Niemann-Pick Disease Type C (NPC):

Pathophysiology, Clinical Impact, & Unmet Needs

NPC Disease Overview & Epidemiology

Infantile-Onset NPC is an Autosomal Recessive, Lysosomal Disorder Characterized by Progressive Neurodegeneration and Premature Death

NPC is caused by a pathogenic variation in *NPC1* or *NPC2*, which encode proteins critical to endolysosomal cholesterol transport[1]

Toxic accumulation of cholesterol in lysosomes results in defective intracellular cholesterol trafficking, lysosomal dysfunction, & deficiency of cytoplasmic cholesterol needed for normal cellular function[1]

Lysosomal dysfunction and imbalance leads to neuronal dysfunction, neurodegeneration, progressive neurological decline, & premature mortality, especially in infantile-onset form[1]

NPC Is Ultra-Rare[2-4]

Global Incidence of NPC

1:89,000 births

Estimated US incidence[a]

~40/year
Incidence of NPC

→

~20/year
Incidence of infantile-onset NPC

[a]These statistics are based on the number of newborn births in the United States from 2024 (3.6 million) using an NPC incidence rateof 1:89,000. Infantile-onset NPC comprises 50% of NPC cases.
Abbreviations: NPC, Niemann-Pick disease type C; US, United States.
1. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 2. Burton BK, et al. *Mol Genet Metab*. 2021;134(1-2):182-187; 3. Bolton SC, et al. *Orphanet J Rare Dis*. 2022;17(1):51. 4. Centers for Disease Control and Prevention. Accessed February 9, 2026. https://www.cdc.gov/nchs/data/vsrr/vsrr038.pdf.

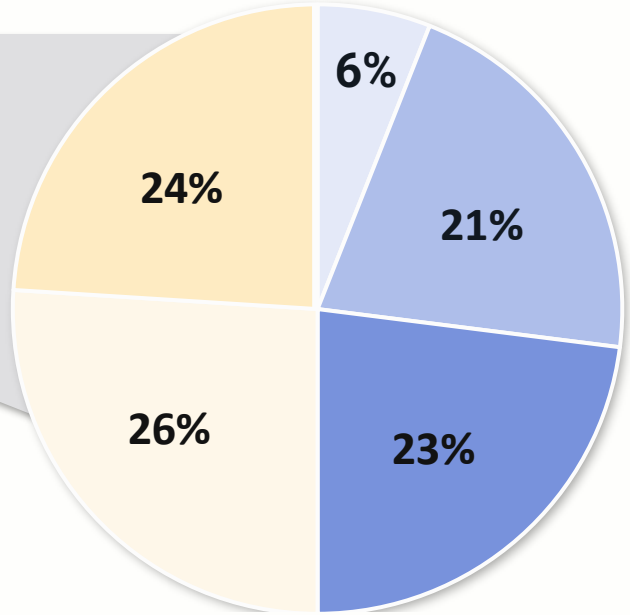
Infantile-Onset of Neurological Symptoms Predicts Faster Disease Progression and Earlier Mortality[1–3]

NPC is a heterogeneous, progressive, and fatal neurodegenerative disorder, with the most rapid neurological progression occurring in the infantile-onset NPC subtype[1]

Clinical subtype[2]	Age of neurological symptom onset[2]	Estimated age of mortality[3]
Early infantile onset	<2 years	5.6 years (±2.0)
Late infantile onset	2 to <6 years	13.4 years (±6.7)
Juvenile onset	6 to 15 years	25.9 years (±8.9)
Adult onset	>15 years	33.7 years (±6.2)
Other[a]	N/A	N/A

Estimated percentage of individuals with each clinical subtype of NPC[2]

~50%
of individuals diagnosed with NPC have **infantile onset**



[a]Including individuals with neonatal rapidly fatal NPC, individuals without neurological manifestations, and individuals with visceral symptoms only.
Abbreviations: NPC, Niemann-Pick disease type C; N/A, not available.
1. Berry-Kravis E. *Semin Pediatr Neurol.* 2021;37:100879. 2. Bolton SC, et al. *Orphanet J Rare Dis.* 2022;17(1):51. 3. Imrie J, et al. *BMC Neurol.* 2015;15(1):257.

Infantile-Onset NPC Has the Poorest Prognosis, With Rapid Progression to Neurologic Symptoms and Decline

The estimated time of death for patients with early infantile-onset NPC is often **prior to the first grade**[1]

Infantile-onset NPC **causes missed developmental milestones and lost function**[2-5]

Aspiration leading to **bronchopneumonia** may occur as a consequence of dysphagia resulting from neurologic/swallowing impairment.[6]

Earlier-onset cholesterol trafficking disruptions interfere with motor development, while later-onset disease affects cognition and behavior; **neuromuscular symptoms such as ataxia** persist across each NPC clinical subtype[5]

Hepatosplenomegaly and pulmonary disease are common systemic features of infantile-onset NPC, often with a history of prolonged neonatal cholestatic jaundice[7]

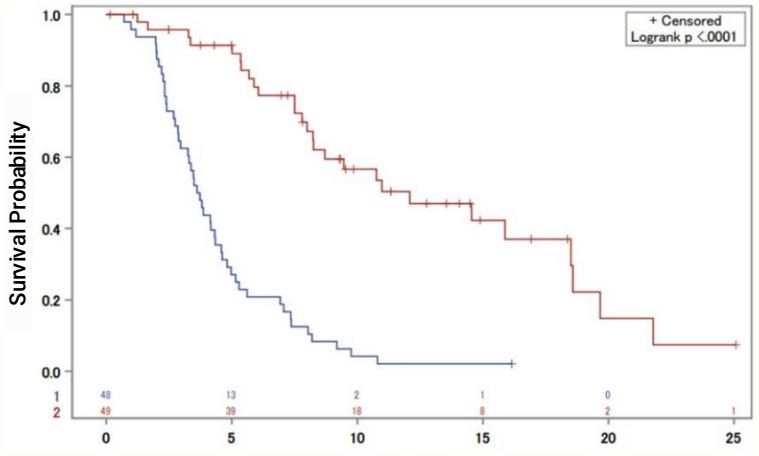
Abbreviations: NPC, Niemann-Pick disease type C.

1. Imrie J, et al. *BMC Neurol*. 2015;15:257. 2. Burton BK, et al. *Mol Genet Metab*. 2021;134(1-2):182-187. 3. Bolton SC, et al. *Orphanet J Rare Dis*. 2022;17(1):51. 4. Bianconi SE, et al. *Mol Genet Metab*. 2019;126(4):466-469. 5. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 6. Walterfang M, et al. *Orphanet J Rare Dis*. 2012;7:76. 7. Hiwot T, et al. *J Inherit Metab Dis*. 2026;49(3):e70185.

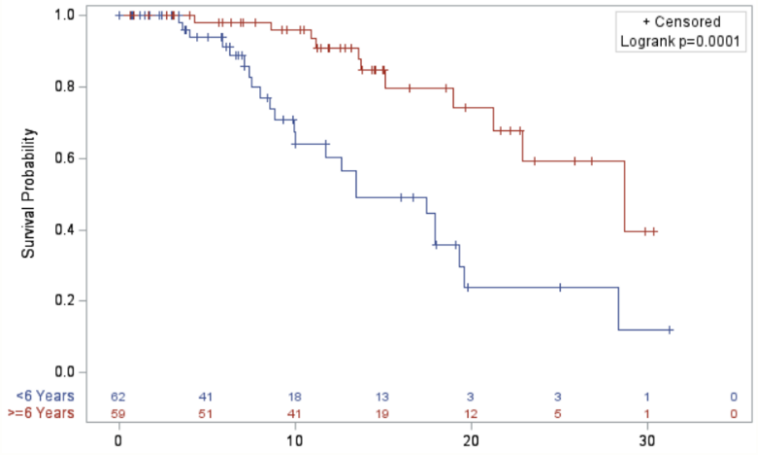
Patients ≤6 Years Old at Symptom Onset Have Significantly Shorter Survival Time Than Patients >6 Years Old at Symptom Onset

Overall Survival Kaplan-Meier Plots in Natural History Cohorts[1,a]

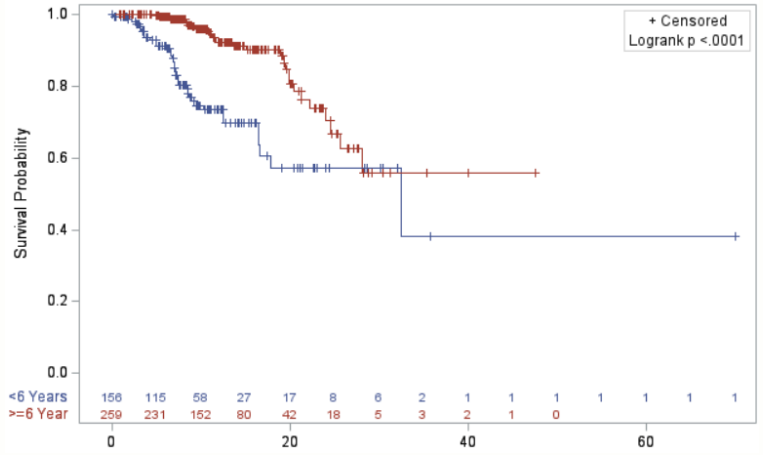
French Cohort



NIH Cohort



YODA Cohort



Age Group — 1: Onset < 6 Yrs of Age — 2: Onset >= 6 Yrs of Age

Time Since Onset of Neurological Symptoms (Years)

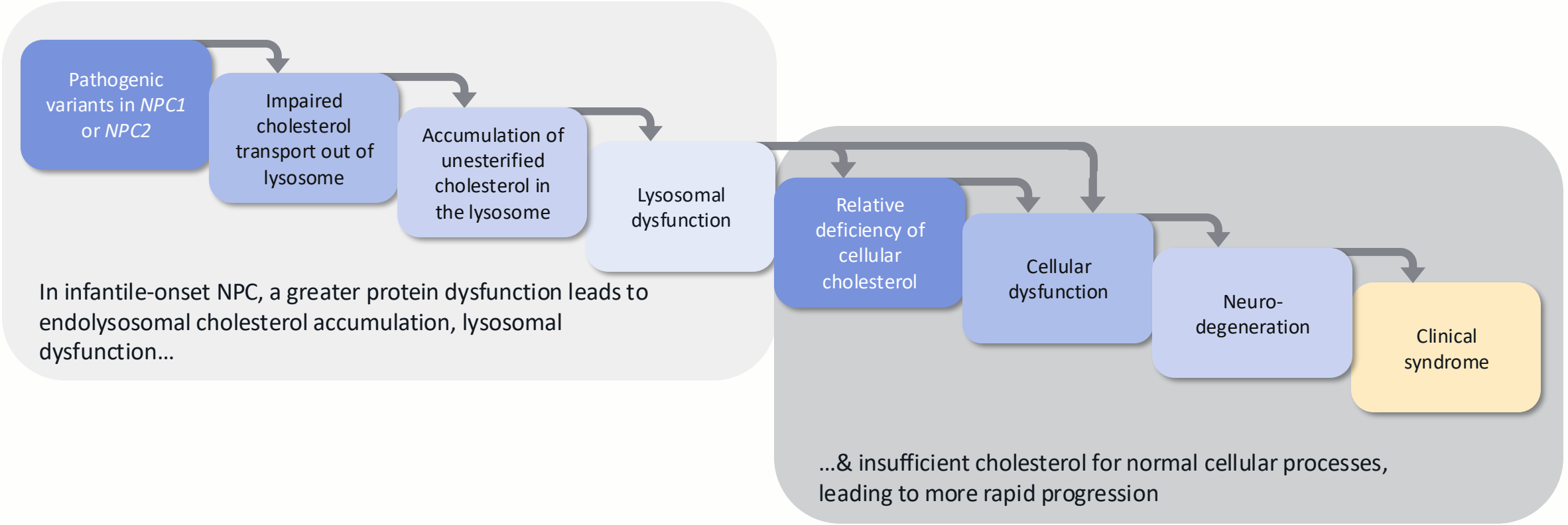
[a]Kaplan-Meier curves were generated from an internal descriptive analysis of patient-level data from the French Cohort (Freihuber 2023, Vanier 2010), NIH Natural History Study (NCT00344331), and YODA NPC Registry (Patterson 2020) natural history cohorts.[2-5]

Abbreviations: NPC, Niemann-Pick disease type C.

1. Data on File. Beren Therapeutics P.B.C. 2. Freihuber C, et al. *Orphanet J Rare Dis.* 2023;18(1):204. 3. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16. 4. NCT00344331. Available at: https://clinicaltrials.gov/study/NCT00344331 5. Patterson MC, et al. *Orphanet J Rare Dis.* 2020;15:104.

Pathophysiology

Impaired Cholesterol Trafficking Underlies Pathophysiology of NPC[1,2]



Targeting impaired cholesterol trafficking represents an upstream, disease-modifying approach in NPC

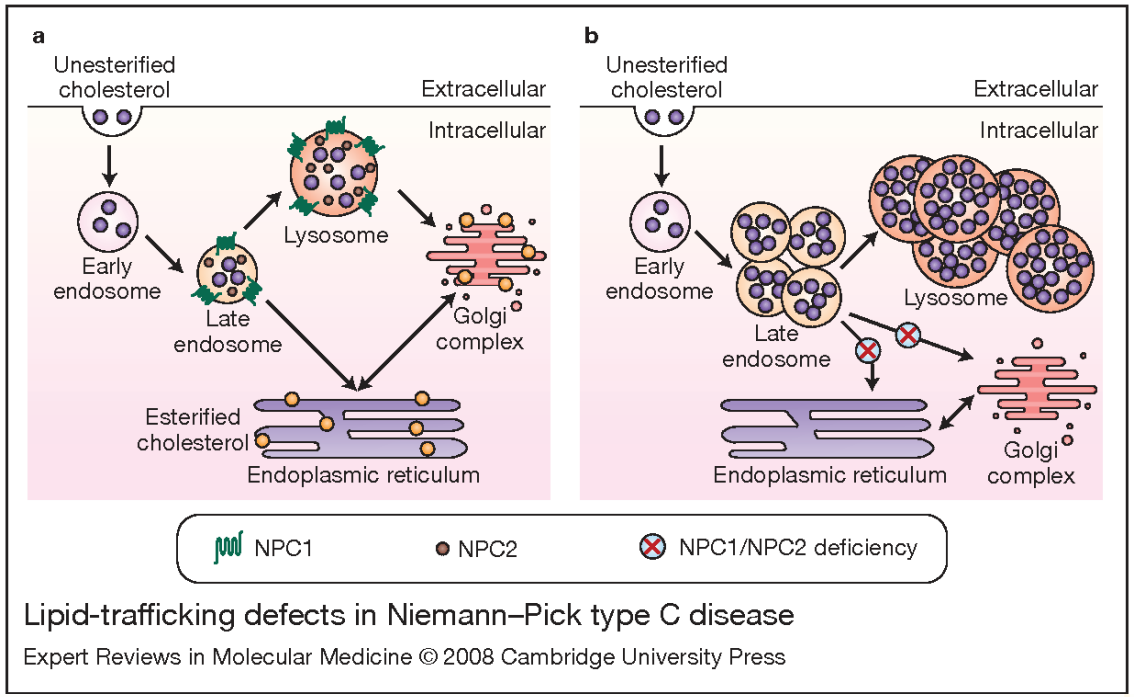
Abbreviations: NPC, Niemann-Pick disease type C.

1. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 2. Walkley SU, Suzuki K. *Biochim Biophys Acta*. 2004;1685(1-3):48-62.

NPC1 & NPC2 Are Lysosomal Proteins Critical for Cholesterol Transport Out of the Lysosome

- **NPC1 and NPC2 are lysosomal cholesterol-binding proteins**[1–3]
  - They work in tandem and are essential for cholesterol transport out of the lysosome
- **In NPC, NPC1 or NPC2 function is lost, causing:**[1]
  - Cholesterol accumulation in lysosomes
  - A relative deficiency of cytoplasmic cholesterol needed elsewhere
- **Cholesterol accumulation drives lysosomal dysfunction, impairing autophagy and limiting the ability of cells to recycle endogenous cholesterol, causing further cellular damage**[4,5]

IMPAIRED LIPID TRAFFICKING IN NPC[6]



Adapted from Pacheco CD, Lieberman AP. *Expert Rev Mol Med*. 2008;10:e26

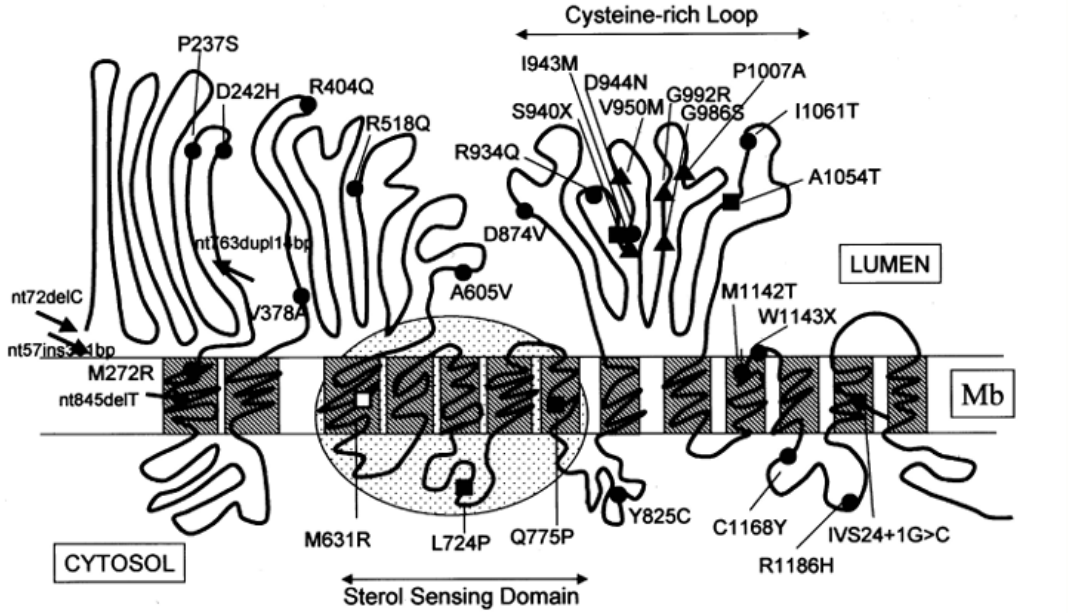
Abbreviations: NPC, Niemann-Pick disease type C.

1. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 2. Pfeffer SR. *J Biol Chem*. 2019;294(5):1706-1709. 3. Infante RE, et al. *Proc Natl Acad Sci*. 2008;105(40):15287-15292. 4. Sarkar S, et al. *Cell Rep*. 2013;5(5):1302-1315. 5. Ishibashi S, et al. *J Clin Neurosci*. 2009;16(7):954-959. 6. Pacheco CD, Lieberman AP. *Expert Rev Mol Med*. 2008;10:e26.

Greater Functional Impact of *NPC1* or *NPC2* Mutations Drives Earlier & More Severe NPC Manifestations

- **95% of NPC cases are due to *NPC1* mutations, though *NPC2* mutations result in clinically similar disease**[1]
  - Over 400 and 26 pathogenic variants in *NPC1* and *NPC2*, respectively, have been described[1,2]
- **Mutations with greater functional impact are typically associated with an impact on disease onset and severity**[1]
  - The level of *NPC1* protein function has been reported to be inversely related to the age of neurological symptom onset, with no or little function associated with infantile onset[3]
  - Frameshift, nonsense, or large deletions in both *NPC1* alleles usually result in early-infantile onset NPC[1]

NPC1 MUTATIONS ASSOCIATED WITH SEVERE FORMS OF INFANTILE-ONSET NPC[4]



Legend:
■ missense or nonsense mutations definitively associated with severe infantile-onset NPC
☐ missense mutation likely correlated with a severe infantile-onset NPC
▲missense mutations definitively correlated with a variant biochemical phenotype
● other missense mutations

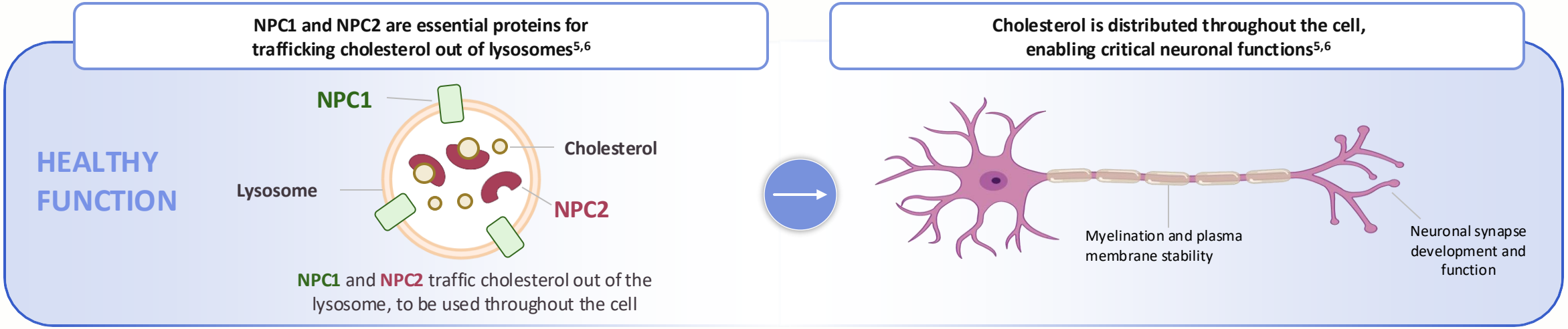
Adapted from Millat G, et al. *Am J Hum Genet*. 2001;68(6):1373-1385.

Abbreviations: NPC, Niemann-Pick disease type C.

1. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 2. Geberhiwot T, et al. *Orphanet J Rare Dis.* 2018; 13(1):50. 3. Musalkova D, et al. *Orphanet J Rare Dis*. 2020;15(1):85. 4. Millat G, et al. *Am J Hum Genet*. 2001;68(6):1373-1385.

In Healthy Individuals, Functional NPC Proteins Enable Cholesterol Trafficking Out of the Lysosomes

- **25% of the body's cholesterol is in the brain**[1]
  - Central nervous system levels are 10x other areas
- **Tightly regulated homeostatic processes hold cholesterol levels constant**[1-3]
  - Including synthesis, intra- and inter-cellular trafficking, and excretion
- **Homeostasis relies on endolysosomal transport of cholesterol and its metabolism into 24(S)-hydroxycholesterol (24[S]-OHC)**[4]
  - 24(S)-OHC is a blood-brain barrier-permeable oxysterol that is cleared through bile synthesis in the liver



Abbreviations: 24(S)-OHC; 24(S)-hydroxycholesterol; NPC, Niemann-Pick disease type C.

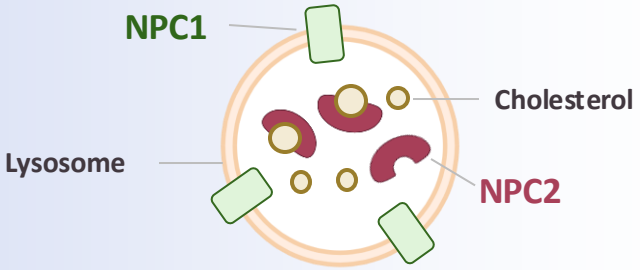
1. Dietschy JM, et al. *Curr Opin Lipidol*. 2001;12(2):105-112. 2. Dietschy JM. *Biol Chem*. 2009;390(4):287-293. 3. Li D, et al. *Trends Neurosci*. 2022;45(5):401-414. 4. Zhang J, et al. *Protein Cell*. 2015;6(4):254-264. 5. Pfeffer SR. *J Biol Chem*. 2019;294(5):1706-1709. 6. Infante RE, et al. *Proc Natl Acad Sci*. 2008;105(40):15287-15292. 7. Lee D, Hong JH. *Antioxidants*. 2023;12(12):2021. 8. Berry-Kravis E. *Semin Pedatr Neurol*. 2021;37:100879.

In Infantile-Onset NPC, Greater Dysfunctional NPC Proteins Cause Impaired Cholesterol Trafficking, Leading to Neurodegeneration

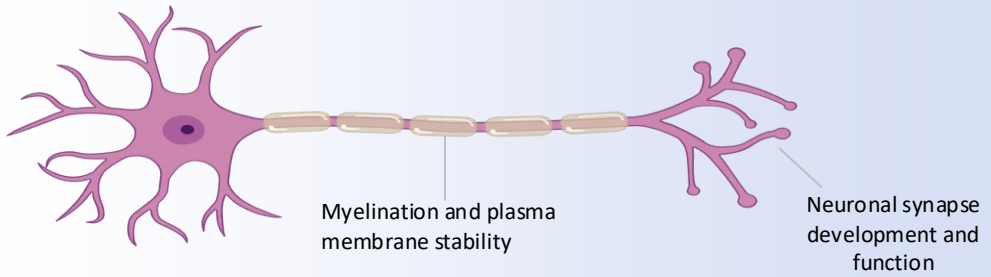
NPC1 and NPC2 are essential proteins for trafficking cholesterol out of lysosomes[1,2]

Cholesterol is distributed throughout the cell, enabling critical neuronal functions[1,2]

HEALTHY FUNCTION



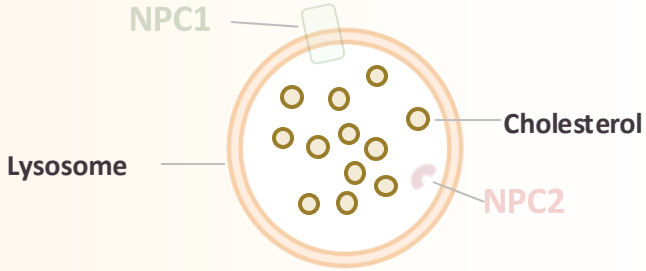
NPC1 and **NPC2** traffic cholesterol out of the lysosome, to be used throughout the cell

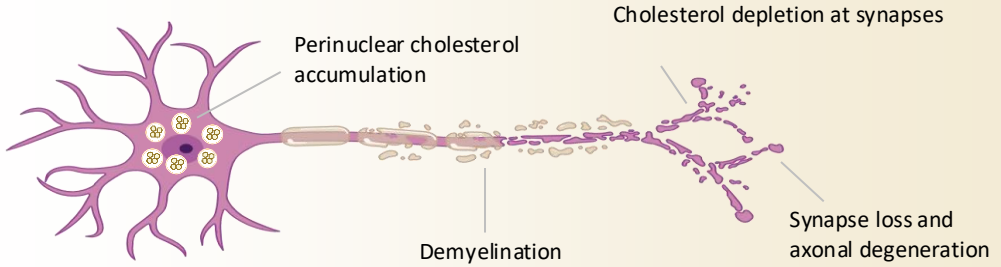


Cholesterol accumulates in lysosomes due to dysfunctional NPC proteins[1,3]

Impaired lysosomal function and insufficient cholesterol for normal cellular processes cause neuronal injury and cell death[4]

NPC



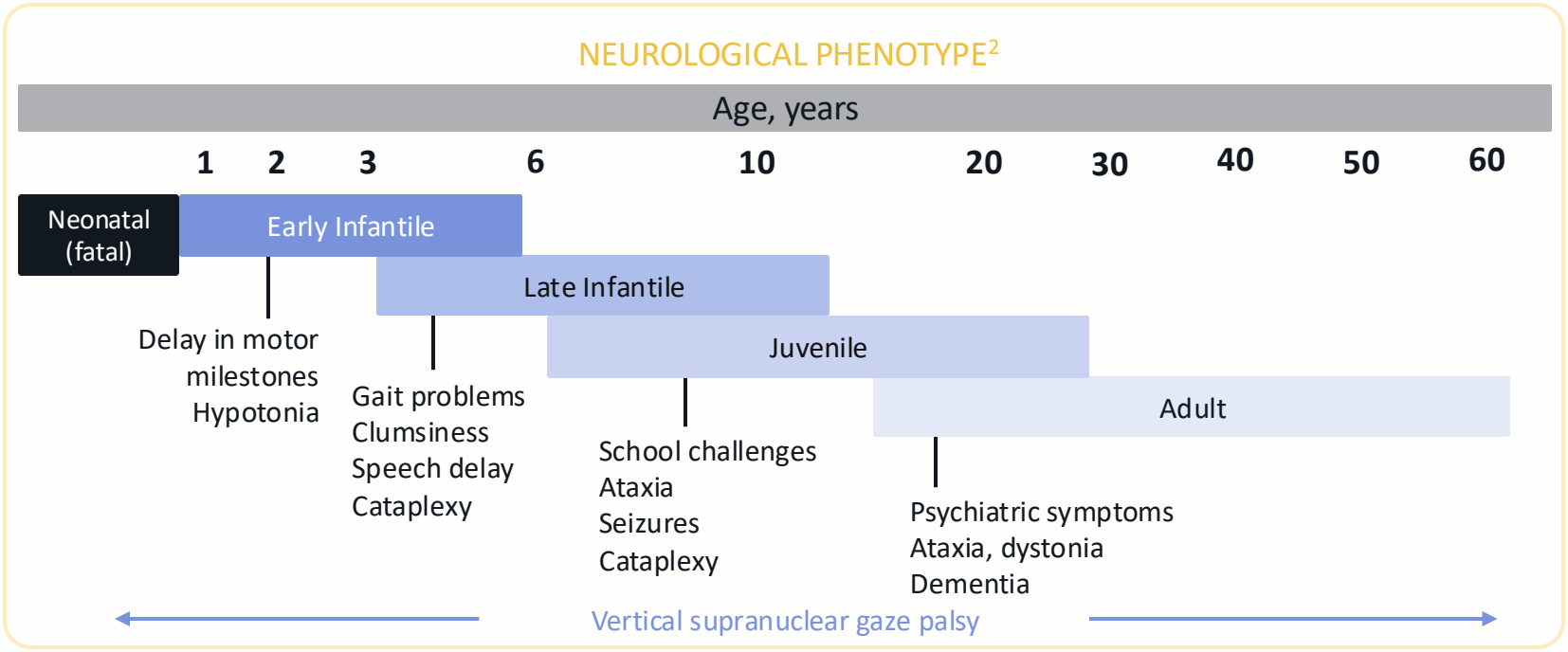


Abbreviations: NPC, Niemann-Pick disease type C.

1. Pfeffer SR. *J Biol Chem*. 2019;294(5):1706-1709. 2. Infante RE, et al. *Proc Natl Acad Sci*. 2008;105(40):15287-15292. 3. Lee D, Hong JH. *Antioxidants*. 2023;12(12):2021. 4. Berry-Kravis E. *Semin Pedatr Neurol*. 2021;37:100879.

Signs, Symptoms, & Diagnostics

NPC is a Heterogenous, Progressive, Terminal Neurodegenerative Disease with Age of Neurological Onset Predicting Speed of Progression



Adapted from Vanier, MT. *Orphanet J Rare Dis.* 2010;5:16.

The **stage of neurodevelopment** at which **cholesterol trafficking** is **disrupted** determines the **pattern of dysfunction**, with **earlier defects causing motor delay and later ones affecting cognition and behavior**

Abbreviations: NPC, Niemann-Pick disease type C.

1. Berry-Kravis E. *Semin Pediatr Neurol.* 2021;37:100879. 2. Vanier MT. *Orphanet J Rare Dis.* 2010;5:16.

Clinical Phenotype Reflects Neurodevelopmental Stage at Time of Pathology-Driven Symptom Onset

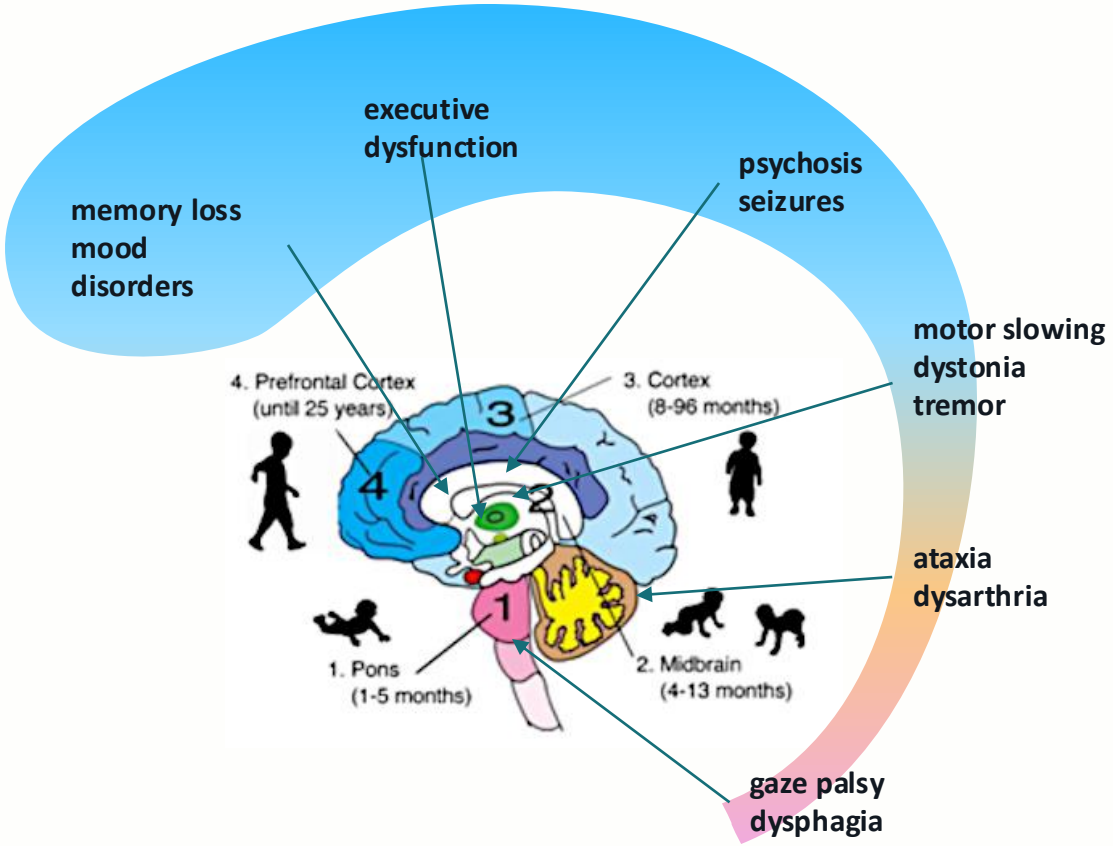
NPC disease is a race of development against dysfunction

Timing of neurological onset

- Complete loss of NPC function produces the earliest and most severe course, as seen in infantile-onset NPC[1,2]
- Residual NPC activity is associated with later onset and a milder trajectory[1,3]

Symptoms reflect the neurodevelopmental stage affected

- Disruption of early myelinating regions (pons and midbrain/cerebellum) manifests as hypotonia, vertical supranuclear gaze palsy (VSGP), dysphagia, and ataxia[3]
- Disruption of later-maturing cortical and prefrontal regions manifests as executive dysfunction, psychosis, and dementia[2,3]



Adapted from Neuroclinic Barrie. Accessed April 7, 2026. https://neuroclinicbarrie.com/neurodevelopment/brain-development/

Abbreviations: NPC, Niemann-Pick disease type C.

1. Liang H, et al. *J Inherit Metab Dis*. 2024;47(2):317-326. 2. Guatibonza Moreno PG, et al. *Eur J Hum Genet*. 2023;31(10):1108-1116. 3. Las Heras M, et al. *NPJ Genom Med*. 2023;8(1):21. 4. Neuroclinic Barrie. Accessed April 7, 2026. https://neuroclinicbarrie.com/neurodevelopment/brain-development/.

Infantile-Onset NPC Reflects the Most Severe Disruption of Cholesterol Trafficking, Leading to Rapid Neurological Onset & Decline

Several mutations in both *NPC1* and *NPC2* genes are related to infantile-onset of NPC and severe form of the early-onset disease, causing major defects in intracellular cholesterol trafficking that result in lysosomal cholesterol accumulation.[1,2]

Early infantile-onset[1,3]

- Hepatosplenomegaly present from the first months of life
- Motor developmental delay, intention tremor, truncal instability, and central hypotonia by ~8 months and present by 1-2 years of age
- Progressive loss of motor skills, mild cognitive regression, spasticity, and dystonia
- Many children never learn to walk
- Pulmonary disease and dysphagia may also be present
- VSSP/VSGP may be subtle and is often unrecognized
- **Death often occurs by around 5 years of age**

Late infantile-onset[1,3]

- Hepatosplenomegaly present during the first years of life
- VSSP (progressing to VSGP), clumsiness, gait disturbances, frequent falls, ataxia, and intention tremor
- Language and articulation delays
- Gelastic cataplexy (sometimes with narcolepsy) and sensory deafness
- Progressive ataxia, dystonia, spasticity, and cognitive impairment
- Emergence of focal or generalized seizures, and epilepsy
- Dysphagia leading to swallowing difficulties and possible gastrostomy tube placement
- **Death commonly occurs between 7–12 years of age**

Abbreviations: VSGP, vertical supranuclear gaze palsy.

1. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 2. Vanier MT. *Orphanet J Rare Dis*. 2010;5:16. 3. Hiwot T, et al. *J Inherit Metab Dis*. 2026;49(3):e70185.

Diagnostic Delay Is Common in Infantile-Onset NPC Due to Its Rarity & Variable Clinical Presentation, Leading to Irreversible Neurological Decline

Diagnostic delay

- **Patients often receive several incorrect diagnoses** due to symptom heterogeneity and rarity of routine testing[1]
- Mean delay between neurological symptom onset and NPC diagnosis:[2]
  - **~2.5 years** for early infantile-onset NPC
  - **4.3 years** for late infantile-onset NPC
- Potential misdiagnoses **include cerebral palsy, autism spectrum disorder, multiple sclerosis, Gaucher disease, epilepsy, and others**[3]

Irreversible damage

- **Neurological damage in NPC is irreversible**, so immediate treatment is needed to prevent further degeneration[4]
  - In rapidly progressive infantile-onset cases, any diagnostic delay has an outsized impact
- **It is critical that health care providers identify the true age of neurological symptom onset in NPC to predict prognosis**[5]
  - Detailed documentation of neurological symptoms is essential for accurate diagnosis and disease management

Early diagnosis & treatment have the potential stabilize or improve the development trajectory of patients with infantile-onset NPC[3]

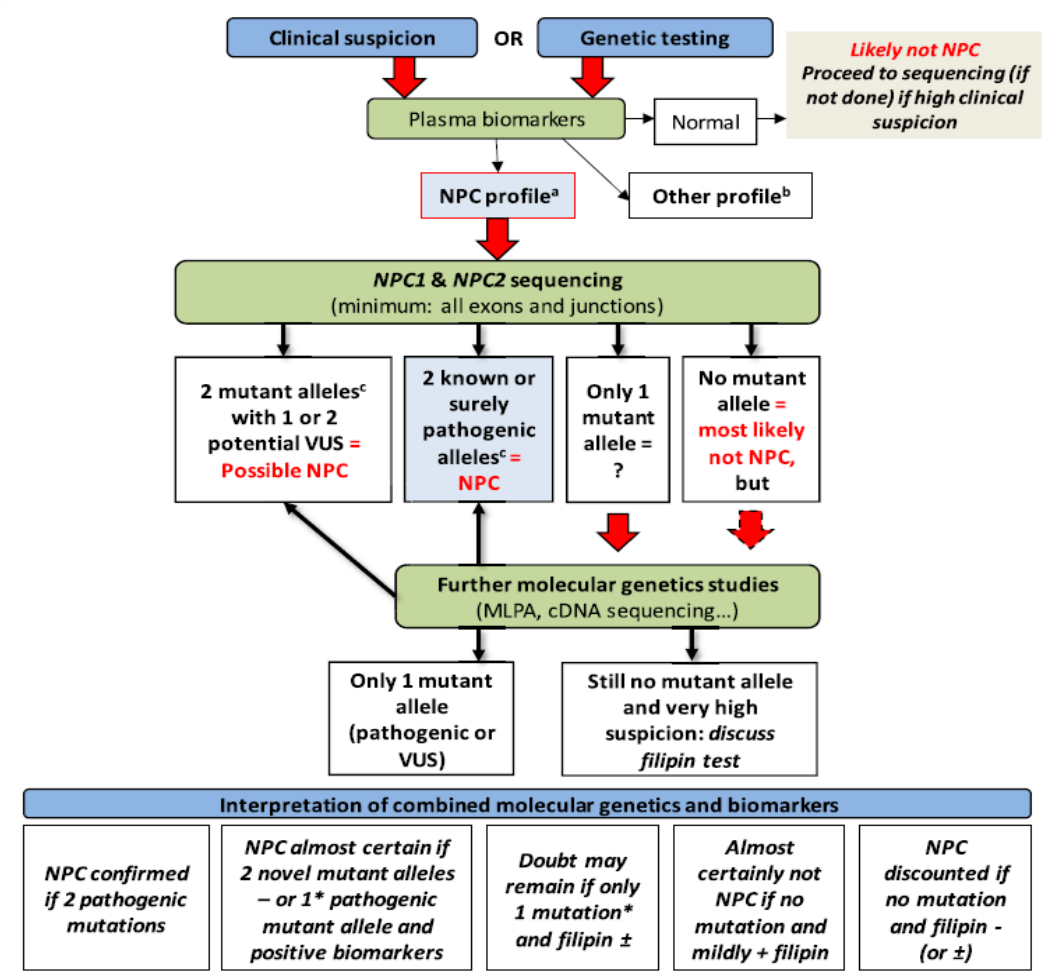
Abbreviations: NPC, Niemann-Pick disease type C.

1. FDA listening session on Niemann-Pick disease. Summary report. April 9, 2021. 2. Patterson MC et al *J Inherit Metab Dis*. 2020;43(5):1060-1069. 3. Ara Parseghian Medical Research Foundation. NPC patient-focused drug development meeting. March 18, 2019. 4. Mengel E, et al. *Orphanet J Rare Dis*. 2013;8:166. 5. Mengel E, et al. *Orphanet J Rare Dis*. 2020;15(1):328.

Early Clinical Suspicion of NPC Should Be Confirmed By a Combination of Biomarker & Genetic Testing

- **Genetic testing is a parallel first-line entry point** alongside clinical suspicion of NPC
- **Plasma biomarker testing considered a first-line step** in the NPC diagnostic process
- **Filipin staining is no longer recommended** in the diagnostic pathway
- **Bile acid is the first-line biomarker test for the infantile-onset population**

NPC LABORATORY DIAGNOSIS ALGORITHM (2025)[1]

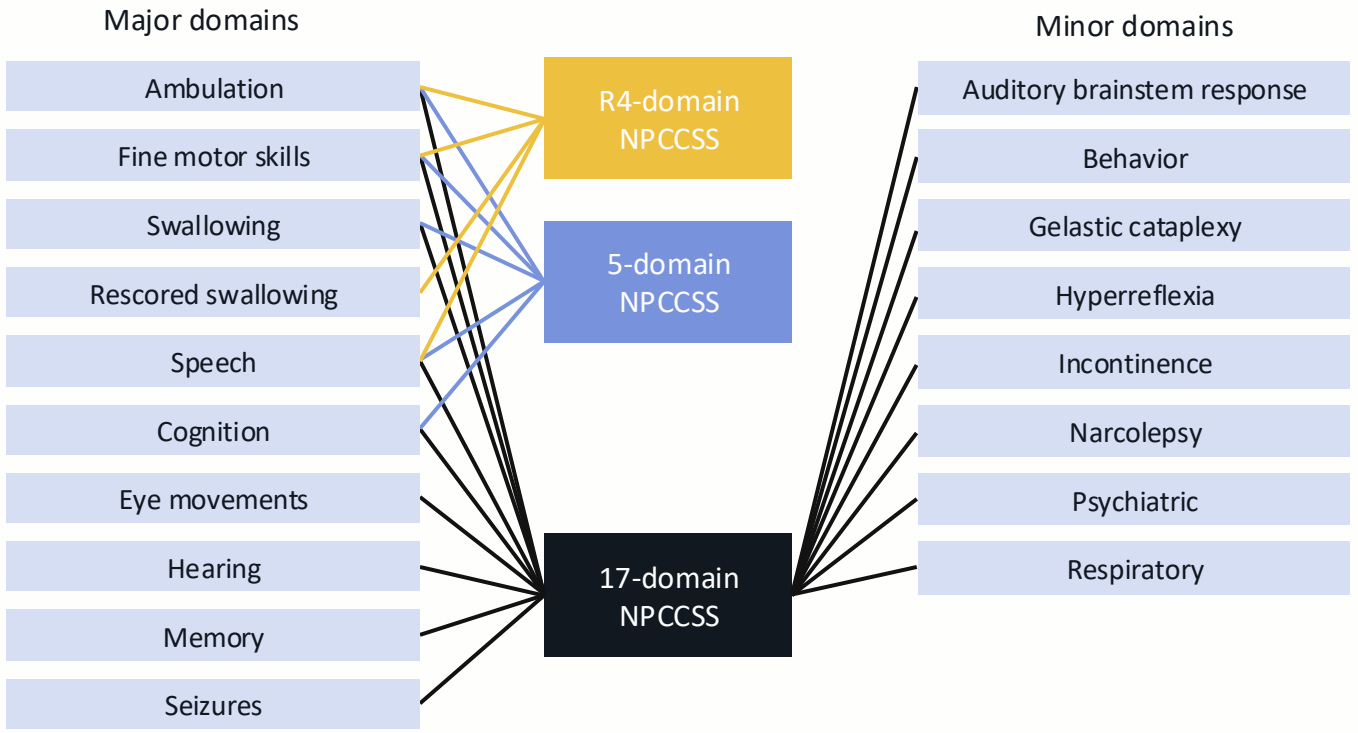


*Profile also seen in heterozygote subjects. [a]Elevated cholestane-triol or bile acid derivative and/or PPCS, with normal or slightly elevated lyso-SM. [b]Cholestane-triol is also elevated in ASMD, acid lipase deficiency, cerebrotendinous xanthomatosis, and certain neonatal cholestasis conditions. All lyso-SM analogues and bile acid derivatives are elevated in ASMD. [c]Check allele segregation by parental study or other test.
Abbreviations: CDNA, complementary DNA; MLPA, Multiplex Ligation-dependent Probe Amplification; VUS, variant of unknown significance; WES, whole exome sequencing; WGS, whole genome sequencing.
Hiwot T, et al. *J Inherit Metab Dis*. 2026;49(3):e70185.

Disease Monitoring & Progression

NPC Clinical Severity Scale (NPCCSS) Is a Disease-Specific, Clinician-Reported Outcome Measure of Disease Severity & Progression in Infantile-Onset NPC

- Full 17-domain NPCCSS covers all major and minor NPC domains—the total sum provides an estimate of overall disease burden[1]
- 5-domain NPCCSS comprises the five domains selected by individuals with NPC, their caregivers, and NPC experts[2]
- **Rescored 4-domain NPCCSS was developed to provide a simpler, more sensitive, and clinically meaningful tool** for individuals with infantile-onset NPC that omits the "cognition" domain from the 5-domain version[2,3]
  - Swallow domain rescored to better reflect the linear progression of swallowing dysfunction (intermittent dysphagia, consistent dysphagia, and tube-feeding)



Adapted from Mengel E, et al. *Orphanet J Rare Dis.* 2020;15(1):328 and Mengel E, et al. *Mol Genet Metab Rep.* 2025;43:101233.

Abbreviations: NPC, Niemann-Pick disease type C; NPCCSS, NPC Clinical Severity Scale.

1. Patterson MC, et al. *Orphanet J Rare Dis.* 2021;16(1):79. 2. Mengel E, et al. *Orphanet J Rare Dis.* 2020;15(1):328. 3. Mengel E, et al. *Mol Genet Metab Rep.* 2025;43:101233.

Regular Assessments Are Required to Track Disease Progression & Ensure Optimal Symptom Management & Treatment Effectiveness in Infantile-Onset NPC

Signs, symptoms, and clinical manifestations	Recommended tools / assessments At diagnosis or symptom onset, and regularly thereafter (every 6 to 12 months)
Growth & developmental delay	Height, weight, and head circumference assessed; developmental progress monitored with age-appropriate instruments.
Mobility	Mobility, balance, core stability, trunk control, spasticity, foot posture, and strength assessed by a physical therapist (SARA for ataxia ≥ 2 infants <18 months old; BOT-2 for children).
Swallowing & diet	Comprehensive clinical swallowing assessment by speech and language therapist; videofluoroscopic swallowing (VFS) assessment in patients with neurological symptoms. Pulmonary function assessment in all patients. Dysphagia, aspiration, and therapy response documented. Nutritional review by dietitian.
Speech	Comprehensive communication evaluation by a speech and language therapist.
Spasticity	Assessment for spasticity and incipient or established contracture.
Bowel dysfunction & incontinence	Screening for IBD (Crohn's disease, ulcerative colitis) in patients with bowel dysfunction.[a]
Bladder dysfunction & incontinence	History reviewed for neurogenic bladder symptoms (recurrent UTI, nocturia, incomplete evacuation, dribbling); refer for urologic evaluation if symptoms present.
Liver dysfunction	Assessment of liver function; ultrasound to monitor liver/spleen size. Alpha-fetoprotein (AFP) if hepatocellular carcinoma (HCC) concern.
Cognitive decline	Cognitive function evaluation using age- and functionally appropriate standardized assessment tools.
Hearing	Audiology assessment to document presence of hearing loss.
Other	Cataplexy, seizures, mental wellbeing, hypersalivation/drooling.

[a]NPC has the highest early-onset penetrance of Crohn's among monogenic diseases.
Abbreviations: IBD, Inflammatory bowel disease; NPC, Niemann-Pick disease; UTI, urinary tract infection;
1. Hiwot T, et al. *J Inherit Metab Dis.* 2026;49(3):e70185.

Biomarkers Associated with NPC Pathophysiology and Diagnosis

- Various biomarkers are known to be altered in individuals with infantile-onset NPC and reflect underlying disease biology, including cholesterol trafficking and neurodegeneration[1–3]
  - Because NPC progression is heterogeneous and clinical trials are often short in duration, CSF and plasma biomarkers may complement symptom-based progression scores and observed pharmacodynamic effects[1]

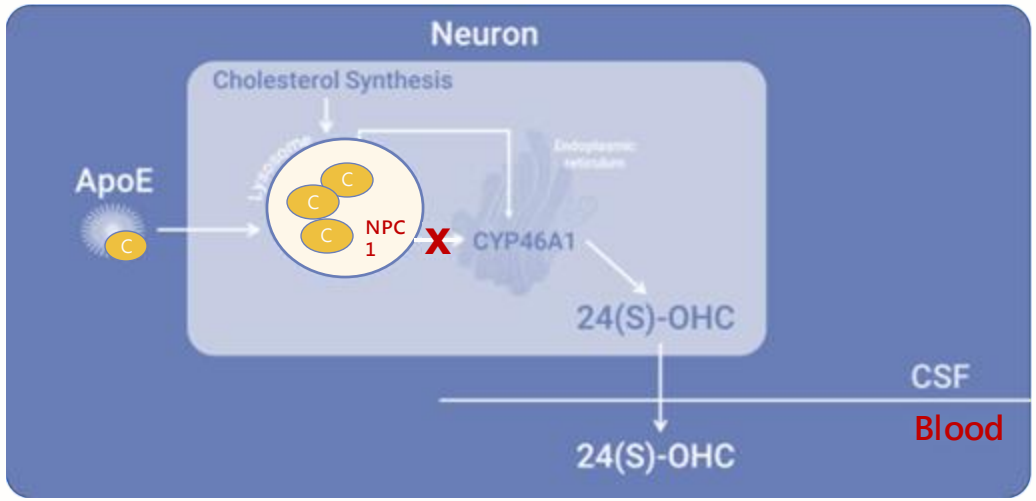
					Concentration Levels	
Biomarker	**Plasma and/or CSF-based**	**Primary utility in NPC**	**Functional correlate of systemic biomarkers**	**Commercial availability**	**Patients with NPC**	**Healthy individuals**
24(S)-OHC[1,4,5]	CSF, plasma	Pharmacodynamic	Cholesterol trafficking	No, research use	0.27 ng/mL (±0.20)	1.509 ng/mL (±0.481)
Calbindin D[1,2,3,5]	CSF	Pharmacodynamic	Purkinje cell death/Cerebellar injury	No, research use	4.78 ng/mL (±4.25)	0.76 ng/mL (±0.34)
FABP3[1,2,6]	CSF	Pharmacodynamic	Neurodegeneration	No, research use	17.41 ng/mL (±3.05)	2.36 ng/mL (±0.72)
C-triol[5,7-9]	Plasma	Diagnostic	Oxysterol derived from cholesterol oxidation	Yes, clinical and research use	88.31 ng/mL (±28.66)	5.97 ng/mL (±1.13)
TCG[10,11]	Plasma	Diagnostic	Bile acid metabolites of C-triol	Yes, clinical and research use	10.1-89.7 ng/mL	<1-16.8 ng/mL
PPCS[4,10,12]	Plasma	Diagnostic, Pharmacodynamic	Lysosphingolipid marker	Yes, clinical use	2492 ng/mL (254–18200)	19.1 ng/mL (1.3–542)
NfL[5,13,14]	Plasma	Diagnostic, Pharmacodynamic	Neurodegeneration	Yes, clinical use (non-NPC-specific)	33.07 pg/mL (8.82–581.40)	7.94 pg/mL (4.56–21.20)

Abbreviations: 24(S)-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; C-triol, cholestane-3β, 5α, 6β-triol; FABP3, fatty acid binding protein 3; NfL, neurofilament light chain; PPCS, N-palmitoyl-O-phosphocholineserine; TCG, trihydroxycholanic acid glycinate.

1. Campbell K, et al. *Biomarker Res*. 2023;11(1):14. 2. Ory DS, et al. *Lancet*. 2017;390(10104):1758-1768. 3. Bradbury A, et al. *J Pharmacol Exp Ther*. 2016;358(2):254-261. 4. Porter FD, et al. *Mol Genet Metab*. 2025;146(4):109254. 5. Casazza K, et al. *J Inherit Metab Dis*. 2025;48(5):e70075. 6. Cologna SM, et al. *PLoS One*. 2012;7(10):e47845. 7. Stern S, et al. *Orphanet J Rare Dis*. 2024;19(1):280. 8. Mengel E, et al. *Orphanet J Rare Dis*. 2020;15(1):328. 9. Reunert J, et al. *EBioMedicine*. 2015;4:170-5. 10. Jiang X, Ory DS. *Explor Neuroprotective Ther*. 2021;1(3):146-158. 11. Sidhu R, et al. *Mol Genet Metab*. 2020;131(4):405-417. 12. Sidhu R, et al. *Mol Genet Metab*. 2020;129(4):292-302. 13. Dardis A, et al. *J Clin Med*. 2021;10(20):4796. 14. Cawley NX, et al. *Genet Med Open*. 2025;3:103443.

24(S)-OHC Production Is the Main Route of Elimination of Excess Cholesterol from the Brain, Making It a Marker of Neuronal Cholesterol Homeostasis

- Under normal conditions, at least two-thirds of brain cholesterol is metabolized by CYP46A1 in neurons to form 24(S)-OHC, which crosses the blood-brain barrier into circulation[2,3]
- In NPC, impaired lysosomal cholesterol trafficking reduces substrate availability for CYP46A1 and leads to decreased CSF 24(S)-OHC[1,2]
  - This reduction reflects impaired neuronal cholesterol trafficking rather than systemic deficiency[1-3]



Adapted from Berry-Kravis E, et al. WORLDSymposium Annual Meeting; 2026.

Because CYP46A1 is localized predominantly in CNS and enriched in neurons, treatment-related increases in CSF 24(S)-OHC demonstrate increased cholesterol trafficking specifically in the central nervous system[1]

Abbreviations: 24(S)-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; CYP46A1, cytochrome P450 46A1; NPC, Niemann-Pick disease type C.

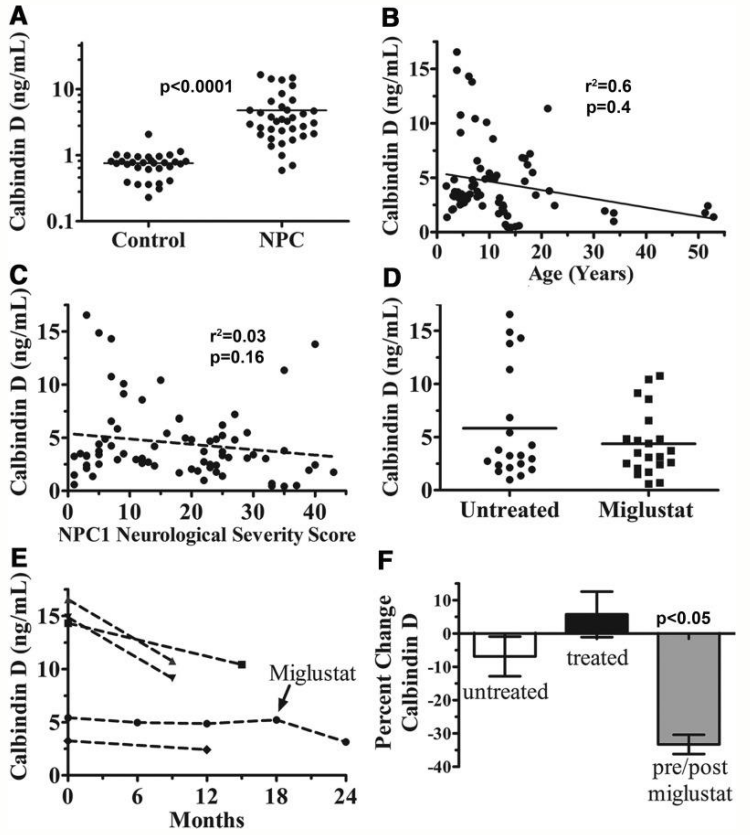
1. Tortelli B, et al. *Hum Mol Genet.* 2014;23(22):6022-6033. 2. Zhang J, et al. *Protein Cell.* 2015;6(4):254-264. 3. Saher G, et al. *Biochim Biophys Acta.* 2015;1851(8):1083-1094. 4. Berry-Kravis E, et al. Poster presented at the WORLDSymposium Annual Meeting; 2026; San Diego, CA.

Calbindin D Reflects Purkinje Cell Loss & May Serve as a Biomarker of Cerebellar Disease Progression in NPC

- Calbindin D is a calcium-binding protein predominantly expressed in cerebellar Purkinje neurons, where it supports intracellular calcium buffering and neuronal stability[1]
- Loss or injury of Purkinje neurons causes release of calbindin D into the CSF, making it a marker of neuronal damage and cell death[1]

In treated patients, reductions in CSF calbindin D have been associated with therapeutic response, suggesting utility as a potential biochemical marker of disease progression and treatment efficacy[1–3]

CSF CALBINDIN D LEVELS IN PATIENTS WITH NPC1[1]



Adapted from Bradbury A, et al. *J Pharmacol Exp Ther*. 2016;358(2):254-261

Abbreviations: CSF, cerebrospinal fluid; NPC, Niemann-Pick disease type C.

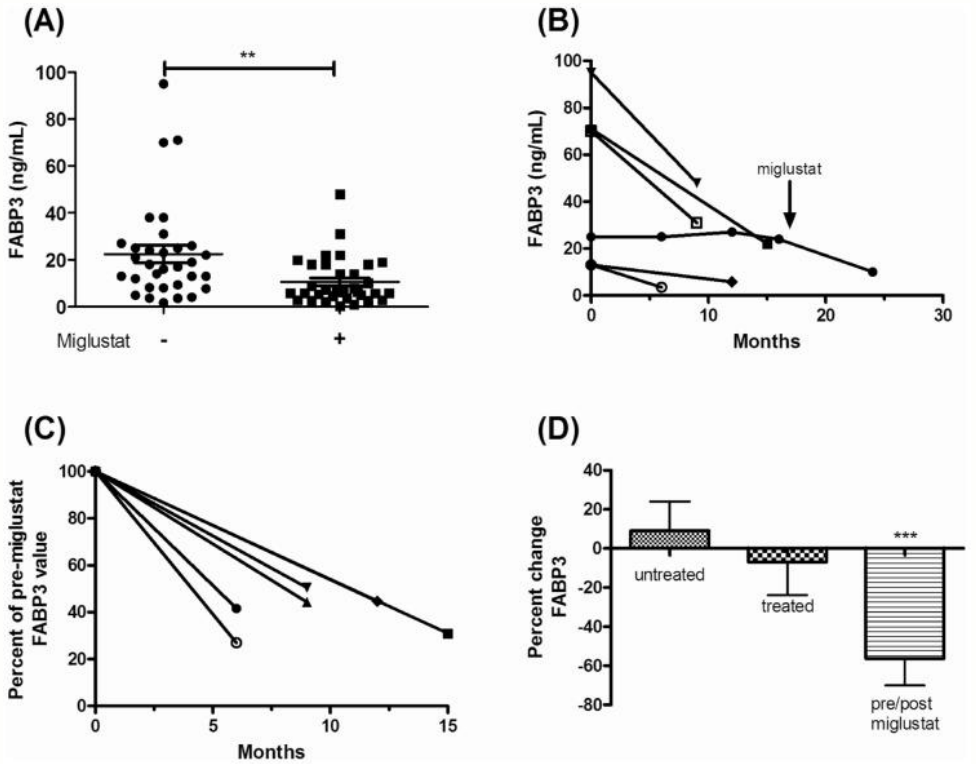
1. Bradbury A, et al. *J Pharmacol Exp Ther*. 2016;358(2):254-261. 2. Jiang X, et al. *Explor Neuroprotective Ther*. 2021;1(3):146-158. 3. Ory DS, et al. *The Lancet*. 2017;390(10104):1758-1768.

Fatty Acid Binding Protein 3 (FABP3) Reflects Neuronal Damage & May Serve as a Biomarker of Neurodegeneration in NPC, Including Infantile-Onset NPC

- FABP3 is expressed at high levels in cerebellum, and its release into extracellular fluids is associated with neuronal damage and death[2]
- FABP3 is a cytosolic protein that preferentially binds omega-6 polyunsaturated fatty acids[3]
- FABP3 is reported to be a cholesterol transport protein contributing to cholesterol efflux from lysosomes[4]
- FABP3 is elevated in CSF in individuals with NPC and animal models of NPC[1,5]

CSF FABP3 levels have been reduced in individuals with NPC in response to different treatments[1]

CSF FABP3 CONCENTRATION IN PATIENTS WITH NPC1 & CONTROLS[4]



Adapted from Cologna SM, et al. *PLoS One.* 2012;7(10):e47845

Abbreviations: CSF, cerebrospinal fluid; FABP3, fatty acid binding protein 3; NPC, Niemann-Pick disease type C.

1. Ory DS, et al. The Lancet. 2017;390(10104):1758-1768. 2. Pelsers MMAL, et al. Clin Chem. 2004;50(9):1568-75. 3. Owada Y. Tohoku J Exp Med. 2008;214(3):213-220. 4. Fang X-X, et al. J Cell Biol. 2024;223(4):e202211062. 5. Cologna SM, et al. PLoS One. 2012;7(10):e47845.

Key Takeaways

NPC is a rare, neurodegenerative disorder caused by **pathogenic mutations in *NPC1* or *NPC2* genes** that impair intracellular cholesterol trafficking, **leading to lipid accumulation, neuronal dysfunction, progressive neurological decline, and premature death.**[1,2]

Earlier neurological symptom onset in NPC correlates with more aggressive disease progression, **with infantile-onset NPC exhibiting rapid clinical decline and earlier mortality**.[1-3]

The heterogeneity of NPC often leads to a mean **delay between neurological symptom onset and NPC diagnosis of 2.5 years in early-infantile NPC and 4.3 years in late-infantile NPC**.[4,5]

As neurological damage with NPC progression is irreversible, **immediate treatment is necessary to stabilize or improve the development trajectory of patients**.[6,7]

The **rescored R4-domain NPC-CSS**, adapted from the 17-domain and 5-domain NPC-CSS, was designed to **improve clinical relevance and sensitivity by focusing on key clinically meaningful domains.**[8,9]

Biomarkers associated with NPC include diagnostic markers **(C-triol, TCG, and PPCS)** and pharmacodynamic markers reflecting cholesterol trafficking and neurodegeneration **(24[S]-OHC, calbindin D, and FABP3)**.[10,11]

Abbreviations: 24(S)-OHC, 24(S)-hydroxycholesterol; CSF, cerebrospinal fluid; C-triol, cholestane-3β, 5α, 6β-triol; FABP3, fatty acid binding protein; NfL, neurofilament light chain; NPC, Niemann-Pick disease type C; NPC-CSS, NPC Clinical Severity Scale. 3; PPCS, N-palmitoyl-O-phosphocholineserine; TCG, trihydroxycholanic acid glycinate.

1. Burton BK, et al. *Mol Genet Metab*. 2021;134(1-2):182-187. 2. Berry-Kravis E. *Semin Pediatr Neurol*. 2021;37:100879. 3. Imrie J, et al. *BMC Neurol*. 2015;15(1):2574. 4. FDA listening session on Niemann-Pick disease. Summary report. April 9, 2021. 5. Patterson MC, et al. *Orphanet J Rare Dis*. 2020;15(1):104. 6. Mengel E, et al. *Orphanet J Rare Dis*. 2013;8:166. 7. Ara Parseghian Medical Research Foundation. NPC patient-focused drug development meeting. March 18, 2019. Hyattsville, MD. 8. Mengel E, et al. *Orphanet J Rare Dis*. 2020;15(1):328. 9. Mengel E, et al. *Mol Genet Metab Rep*. 2025;43:101233. 10. Campbell K, et al. *Biomarker Res*. 2023;11(1):14. 11. Hiwot T, et al. *J Inherit Metab Dis*. 2026;49(3):e70185.