviations: cDNA, complementary DNA; LysoSM, Lyso-sphingomyelin; MLPA, multiplex ligation-dependent probe amplification; PPCS, N-palmitoyl-O-phosphocholine-serine
Created with biorender. Adapted from: [9,25]

Figure 1 N-PC: diagnostic algorithm. NPC, Niemann–Pick disease type C

(general practitioners, general paediatricians).[15] The Rare Awareness Rare Education (RARE) Portal is a national resource centre providing rare disease education, information, resources, services and support for healthcare providers (https://www.rareportal.org.au).

Confirming the diagnosis: is it really NP-C?

In the absence of a single definitive test for NP-C, diagnosis requires a combination of biochemical and molecular genetic testing techniques.[16] A high index of suspicion of NP-C should prompt referral for biomarker assessment and genetic testing to confirm the diagnosis. A direct pathway to genetic testing should be considered in individuals with a known family history of NP-C and in those individuals who fall into one of the identified clinical 'at-risk' niche populations (Table 3).

Biomarker assessment

The threshold for referral for biochemical testing should be low in neonates/infants presenting with visceromegaly or long-lasting cholestatic jaundice and in individuals of any age with VSSP, ataxia, dystonia, frontotemporal dementia and untreatable schizophrenia or psychosis.[2,9]

Blood-based biomarkers have replaced filipin staining.[17] Biomarkers with high sensitivity for identifying NP-C

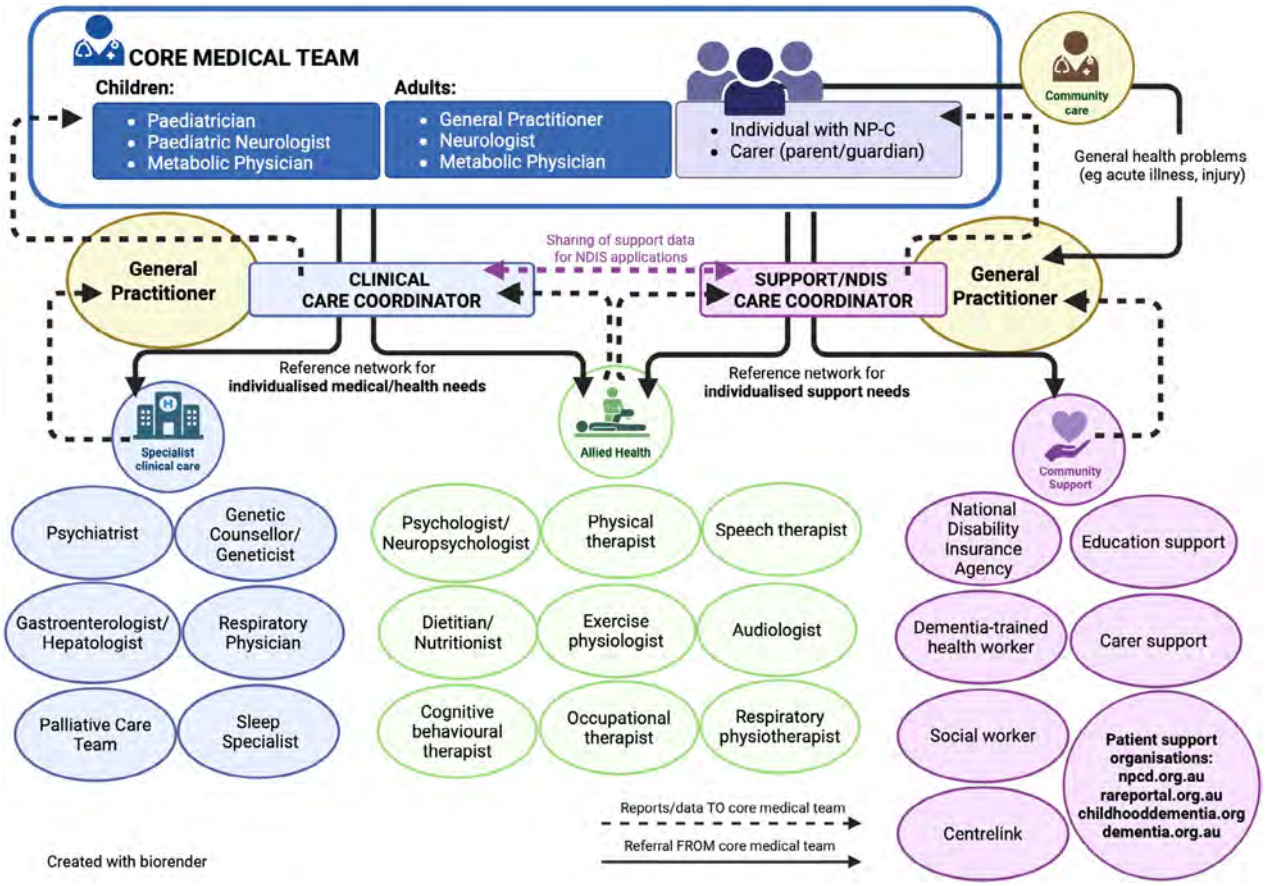


Figure 2 NP-C: multidisciplinary team referral and information-sharing framework. NP-C, Niemann–Pick disease type C.

include oxysterols, bile acids, lysosphingomyelin (Lyso-SM), and N-palmitoyl-O-phosphocholineserine (PPCS, previously called lysoSM-509).[3,17–20] PPCS-based assays now offer 100% sensitivity, 96.6% specificity in identifying NP-C1 cases from controls and NP-C1 carriers.[21] Combined testing of lysoSM and PPCS may aid in discriminating between ASMD and NP-C.[22]

Correlation of PPCS levels with age at diagnosis (higher in patients <5 years old) and type of NP-C1 variant (higher in loss of function variants and visceral phenotypes) suggests that it may also have utility as an indicator of disease severity.[23]

Practical implications: Within Australia, PPCS has replaced oxysterol as the biomarker for NP-C testing. This test is not Medicare-funded. Clinicians seeking advice and/or referral for biomarker testing should consult with a specialist experienced in the diagnosis of NP-C. More information on PPCS testing requirements is available from the National Referral Laboratory, a nationally recognised centre of excellence for diagnostic testing of lysosomal storage disorders (National Referral Laboratory and Metabolic Laboratory, SA Pathology Women's and Children's Hospital Adelaide; https://www.sapathology.sa.gov.au).

Molecular characterisation of NP-C

Any individual suspected of having NP-C based on their clinical manifestation and/or biomarker profile should undergo molecular genetic testing (Fig. 1).

Historically, genomic testing involving *NPC1* and *NPC2* sequencing has been the most commonly used method to confirm a diagnosis of NP-C.[24] However interpretation of novel variants of unknown significance can be a challenge and may require additional comprehensive genetic tests (e.g. cDNA analysis, multiplex ligation-dependent probe amplification, chromosomal microarrray).[25] Interpretation, assessment and classification of the risk of pathogenicity of identified variants should be undertaken following established guidelines.[26,27] If one pathogenic variant is identified, further analysis is needed to determine whether a second variant is present and whether it is also disease-causing.

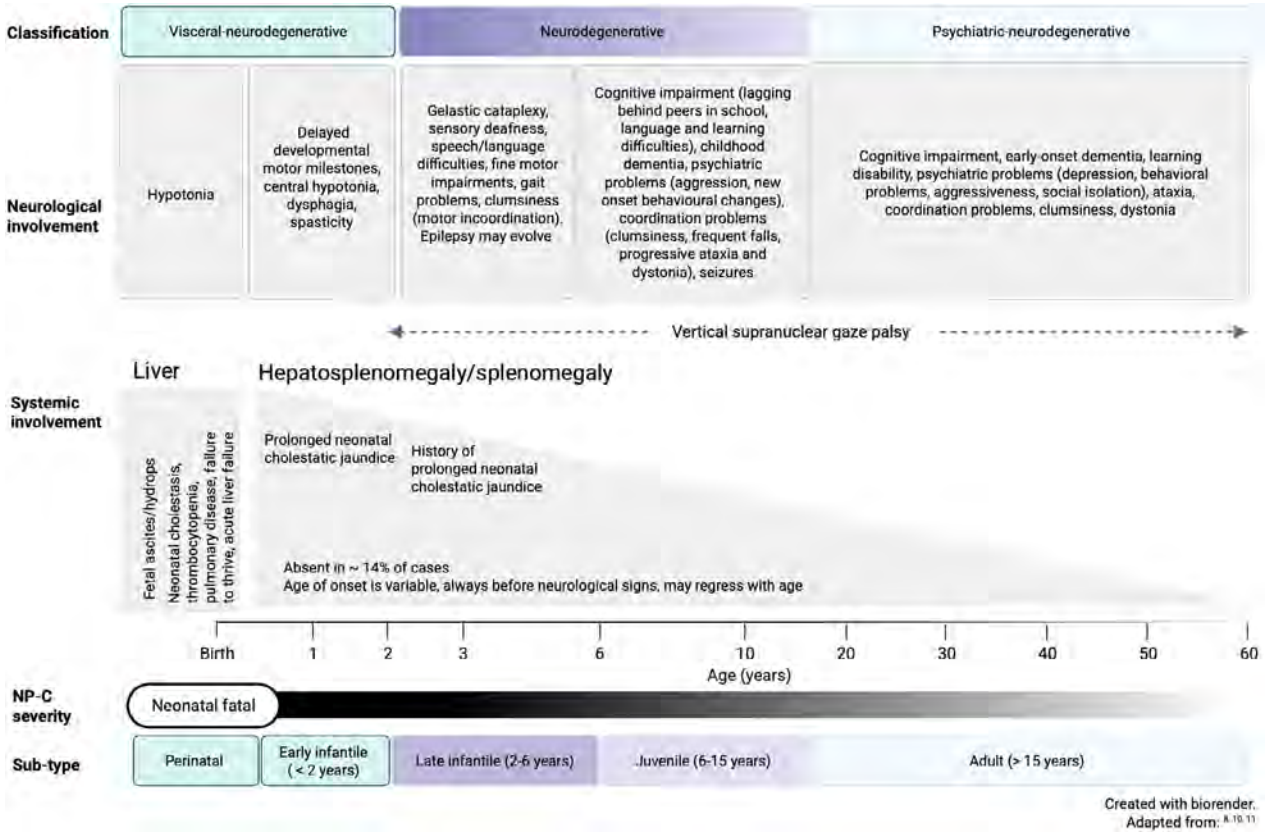


Figure 3 NP-C: spectrum of phenotypic variation. NP-C, Niemann–Pick disease type C.

Table 2 Select signs and symptoms of age-related NP-C phenotypes

	Early infantile (<2 years)	Late infantile (2 to <6 years)	Juvenile (6–15 years)	Adolescent/ adult (>15 years)
Prolonged cholestatic jaundice	P	P		
Hepatomegaly	P			
Splenomegaly	P	P	P	[P]
Ataxia		P	P	P
Epilepsy		P	P	[P]
Cataplexy		[P]	P	P
Dementia			[P]	P
Psychiatric				P
Dystonia		[P]	P	P
VSSP		P	P	P

Adapted from Patterson.[2] NP-C, Niemann–Pick disease type C; [P], sometimes present; P, usually present; VSSP, vertical supranuclear saccade palsy.

Multigene panels are becoming more accessible and cost-effective. Unlike genomic testing, the use of a gene panel requires the clinician to know what genes are likely to be involved.[2] Gene panels are more likely to be used in at-risk clinical populations with signs suggestive of increased clinical suspicion of NP-C (see Table 3). Copy number variants (CNVs) can be seen in up to 5% of cases, a rigorous process of analysis and validation (e.g. mini exome and read-depth based CNV analyses) should be considered in cases with a single allele or negative sequencing.[28] When gene panel tests are used, they should be symptom-specific and must include the *NPC1* and *NPC2* genes.

Newborn screening has the potential to enable earlier diagnosis prior to the onset of neurological symptoms. NP-C is not currently included in the Australian newborn screening programmes.[6]

Practical implications: NP-C diagnosis is conclusively established when two copies of pathogenic or likely pathogenic variants in either the *NPC1* or *NPC2* gene are identified, and these variants are located on separate alleles.

Management principles

Coordinated approach to patient care

Following the diagnosis of NP-C, comprehensive evaluations should be undertaken to establish disease

Table 3 Clinical red flags: what to look for in patient groups with an increased risk of NP-C

Clinical group	Signs suggestive of increased clinical suspicion of NP-C	
Ataxia	Early onset <40 years of age Without neuropathy Of unknown aetiology	Plus any of the following: VSSP Dystonia Cognitive decline Atypical psychiatric disturbances Extensor plantar reflexes Intellectual impairment Myoclonus
Intellectual disability and developmental delay	Hepatosplenomegaly Splenomegaly	Plus any of the following: VSSP Dystonia Ataxia
Cognitive impairment and early-onset cognitive decline	Early onset <40 years of age	Plus any of the following: VSSP Dystonia Ataxia
Dystonia (generalised or multifocal)	Early onset <40 years of age	Plus any of the following: VSSP Cognitive decline Psychiatric disturbances
Frontotemporal dementia	Early onset <40 years of age	
Atypical schizophrenia/ early-onset psychosis	Resistance to treatment Neurologic signs (ataxia, dystonia, VSSP) Visual hallucinations, comorbid cognitive impairment	
Visceral symptoms (paediatric patients)	Isolated infantile splenomegaly, cholestasis or hepatosplenomegaly Fetal/neonatal ascites and neurological signs (ataxia, VSSP, dystonia)	

Adapted from Patterson *et al.*[9] NP-C, Niemann–Pick disease type C; VSSP, vertical supranuclear saccade palsy.

severity, determine clinical and support needs and help develop individual treatment plans.[2] NP-C is multisystemic; therefore, an MDT approach (Fig. 2) is recommended.[8] The use of MDTs has been demonstrated to improve outcomes in patients with complex disease; they may be of benefit across the patient journey (diagnosis, management, transition care, palliative care), while also helping to reduce caregiver burden.[29]

There is no current guidance on how to organise an MDT in NP-C. Depending on the age of an individual with NP-C, the core medical team should include a paediatrician (children) or a general practitioner (adults), supported by a neurologist (or paediatric neurologist) to guide the management of neurological features and a metabolic specialist. This core team is the central point of contact for the individual with NP-C and should help to facilitate continuous, two-way communication with them and their carer. Carers can provide essential insights drawn from lived experience; their knowledge of the individual's daily needs, symptom progression and response to interventions is invaluable in guiding clinical decision-making. Members of the core team should utilise reference networks to identify and communicate with a wider group of practitioners.

In Australia, children with rare diseases can have up to 15 different healthcare professionals in their MDT, but only one in five have access to a healthcare professional to help coordinate their care.[7] Barriers to access are significantly increased among children living outside major metropolitan cities, and there has been a call for the establishment of, and improved equity of access to, coordinated care models for rare diseases.[7,30–32] The burden of care coordination places significant strain on the carer.

Disease-specific patient care is primarily conducted within the tertiary setting, with allied health, disability support services and general medical care occurring in a variety of external settings. Where possible, tertiary care centres should strive to develop models of care with a central coordinator, such as a clinical nurse consultant with rare disease experience/training, to provide an accessible point of contact for the individual with NP-C and their carer, to facilitate scheduling of appointments and to ensure feedback to the core team. Where this is not practical, such as in remote and rural settings, this care coordination role should be undertaken by a paediatrician/general practitioner. In such a model, ongoing care could be achieved locally and supplemented with access to the core medical team via the use of telehealth. Coordination of community services via the National Disability Insurance Agency (NDIA) provides crucial support for families and should be integrated early in the management plan. Similarly, this should be undertaken with the support of a dedicated coordinator and/or the paediatrician/general practitioner.

An overarching aim of the MDT approach is to ensure efficient use of resources and consistency of medical advice.[29] Ideally, the MDT should establish a tailored schedule for assessments and monitoring based on the needs of the individual with NP-C. To further relieve

the burden on the family caregiver, consideration should be given to developing systems and infrastructure to support timely sharing of medical information between the different healthcare practitioners in the care plan and between community services.

Practical implications: Clear, two-way communication is the most important aspect of an MDT – this includes 'external' communication with the patient/family members and 'internal' communication among healthcare team members. The MDT should strive to provide individuals with NP-C and their carers with a single treatment plan that accounts for regular assessments, examinations and medications. Ideally the MDT should centre around an integrated care coordinated model.

Guidance on accessing NDIS funding

Funding support via the National Disability Insurance Scheme (NDIS) is based on individual needs and the extent to which a condition affects daily life activities, not the diagnosis of NP-C. The key eligibility criteria are the ability to provide strong evidence that NP-C is having a permanent functional impact on activities of daily living, including but not limited to moving, communicating, learning and self-care. Supporting evidence from all members of the MDT should confirm the permanent nature of the impairment(s) and provide suggestions of the types of supports that would be of benefit. For younger individuals seeking access via early intervention requirements, emphasis should be placed on how early, ongoing interventional support will help prevent deterioration. Because NP-C is a progressive condition, needs will change over time, requiring ongoing collation of supporting documents to justify requests for additional funding or service changes.

Practical implications: Members of the MDT should be cognisant of the requirements and eligibility criteria for accessing NDIS funding when monitoring and assessing patients (per Table 4).

Genetics and peri-conception planning

If NP-C-causing pathogenic variants have been identified in an affected individual, testing of other at-risk family members can be considered. Additionally, segregation studies of parents and carrier testing for other family members should be considered as part of family planning. At-risk couples (e.g. family history of NP-C) should be provided with information regarding reproductive genetic carrier screening of parents and family members, prenatal testing and *in vitro* fertilisation with preimplantation genetic testing.[2]

Reproductive genetic carrier screening should be offered to all couples planning a pregnancy, ideally before conception or in early pregnancy. Couples identified as being at risk of having a child with NP-C should be offered genetic counselling to explain the results, implications for the couple and their reproductive options.[33]

Transition through the care pathway

Optimal transition aims to ensure seamless provision of healthcare services in the adult setting. The process of transition from paediatric to adult services should begin early and should be supported by clear communication between the individual living with NP-C/carer, the paediatric care team and the adult care team. Suggestions to facilitate this process include information to explain the transition, systems to support the transfer of medical records and the involvement of a designated coordinator.[34]

In the rare disease setting, many challenges and barriers prevail, including costs, access, trust and limited disease-specific skills/knowledge among adult treaters.[35] Care coordination and transition readiness have emerged as priority areas. While structured, step-wise pathways have been shown to be of benefit, implementation may be constrained by funding and resources.[36]

Palliative and hospice care

Prognosis of NP-C depends on the age of onset and age of neurological symptom onset.[12,37,38] Families face uncertainty and complex decisions. Palliative care aims to improve quality of life throughout the disease course. Lack of resources, late referral and limited tools to support advanced care planning have been identified as major gaps.[39] This is confounded further by a misunderstanding of the meaning of palliative care in the context of rare disease and the need to separate it from end-of-life care.[40] These limitations cumulate in sub-optimal palliative care.[41]

It is vital that palliative care planning be broached in a time-sensitive manner and that the spectrum of changing palliative care needs across the disease trajectory is carefully communicated.[40] Its introduction too soon can be confronting to the family when they are still coming to terms with a new diagnosis. Effective palliative care communication requires the clinician to take an adaptable approach informed by carers' perspectives and accounting for context at any given time.[42]

Palliative care coordination and planning should also encompass access to hospice and respite care. Successful palliative care models for rare disease focus on patient-centric, quality-driven, collaborative frameworks,[41] alongside assessment tools to elicit individualised needs and choices.[43] Changing needs and requirements should be captured in updated plans, with timely reassessments taking place to ensure ongoing equity of access.

Practical implications: There are no nationally formulated rare diseases transition care or palliative care

Table 4 Multisystemic assessment, monitoring and management of patients with NP-C

Area of disease impact	Who conducts the assessment and why	Management strategies
Interval medical history and physical examination *Every 3–6 months* *(May need more frequent review soon after diagnosis for holistic support and care co-ordination)*	Core medical team: • Establish rate of disease progression • Document growth parameters (infants/children) • Assess neurologic features • Assess organomegaly • Document disease progression (using five-domain NPCCSS) • If treated – document response to therapy (compliance, efficacy, adverse events)	Disease-modifying therapy Clinical trial participation
Neurologic symptoms *Every 6 months*	Neurologist: • Assess and manage cataplexy and seizures • Assess and manage ataxia • Document progression of saccadic eye movement impairment, presence of gaze palsy • Conduct neuroimaging studies (MRI, MRS) as indicated	Cataplexy and seizures are common manifestations of NP-C, early recognition and prompt management is important Epilepsy should be treated by a neurologist aware of the disease
Mobility *Every 6–12 months*	Physical therapist suitably qualified in complex chronic disease or neurological disease care: • Assess and manage mobility, balance, core stability, trunk control, foot posture, muscle tone and strength	Proactive strategies to maintain optimal mobility and reduce falls: • Appropriate walking/mobility aids • Ankle-foot orthotics • Exercise programmes
Spasticity *Every 6–12 months*	Physical therapist or occupational therapist suitably qualified in complex chronic disease or neurological disease care: • Assess and manage spasticity and incipient or established contracture	When clinically indicated, patients should be referred to a specialist for support and treatment plan decision-making based on the most appropriate non-pharmacological and/or pharmacological strategies
Developmental/cognitive function *Initially, every 6 months* *Every 12–24 months if asymptomatic and stable*	Neuropsychologist and dementia-trained health worker: • Assess and manage childhood dementia/dementia • Document developmental milestones (children) • Monitor educational support needs (children) • Monitor cognitive abilities	Individualised strategies to ensure safety, provide support, and to maximise independence and function should be pro-actively introduced based on assessment results Appropriately tailored exercise and/or physically active movement programmes should be considered as adjunct therapy for mental health, neurological and cognitive symptoms[80]
Nutrition and feeding/swallowing *Every 6 months* *Every 12 months if asymptomatic and stable*	Speech therapist and/or dietitian, with specialist support Gastroenterologist as needed: • Assess and manage nutritional status/diet • Assess and manage swallowing in infants with hypotonia • Assess and manage dysphagia • Assess and manage aspiration risk (including videofluoroscopic assessment) • Assess and manage diet-related bowel dysfunction • Assess and manage hypersalivation	A best interests approach should be taken, and all mealtime management plans developed in consultation with the patient/family and appropriate members of the MDT[81] Hypersalivation/drooling: treat with established non-pharmacological measures, with the addition of pharmacological agents, as appropriate Bowel dysfunction: Modify diet and lifestyle in combination with appropriate medication to optimise stool consistency
Respiratory function *Initially, every 6 months* *Every 12–24 months if asymptomatic and stable*	Respiratory physiotherapist, with Respiratory specialist support as needed: • Assess and manage pulmonary infections • Provide training on airway clearance techniques	When clinically indicated, devices and/or lifestyle modification strategies should be individualised

Table 4 *Continued*

Area of disease impact	Who conducts the assessment and why	Management strategies
		Patients/carers should: • Receive education in airway clearance techniques • Be provided with simple monitoring steps to identify early symptoms of respiratory illness before progression to pneumonia (e.g. checking temperature twice daily) Patients should be vaccinated against common respiratory pathogens and receive treatment for pulmonary infections when clinically appropriate[82]
Speech, language and communication *Initially, every 6 months* *Every 12–24 months if asymptomatic and stable*	Speech therapist: • Support with swallow assessment • Assess and manage spoken communication problems • Assess and provide training/intervention for augmentative and alternative communication as appropriate	When clinically indicated, patients should be offered appropriate therapy and/or augmentative and alternative communication
Hearing *At diagnosis* *Every 12–24 months if asymptomatic and stable*	Audiologist: • Assess for and document new onset hearing loss • Assess and manage hearing loss	When clinically indicated, patients should be offered hearing devices to improve general communication
Neurogenic bladder dysfunction *Initially, every 6 months* *Every 12–24 months if asymptomatic and stable*	Neurologist: • Review medical history for symptoms of neurogenic bladder • Refer for specialist assessment and review	When clinically indicated, refer for specialist assessment and medical management
Sleep hygiene *Initially, every 6 months* *Every 12–24 months if asymptomatic and stable*	Sleep specialist: • Assess and manage sleep disruption • Assess and manage sleep apnoea	Ensure an optimal environment for sleep (quiet, cool, dark room, regular sleep/wake hours) When clinically indicated, sleep-inducing medicines should be trialled. Where there is sleep apnoea, consultation with a sleep specialist and an overnight sleep study may be helpful[83]
Mental, social and emotional well-being *Initially, every 6 months* *Every 12 months if stable*	Psychiatrist/Psychologist: • Assess and manage psychiatric manifestations (e.g. depression, anxiety, psychosis, catatonia) • Assess and manage behavioural problems	Be aware of increased prevalence of behavioural problems, anxiety, depression, and psychosis in NP-C Early referral to a team specialised in behavioural and mental healthcare A low threshold for pharmacological and non-pharmacological treatment is advised When clinically indicated, patients should be offered appropriate pharmacotherapy
Family/caregiver needs *Initially, every 6 months* *Every 12 months if stable*	NDIA/Social Worker: • Assess need for caregiver support	Provide education on available resources Facilitate access to NDIS community services and funding
General health *Every 12 months or as needed for acute medical issues*	Family Doctor/General Practitioner: • Order general laboratory evaluations (blood tests) • Ensure vaccinations are up to date • Assess and manage medical issues not related to NP-C	Manage medical issues not related to NP-C as clinically appropriate, refer questions to the core medical team

MDT, multidisciplinary team; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NDIA, National Disability Insurance Agency; NP-C, Niemann–Pick disease type C; NPCCCSS, NP-C clinical severity scale.

models in Australia. Information about available transition services provided by local health services can be accessed via the rare diseases portal (www.rareportal.org.au).

Symptom assessment and management

In the absence of a curative treatment for NP-C, the focus of management is supportive and requires intervention by a wide number of healthcare and allied health specialists (Fig. 2).

To aid with timely intervention, ongoing multisystemic assessment and monitoring should be included in the care plan (Table 4).[2,8,44] The timeframes of these assessments are dictated by the clinical needs of the patient. Typically, baseline assessments will be undertaken at the time of diagnosis, with paediatric patients then seen by a paediatrician once every 6 months, extending to 12 months in the adult setting. There should be a low threshold for referral and access to care services and, where possible, communication with families should emphasise strengths-based outcomes.[45] A rare disease diagnosis has a significant psychosocial/emotional impact and burden on the family; extending support to family members is a vital aspect of the care plan.[46]

Assessment of disease severity

Several NP-C assessment scales have been developed for use in different settings (clinical practice, clinical trial enrolment and clinical trial assessment).[47] The 17-domain NP-C Clinical Severity Scale (NPCCSS) is the first choice for use in research and clinical trial settings and the five-domain NPCCSS is the first choice for use in clinical practice.[47] The five-domain NPCCSS measures five core domains, which were identified by NP-C individuals, their carers and NP-C experts as being the most clinically relevant.[48,49] This scale is simple and quick to administer in the clinical setting without the need for additional tools or expertise.[47] It has been validated as a suitable scale to measure clinically meaningful change in symptom severity (Fig. S1).[50]

Practical implications: A one-category worsening on any domain of the five-domain NPCCSS (equivalent to one-point change or greater in the five-domain NPCCSS total score) is clinically meaningful and represents a loss of complex function and increased disability.[50]

Disease-modifying and other future therapies

Disease-modifying treatment options for NP-C are limited (Table 5). For many individuals, clinical trial participation may be the only way to access disease-modifying treatment. It is hoped that recent initiatives, such as the establishment of the collective group of childhood dementia disorders, might harness greater traction to improve identification of and access to targeted therapies.[4,14]

Miglustat (Zavesca, Johnson & Johnson, USA) has been demonstrated to delay disease progression and stabilise neurological symptoms,[44,51–53] including dysphagia and cognitive function.[38,54] The majority of studies evaluating the use of miglustat are in children and adults, with treatment commencing after the onset of neurological impairment in all age groups.[44,53] Emerging data support a disease-modifying effect when miglustat is commenced early (age <12 months) in neonatal and early infantile NP-C.[55] Long-term outcome data in this patient population are lacking.

Practical implications: Miglustat is accessible only via state or hospital-based funding on an individual patient approval basis (Table S1). The ANPDF continues to advocate for funded access to treatments for NPC.

In 2024, two new therapies were approved by the US Food and Drug Administration; both are indicated for the treatment of neurological symptoms within specified NP-C populations.

Levacetylleucine (Aqneursa, IntraBio Inc., USA) is a modified amino acid.[56] It is approved in the United States as a monotherapy for adults and children weighing at least 15 kg.[57] Short-term treatment (12 weeks) with levacetylleucine (*N*-acetyl-L-leucine (NALL)) improved neurological status assessed using the Scale for the Assessment and Rating of Ataxia.[58,59] Long-term follow-up data (12 and 18 months) have shown a significant reduction in disease progression.[60]

Practical implications: Patients may be aware of, or ask about, acetyl-leucine (also available as *N*-acetyl-DL-leucine; Tanganil, Pierre Fabre Laboratories, France), a long-standing treatment for acute vertigo.[58] It is a racemic mixture that contains both NALL (L-enantiomer) and *N*-acetyl-D-leucine (D-enantiomer). Preclinical research has shown that the L- and D-enantiomers have different pharmacokinetic profiles,[61] and that the L-enantiomer within this mixture is the therapeutic component.[62,63] The D-enantiomer competes with the L-enantiomer for monocarboxylate transporter uptake, which may reduce the efficacy of NALL.[56] To date, only NALL has been clinically proven to have a benefit in NP-C; Aqneursa and Tanganil have not therefore been shown to be interchangeable.

Arimoclomol (Miplyffa, Zevra Therapeutics, USA) is a brain-penetrant, hydroxylamine derivative and a heat-shock protein-70 co-inducer.[64] It is approved in the United States in combination with miglustat in adults

Table 5 NP-C: disease-modifying treatment options

Treatment	Target/Action	Study population/indication	Status/Development phase
Miglustat (Zavesca, Johnson & Johnson, USA)	• Iminosugar • Ceramide glucosyltranferase inhibitor	• Monotherapy • Treatment of neurological symptoms • Adults and children	• Approved in Australia, European Union, Canada and Japan Note: Access in Australia is not government-funded
Levacetylleucine (Aqneursa, IntraBio Inc., USA)	• Modified amino acid • Molecular target unknown.[56] • Possible mechanism: activation of cerebral glucose metabolism in the cerebellum[84]	• Monotherapy • Treatment of neurological symptoms • Adults and children weighing at least 15 kg	• Approved in the United States (2024)
Arimoclomol (Miplyffa, Zevra Therapeutics, USA)	• Brain-penetrant, hydroxylamine derivative and a HSP-70 co-inducer[64] • Mechanism not fully described, believed to modulate HSP-70.	• Combination therapy with miglustat • Treatment of neurological symptoms • Adults and children aged 2 years and older	• Approved in the United States (2024)
Cyclodextrin (Trappsol Cyclo, Cyclo Therapeutics Inc., USA)	• 2-hydroxypropyl-β-cyclodextrin (2HPBCD) • Interacts with cholesterol to form a complex and facilitate its release and transport out of the cell.[71]	• Trial enrolment criteria: Patients aged 3 years and older (treated or not treated with miglustat) • Sub-study in patients 0–3 years who may be symptomatic or asymptomatic	• FDA ODD/RPDD (2010) • TransportNPC (NCT04860960) Phase 3 active, fully recruited. Completion June 2026.
Nizubaglustat (AZ-3102) (AzafarosAG, Switzerland)	• Brain-penetrant azasugar • Dual inhibitor of ceramide glucosyltranferase and non-lysosomal neutral glucosylceramidase	• Trial enrolment criteria: Patients aged 12–20 years (with or without prior miglustat exposure)	• FDA ODD/RPDD (2022) • RAINBOW (NCT05758922) Phase 2; completed December 2024.[85] • Phase 3 study planned for 2025

2HPBCD, 2-hydroxypropyl-β-cyclodextrin; FDA, Food and Drug Administration; HSP-70, heat-shock protein-70; OOD, orphan drug designation; RPDD, rare paediatric disease designation.

and children aged 2 years and older.[65] When combined with miglustat, arimoclomol has been shown to significantly stabilise disease measured by the five-domain NPCCSS over a period of 12 months.[66]

Future therapies

Several early phase clinical trials evaluating 2-hydroxypropyl-β-cyclodextrin (HPβCD; Trappsol, VTS-270),[67,68] histone deacetylase inhibitors (HDACi; vorinostat),[69] and lithium carbonate[70] have recently completed. Of these, the cyclodextrin Trappsol Cyclo (Cyclo Therapeutics Inc., USA) is the most advanced. Cyclodextrin interacts with cholesterol to form a complex and facilitate its release and transport out of the cell.[71] It is currently in Phase 3 development. Preliminary data suggest a favourable outcome with stabilisation or improvement in clinical-global impression change scale in six out of eight patients who have been treated for 48 weeks.[72] Further research is needed to determine the optimal role of these novel therapies in the clinical setting.[73]

Research into future therapeutic options for NP-C continues to focus on different points in the pathological cascade, and includes gene therapies, proteostatic therapies to address misfolding/mistrafficking, substrate reduction/clearance inducing therapies to address lipid build-up and other novel therapeutics targeting organelle dysfunction.[74] Gene therapy and cell-based therapies (mesenchymal stem cells) have gained much interest in the pre-clinical setting,[73,75–77] but there have been no clinical trials to our knowledge to date.

Conclusion

NP-C is a severe life-limiting neurodegenerative disease. The diagnostic journey is often prolonged, with far-reaching consequences that vary widely with age at diagnosis, symptom severity and symptom onset.[78] With no cure and limited access to disease-modifying therapy, optimal management in Australia comprises symptomatic treatment of clinical manifestations and ongoing monitoring. Key priorities include a need for broader clinician awareness, early recognition and structured support for carers who often serve as primary coordinators of care.

This consensus document was adapted from international guidance[8,9] and was reviewed through an iterative voting involving clinicians, allied health professionals and carers. The collaborative nature of this group has revealed the significant knowledge possessed by parents and carers. The proposed MDT recognises the carer as a vital part of the core care team, where they can provide invaluable insights as genuine experts in home care and add value to the team's effectiveness beyond the role of a care coordinator. Identified limitations are the lack of input from wider stakeholders/policymakers and absence of State-specific information.

This document defines Australia's first unified new standard of care for NP-C, defining expectations for recognition, diagnosis and management. Ongoing enhancement through the adoption of collaborative MDT care models and the future expansion of therapeutic options will further strengthen this framework.

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Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Miglustat: clinical start–stop criteria in Niemann–Pick type C disease.
Figure S1. Scoring of the five-domain Niemann–Pick type C Clinical Severity Scale.