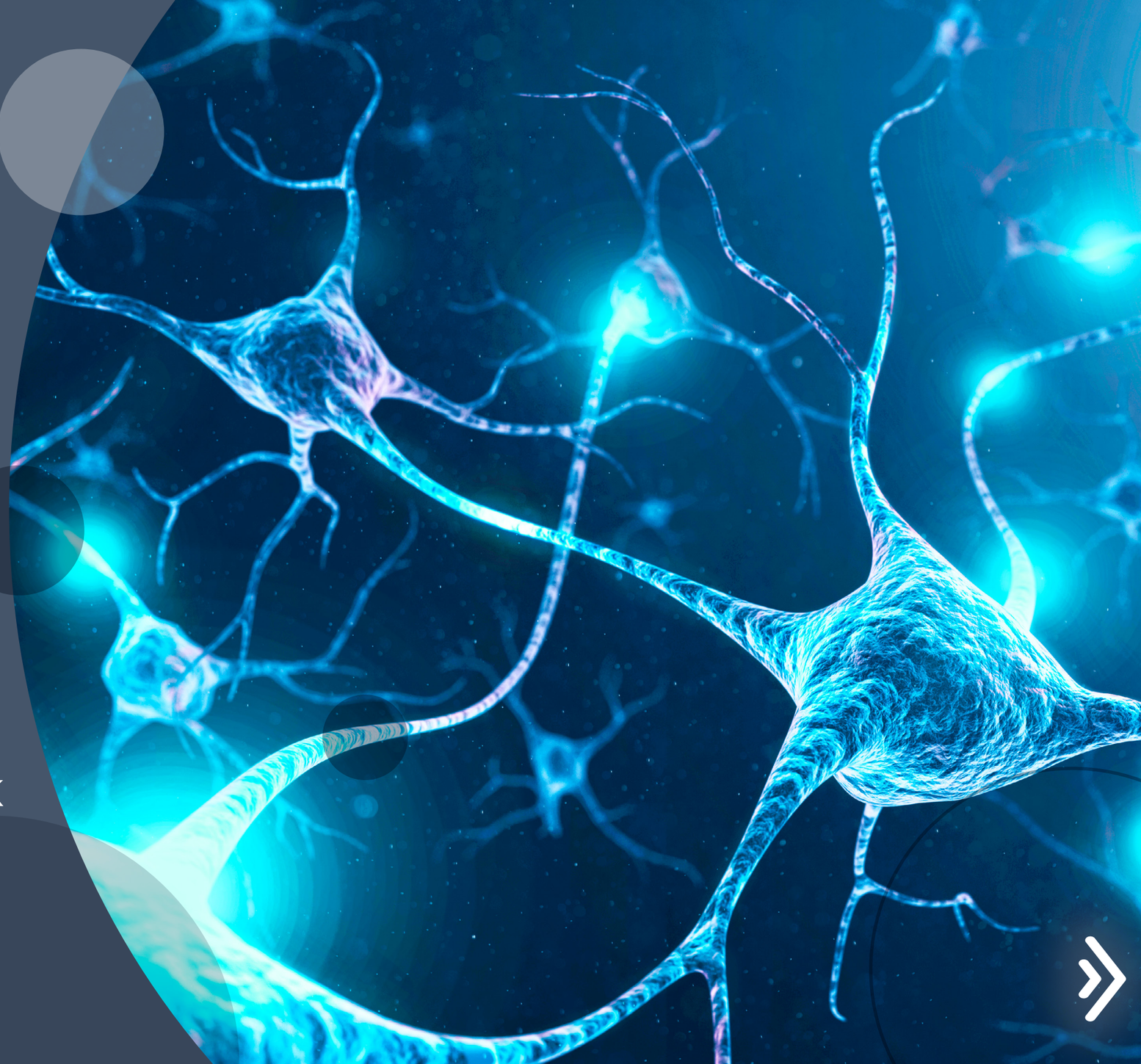
Recognizing and Diagnosing Niemann-Pick Disease Type C (NPC)



What Is Niemann-Pick Disease Type C (NPC)?

- NPC is an ultra-rare, life-limiting autosomal recessive disease characterized by neurovisceral symptoms and progressive neurodegeneration[1,2]
- It is caused by mutations in the *NPC1* or *NPC2* genes, which result in dysfunctional proteins and impaired lysosomal function, leading to accumulation of multiple lipid species in endosomal and lysosomal compartments[1,2]

- The estimated incidence of NPC is 1/100,000 live births; however, it may be underestimated due to low clinical awareness and heterogenous presentation of the disease[1,3,4]

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- Diagnosis of NPC is delayed an average of 4.1 years after the first onset of neurologic symptoms, which narrows the window of therapeutic intervention[3,5]

Detecting and Diagnosing Niemann-Pick Disease Type C (NPC)

Recognizing and diagnosing NPC

- In May 2016, the NPC Diagnostic Recommendations Expert Panel identified 3 approaches for the detection and diagnosis of NPC: clinical assessment, biomarker testing, and genetic analysis[3]

Clinical suspicion for NPC

- The clinical manifestations of NPC may present as nonspecific symptoms[3]
- NPC should be considered as a differential diagnosis for any patients with similar, nonspecific symptoms in certain at-risk groups[3]

Click here for more information

NPC Diagnostic Algorithm[1,3]

- This diagnostic algorithm outlines the steps involved for detecting and diagnosing NPC. Click “NEXT STEP” to move to the next diagnostic step in the algorithm

NEXT STEP

Clinical suspicion

NPC, Niemann-Pick disease type C.

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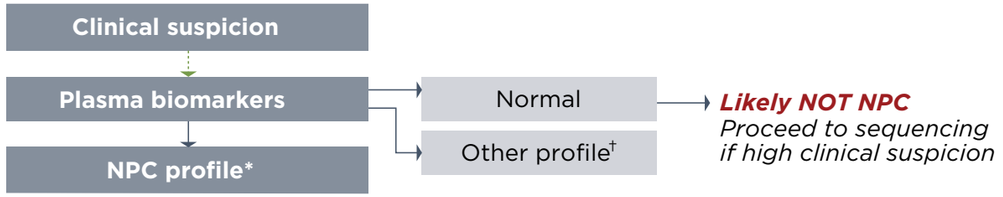

*Elevated cholestane-triol or bile acid derivative and/or lyso-SM-509, with normal or slightly elevated lysoSM.[1]

†Cholestane-triol also elevated in ASMD, acid lipase deficiency, cerebrotendinous xanthomatosis, certain neonatal cholestasis conditions. All lysoSM analogues and bile acid derivatives are elevated in ASMD.[1]

ASMD, acid sphingomyelinase deficiency; lysoSM, lysosphingomyelin; NPC, Niemann-Pick disease type C.

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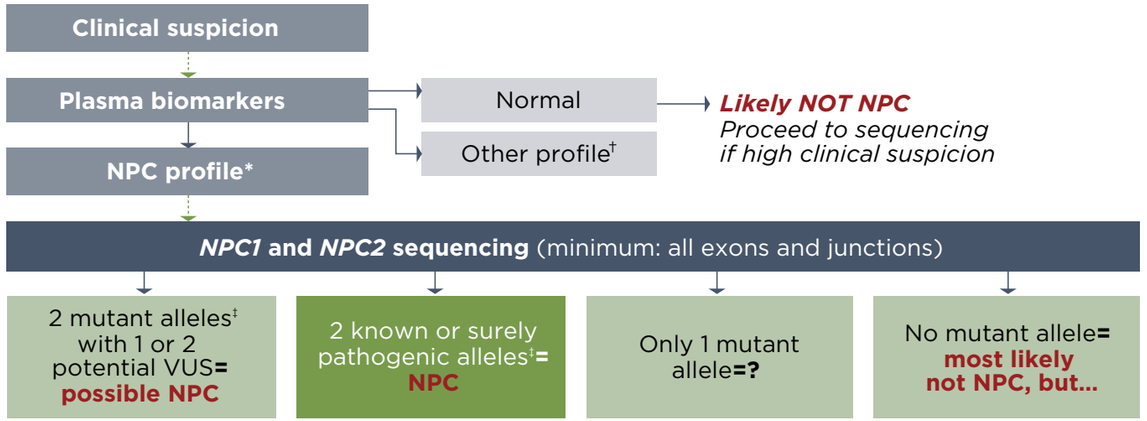

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‡Check allele segregation by parental study or other test.[1]

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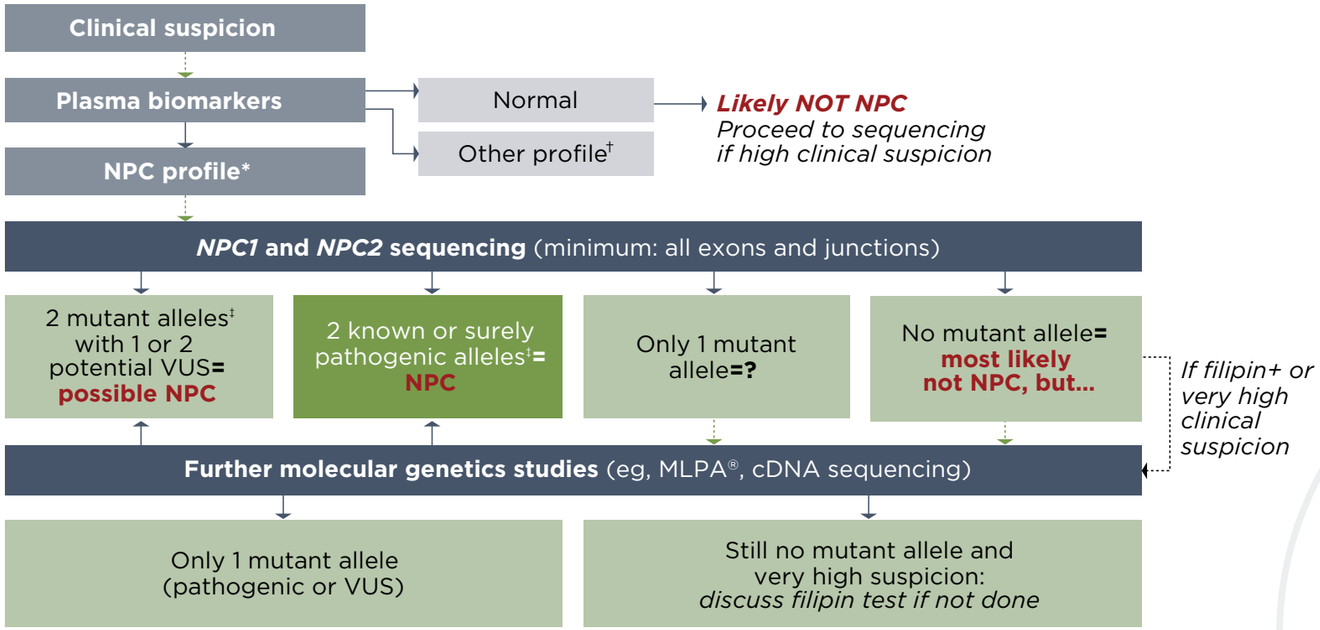

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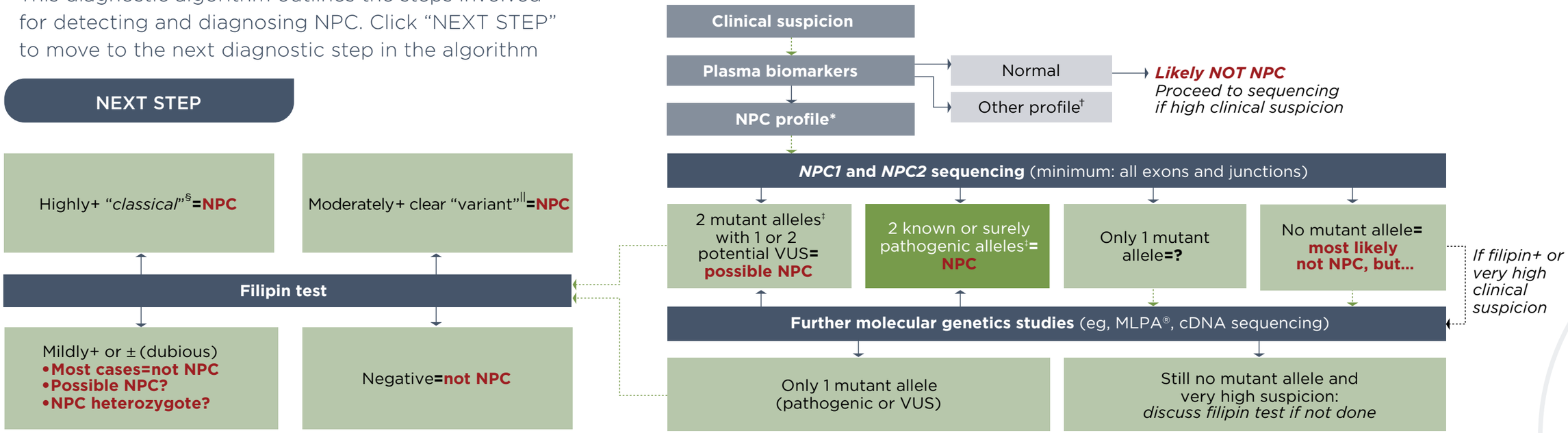

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§I-cell disease (ML-II and -III) gives a false positive result (very different clinical features).[1]

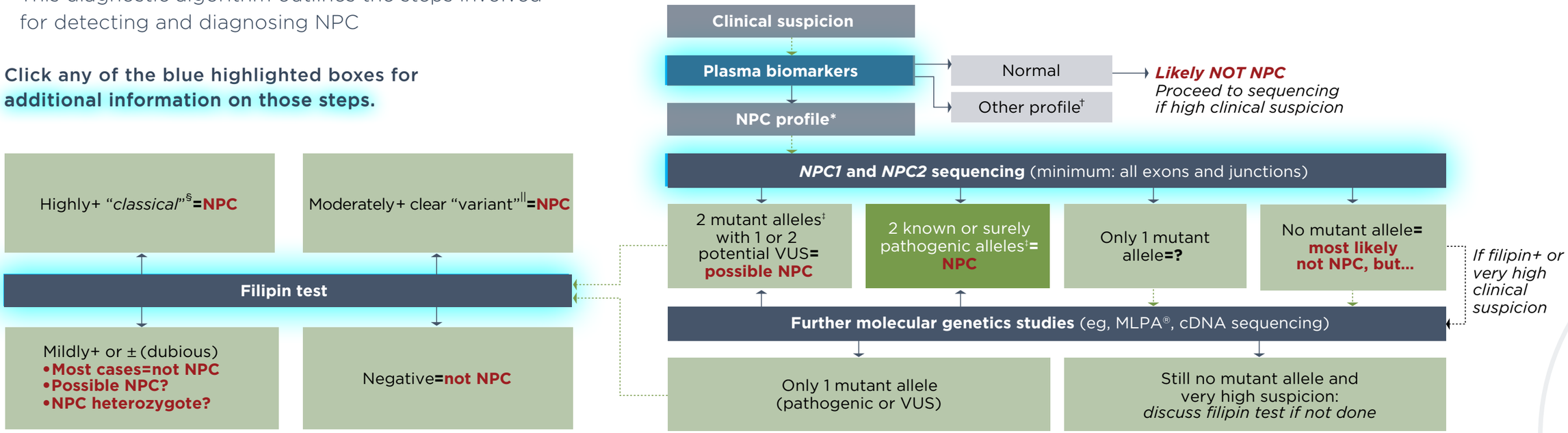
‖ASMD can give a similar filipin pattern.[1]

ASMD, acid sphingomyelinase deficiency; cDNA, complementary DNA; lysoSM, lysosphingomyelin; ML, mucolipidosis; MLPA, Multiplex Ligation-dependent Probe Amplification; NPC, Niemann-Pick disease type C; VUS, variant of unknown significance.

NPC Diagnostic Algorithm[1,3]

- This diagnostic algorithm outlines the steps involved for detecting and diagnosing NPC

Click any of the blue highlighted boxes for additional information on those steps.



Interpretation of combined molecular genetics and filipin results

NPC confirmed if 2 pathogenic mutations (whatever the filipin profile)	NPC confirmed if repeated highly+ filipin¶ (whatever the mutational profile)	NPC almost certain if 2 novel mutant alleles or 1# pathogenic mutant allele and "variant" filipin	Doubt may remain if only 1 mutation# and filipin±	Almost certainly not NPC if no mutation and mildly+ filipin	NPC discounted if no mutation and filipin- (or ±)

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¶Profile also seen in ML-II or -III.[1]

#Profile also seen in heterozygote subjects.[1]

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References: 1. Geberhiwot T et al. *Orphanet J Rare Dis.* 2018;13:50; **2.** Gelsthorpe ME et al. *J Biol Chem.* 2008;283:8229-8236; **3.** Patterson MC et al. *Neurol Clin Pract.* 2017;7:499-511; **4.** Vanier MT. *Orphanet J Rare Dis.* 2010;5:16; **5.** Patterson MC et al. *Orphanet J Rare Dis.* 2013;8:12; **6.** Dardis A et al. *J Clin Med.* 2020;9:679; **7.** Vanier MT, Latour P. *Methods Cell Biol.* 2015;126:357-375.

ORPHAZYME

The heterogenous presentation of NPC makes the disease difficult to identify[1,4]

The age of onset of NPC varies widely. NPC may present early as a rapidly fatal neonatal disorder, or later, as an adult-onset, slowly progressive neurodegenerative disease[4]

NPC can be characterized by visceral and neurologic symptoms; however, these may differ in their presentation depending on the age of onset[4]

There is a wide range of neurologic symptoms, such as ataxia, dystonia, vertical supranuclear saccadic palsy (VSSP), and psychiatric illness[4]

The neurologic symptoms of NPC progress at different rates, with neurological symptom onset at a younger age being associated with more severe disease[1,4]

NPC, Niemann-Pick disease type C.

The following table highlights these at-risk patient groups where NPC should be considered. Patients with these symptoms and criteria should be further evaluated for an NPC diagnosis[3]

At-Risk Groups for NPC	Signs to Look Out For
Ataxia	• Early-onset ataxia (onset <40 years of age) • "Ataxia plus": VSSP, dystonia; cognitive decline; atypical psychiatric disturbances; optional extensor plantar reflexes rather than genuine spastic paraparesis; mental retardation • Ataxia without neuropathy • Ataxia of unknown etiology
Intellectual disability and developmental delay	• Visceral signs (eg, [hepato-] splenomegaly) • Subtle movement dysfunction (ataxia/dystonia), VSSP
Cognitive impairment and early-onset cognitive decline	• <40 years of age, neurologic signs (eg, ataxia, VSSP, dystonia)
Dystonia	• Generalized dystonia • <40 years of age • "Dystonia plus": VSSP, cognitive decline, or psychiatric disturbances
Frontotemporal dementia	• <40 years of age
Atypical schizophrenia/ early-onset psychosis	• Treatment resistance • Neurologic signs (eg, ataxia, VSSP, dystonia) • Organic features: visual hallucinations, comorbid cognitive impairment
Visceral symptoms in the pediatric population	• Isolated infantile splenomegaly or cholestasis or hepatosplenomegaly or fetal/neonatal ascites and neurologic signs (eg, ataxia, VSSP, dystonia)

NPC, Niemann-Pick disease type C; VSSP, vertical supranuclear saccadic palsy.

Plasma Biomarkers

- Biomarker screening can now be considered a first-line approach for the diagnosis of NPC[3]
- Filipin staining was previously the gold standard for NPC detection. However, the biomarkers outlined here have the advantages of noninvasiveness, rapidity, higher throughput, lower cost, and ease of use[3]

Click here for full table

Biomarker	Important Details
Oxysterols[3]	• Most established, accessible, and widely used biomarkers for NPC • Cholestane-3β,5α,6β-triol (C-triol) is the preferred biomarker, shown to be elevated in patients with NPC • 7-ketocholesterol (7-KC) has also been shown to be elevated in patients with NPC • C-triol and 7-KC may be elevated in other diseases, specifically Niemann-Pick disease type A (NPA) and Niemann-Pick disease type B (NPB)
Lysosphingomyelin-509 and other lysosphingolipids[3]	• Lysosphingomyelin-509 (Lyso-SM-509) is elevated in patients with NPC, but also NPA and NPB
Bile acids[3]	• 3β,5α,6β-trihydroxy-cholanoyl-glycine is the preferred bile acid biomarker • Shown to be elevated in NPC, but also NPA and NPB

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Genetic Sequencing

- The expert panel states it is crucial to genetically confirm a diagnosis in patients with high clinical suspicion and/or a biomarker profile consistent with NPC[3]
- There is an estimate of 486 known mutations in *NPC1* and 27 in *NPC2*[6]
- The use of routine sequencing methods can detect mutations on both alleles in >90% of patients with suspected NPC[3]
- Depending on the results from the genetic analysis, an NPC diagnosis may be able to be made or additional genetic or biomarker testing may be necessary[3]

Click here for full table

Genetic Finding	Recommendations
2 pathogenic mutations[3]	• Confirm compound heterozygosity by allele segregation in parents
1 pathogenic mutation + 1 VUS[3]	• Confirm compound heterozygosity by allele segregation in parents • Confirm high clinical suspicion of NPC (clinical signs and biomarker profile) and perform filipin staining test • Perform additional molecular genetic tests (eg, full-gene sequencing, DNA array, MLPA®, qPCR, cDNA sequencing) to identify further mutant alleles
1 pathogenic mutation only or 1 VUS only[3]	• Confirm high clinical suspicion of NPC (clinical signs and biomarker profile) and perform filipin staining test • Perform additional molecular genetic tests (eg, full-gene sequencing, DNA array, MLPA, qPCR, cDNA sequencing) to identify further mutant alleles
0 pathogenic mutations[3]	• Perform additional molecular genetic tests (eg, full-gene sequencing, DNA array, MLPA, qPCR, cDNA sequencing) to identify hidden mutant alleles • Confirm high clinical suspicion of NPC (clinical signs and biomarker profile) and perform filipin staining test

cDNA, complementary DNA; MLPA, Multiplex Ligation-dependent Probe Amplification; NPC, Niemann-Pick disease type C; qPCR, quantitative polymerase chain reaction; VUS, variant of unknown significance.

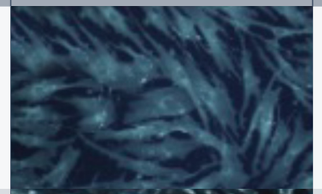
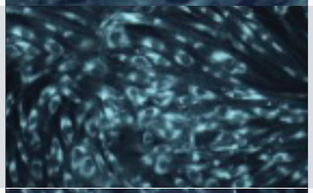
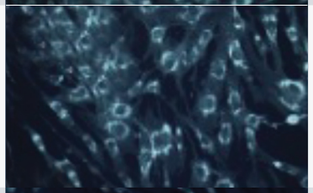
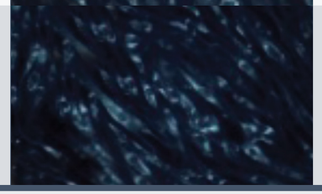
[3]I-cell disease (ML-II and -III) gives a false positive result (very different clinical features).

Filipin Testing

Filipin staining may be used when the genetic analysis is not confirmatory, but the patient has a high clinical suspicion of NPC due to symptoms and/or biomarker results.[3]

Click here for full table

The Following Images Outline the Potential Outcomes of Fluorescent Staining When Performing a Filipin Test

Staining Pattern	Example of Filipin Staining	Staining Details and Potential Mutation Types
Normal		Healthy individual with very low staining[7]
Classical		NPC patient demonstrating a large number of cells intensely staining in a perinuclear pattern. These patients may have a homozygous nonsense or frameshift mutation. The most frequent *NPC1* mutation, p.I1061T, stains in a classical pattern[7]
Intermediate		NPC patient demonstrating a similar pattern of staining to classical, but with less intensity[7]
Variant		NPC patient demonstrating a less intense staining pattern than classical and intermediate, and staining is not present in all cells. These patients may have mutations with compound heterozygosity[7]

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[1]Check allele segregation by parental study or other test.[1]

**Profile also seen in heterozygote subjects.[1]