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► **To cite this version:**

Pfrieiger Fw. The Niemann-Pick type diseases – A synopsis of inborn errors in sphingolipid and cholesterol metabolism. *Progress in Lipid Research*, 2023, 90, pp.101225. 10.1016/j.plipres.2023.101225 . hal-04235098

**HAL Id: hal-04235098**

**<https://cnrs.hal.science/hal-04235098v1>**

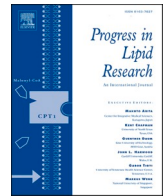
Submitted on 10 Oct 2023

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## Review

# The Niemann-Pick type diseases – A synopsis of inborn errors in sphingolipid and cholesterol metabolism

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## ARTICLE INFO

## Keywords:

Cholesterol  
Lipidosis  
Sphingolipids  
Ceramide  
Lysosome  
Lysosomal storage disorder  
Neurologic  
Psychiatric  
Sterol  
Neurodegeneration

## ABSTRACT

Disturbances of lipid homeostasis in cells provoke human diseases. The elucidation of the underlying mechanisms and the development of efficient therapies represent formidable challenges for biomedical research. Exemplary cases are two rare, autosomal recessive, and ultimately fatal lysosomal diseases historically named "Niemann-Pick" honoring the physicians, whose pioneering observations led to their discovery. Acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD) are caused by specific variants of the *sphingomyelin phosphodiesterase 1 (SMPD1)* and *NPC intracellular cholesterol transporter 1 (NPC1)* or *NPC intracellular cholesterol transporter 2 (NPC2)* genes that perturb homeostasis of two key membrane components, sphingomyelin and cholesterol, respectively. Patients with severe forms of these diseases present visceral and neurologic symptoms and succumb to premature death. This synopsis traces the tortuous discovery of the Niemann-Pick diseases, highlights important advances with respect to genetic culprits and cellular mechanisms, and exposes efforts to improve diagnosis and to explore new therapeutic approaches.

## 1. Introduction

Inborn errors of lipid metabolism cause havoc in vulnerable cells, notably neurons, provoking rare but often fatal diseases [1–5]. Variants of lipid-related genes also increase the risk of prevalent disorders presenting age-dependent neurodegeneration [6–10]. Although the genetic culprits for many pathologic conditions have been uncovered, it is unclear how defective homeostasis of specific lipids provokes progressive neurologic symptoms and shortens the life span of patients, in the most severe cases to just a few months. The elucidation of mechanistic links between the genetic defects and the pathologic changes in specific organs, notably the nervous system, and the development of efficient diagnostic and therapeutic approaches represent formidable challenges for biomedical research. The Niemann-Pick diseases are prime examples for pathologic conditions provoked by deficient lipid homeostasis. This synopsis aims to trace their tortuous discovery, highlights important advances with respect to genetic culprits and disease mechanisms, and exposes efforts to improve diagnosis and to explore new therapeutic approaches.

The historic term "Niemann-Pick" encompasses two rare, autosomal

recessive lysosomal disorders [11–13] (Table 1). Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick type A, A/B and B disease (Table 1), is caused by mutations in the *sphingomyelin phosphodiesterase 1 (SMPD1)* gene encoding the enzyme acid sphingomyelinase (ASM; EC 3.1.4.12) [14–20]. The different forms of Niemann-Pick type C disease (NPCD) are caused by mutations in *NPC intracellular cholesterol transporter 1 (NPC1)* disease) or—less frequently—in *NPC intracellular cholesterol transporter 2 (NPC2)* disease) [21–26] (Table 1).

ASMD and NPCD are rare with estimated birth rates of 1 in 100,000 though higher incidences of specific forms have been reported [27,28]. Numerous variants of the *SMPD1* and *NPC1* or *NPC2* genes (<http://www.hgmd.org/>) have been identified in ASMD and NPCD patients, respectively, that provoke a wide spectrum of visceral, neurologic and psychiatric symptoms with spleen, liver, lung and brain being the most severely affected organs. Different forms of ASMD [14,16] and NPCD [22,29–31] can be distinguished (Table 1) based on the age of disease onset and the presence of neurologic symptoms, although there is symptomatic overlap between the forms. Patients with the most severe phenotypes present visceral (pre- or perinatal NPCD) and neurovisceral signs (infantile neurovisceral ASMD) during the first months after birth

**Abbreviations:** ASM, acid sphingomyelinase; ASMD, acid sphingomyelinase deficiency; HPBCD, hydroxypropyl-beta-cyclodextrin; NPCD, Niemann-Pick type C disease; PPCS, N-palmitoyl-O-phosphocholineserine; rhASM, recombinant human ASM.

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<https://doi.org/10.1016/j.plipres.2023.101225>

Received 2 February 2023; Received in revised form 27 March 2023; Accepted 27 March 2023

Available online 31 March 2023

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**Table 1**  
Classification of Niemann-Pick diseases.

Disease	OMIM	Genes	Historic	Forms (age of onset)
Acid Sphingomyelinase Deficiency	257200	<i>SMPD1</i>	Type A	- Infantile neurovisceral (early infantile)
	607616		Type A/B Type B	- Chronic neurovisceral (childhood) - Chronic visceral (child-/adulthood)
Niemann-Pick Type C1	257220	<i>NPC1</i>	Type C or D	- Perinatal (2 mths)
Niemann-Pick Type C2	607625	<i>NPC2</i>		- Early infantile (2-24 mths) - Late infantile (2-6 yrs) - Juvenile (6-15 yrs) - Adolescent/Adult (>15 yrs)

**Table 2**  
Symptoms common to ASMD and NPCD.

Type	Symptom
Systemic	Hepatosplenomegaly
	Liver fibrosis, cirrhosis
	Cholestatic jaundice
	Fetal hydrops
	Portal hypertension
	Interstitial lung disease
	Thrombocytopenia
Neurologic	Dystonia
	Dysphagia
	Hypotonia
	Ataxia
	Intention tremor
	Speech delays
	Delayed motor development
	Loss of motor skills
	Cognitive impairment
	Intellectual decline
Psychiatric	Disruptive/aggressive behaviour
	Depression
	Psychosis

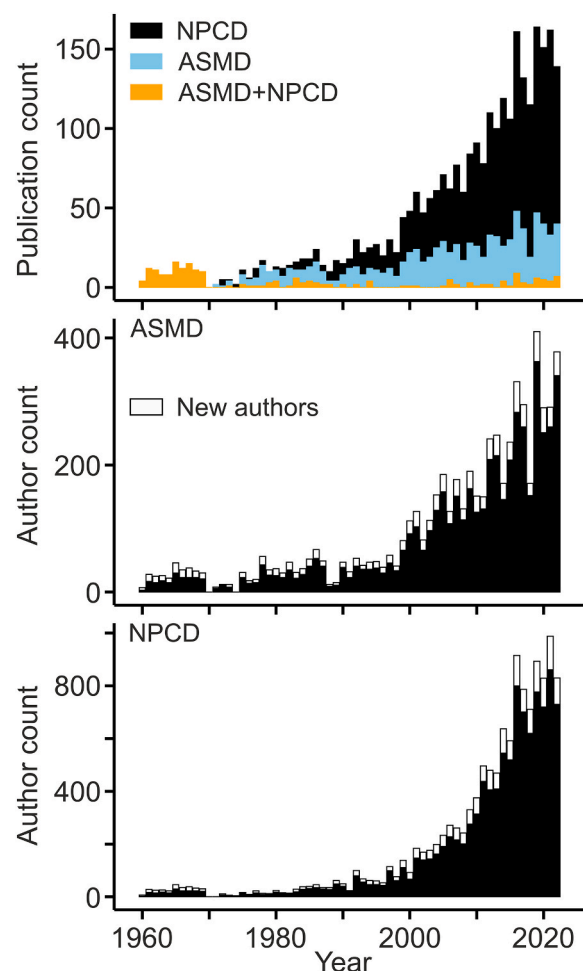
and die within the first years of life. On the other side of the spectrum are NPCD patients presenting neurologic or psychiatric symptoms as adolescents or adults, and ASMD patients with the chronic visceral form presenting progressive visceral symptoms at childhood or later with no neurologic signs. Although individual presentation varies widely, several symptoms are common to both diseases (Table 2). Based on current diagnoses, most NPCD and ASMD patients show the infantile [29,31,32] and the chronic visceral form [33], respectively. Regardless of the form, the relentless progression of ASMD and NPCD degrades the quality of life of patients [34,35] and demands multidisciplinary medical care [36,37].

The primary defects of the diseases concern proteins that ensure the homeostasis of sphingomyelin (ASMD) and cholesterol (NPCD) in cells. These very prominent molecules are intensely studied in numerous biological contexts, as they serve as intimately linked building blocks of eukaryotic membranes [38–42] and as key components of cellular signaling pathways [43–49].

## 2. Early history

The research history of the diseases bearing the name Niemann-Pick started at the beginning of the 20th century. While working as an intern at the children's hospital of the Charité in Berlin, Germany, the pediatrician Albert Niemann tried to diagnose a 17-months-old girl named Irene. The infant presented a "colossally swollen abdomen (circumference 50 cm)", apathy and a "quite miserable nutritional state". Following the practice and the methods known at the time, Niemann tested and treated the child for congenital syphilis—without success. Irene died

within 4 weeks. In 1914, Niemann published a case report with the blatantly honest title "An unknown clinical picture" ["Ein unbekanntes Krankheitsbild"]. He wrote that he never saw or read about a similar case, and he noted differences to morbus Gaucher [50]. Niemann died in 1921 from tuberculosis, but his observations were followed up by other



**Fig. 1.** Development of the ASMD and NPCD field based on publications and authors.

Stacked bar graphs showing (top) the annual count of publications related to both diseases (orange), to ASMD only (sky blue) and to NPCD only (black), and the annual counts of authors contributing articles to ASMD (center) and NPCD (bottom). White bars indicate number of authors publishing for the first time in each field (New authors; see the appendix for the Web of Science queries). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

colleagues, notably the eminent German pathologist Ludwig Pick. The protocol of the scientific discussion following a presentation given by Pick in 1922 documents his clairvoyant assessment. He stated that the cases reported by Niemann and others [51,52] belong to a distinct group of "lipoidcell splenohepatomegaly of infants" ["Lipoidzellige Splenohepatomegalie der Kinder"] [53]. In an article published in 1924, he summarized histopathologic changes in these patients, and he coined the new nosologic term "lipoidcell splenomegaly (type Niemann)" ["lipoidzellige Splenomegalie (Typus Niemann)"] [54]. In a comprehensive review published in 1926, Pick outlined thoroughly what distinguishes the cases with "lipoidcell hepatosplenomegaly type Niemann" from Gaucher disease [55]. He stated that central to the pathogenesis is a primary defect in metabolism, which causes an overload of blood and tissues with fat-like substances ("lipoids"). In the same year, when Pick published his review, the yet-to-become famous pediatrician Erwin Schiff was the first to use the term "type Niemann-Pick" for his diagnosis of a 17-months-old boy. Remarkably, Schiff accomplished this diagnosis *ante-mortem* by splenic biopsy [56]. Curiously, at least one author used transiently the term "Pick-Niemann" disease [57]. In 1927, Brahn and Pick reported several-fold increased levels of cholesterol in spleens of Niemann-Pick patients compared to normal controls [58]. In the 1930s, Ernst Klenk discovered elevated levels of sphingomyelin in their spleen [59], liver and brain [60,61], which were confirmed by other colleagues [62,63]. Fast forward to 1961, when Allen C. Crocker working at the Children's Hospital of the Harvard Medical School (USA) distinguished four forms of the disease (A though D; Table 1) [64] based on a previous review of visceral and neurological symptoms, and biochemical measures in patients [65]. "Type D" comprised exclusively patients from a large Acadian family living in Nova-Scotia since the 17th century [66]. Given the symptomatic variation among patients and the limited diagnostic methods, the classification of Niemann-Pick patients remained problematic until the 1980s (see for example [67]). Two additional categories of Niemann-Pick disease appeared in the 1970s that are now obsolete. Niemann-Pick type E presenting visceral sphingomyelin storage without neurologic involvement and normal ASM activity was proposed in 1972 by Fredrickson and Sloan based on several patients with mostly non-familial disease [68]. Type F was proposed in 1978 by Schneider and colleagues based on their discovery of a heat-labile form of ASM in patients from two families presenting hepatosplenomegaly in their childhood but no neurologic symptoms [69].

### 3. Foundational research

The nosology established by Crocker started the modern era of research on the Niemann-Pick diseases. Selected publications that provided insight into molecular and cellular mechanisms, that established methods and tools, and that explored diagnostic and therapeutic approaches are mentioned in the following paragraphs. Fig. 1 shows the development of the fields based on annual counts of scientific articles and contributing authors including newcomers.

In 1966, Roscoe O. Brady and colleagues working at the National Institutes of Health in the USA identified a defect in an enzyme that cleaves sphingomyelin, the ASM, as cause for the "classic infantile form of Niemann-Pick disease". This form corresponded to Crocker's type A [70,71]. The group further established a first enzymatic test to diagnose ASMD based on blood samples [72] and on skin or bone marrow cells derived from patient biopsies [73]. These findings marked a breakthrough for ASMD, but they confused research into the cause of NPCD. The latter field squandered for more than 10 years in the labyrinth of the sphingomyelinase hypothesis (see for example [74–78]). Nonetheless, Crocker already presumed distinct genetic causes for the different forms of the disease, and normal levels of ASM activity were detected in organs from Niemann-Pick Type C and D patients [75,79–81]. In the 1980s, evidence for a distinct molecular cause for NPCD came from studies on a strain of mice presenting progressive neurologic symptoms and premature death [82]. They revealed impaired cholesterol esterification

[83–85] and disturbed intracellular transport of unesterified cholesterol [86,87] causing its accumulation in late endosomes/lysosomes [88–90]. Together, these findings established NPCD as a distinct nosologic entity.

### 4. Genetic culprits of the diseases

Key steps to advance research on inherited diseases are the identification of the mutated gene(s) and the characterization of the encoded proteins. In the case of ASMD, the cloning, expression and chromosomal localization of human and mouse *SMPD1* [91–95] allowed for the identification of disease-causing mutations in patients [96–98], measurements of their impact on ASM activity [99], the detection of carriers [100], and a first exploration of genotype-phenotype relations [101,102]. Comparisons of patient-derived cells and organs indicated that the infantile neurovisceral form of ASMD is provoked by extremely low levels of ASM activity [79,103–106]. The discovery of paternal imprinting at the *SMPD1* locus helped to explain at least in part the wide clinical spectrum of ASMD patients [107].

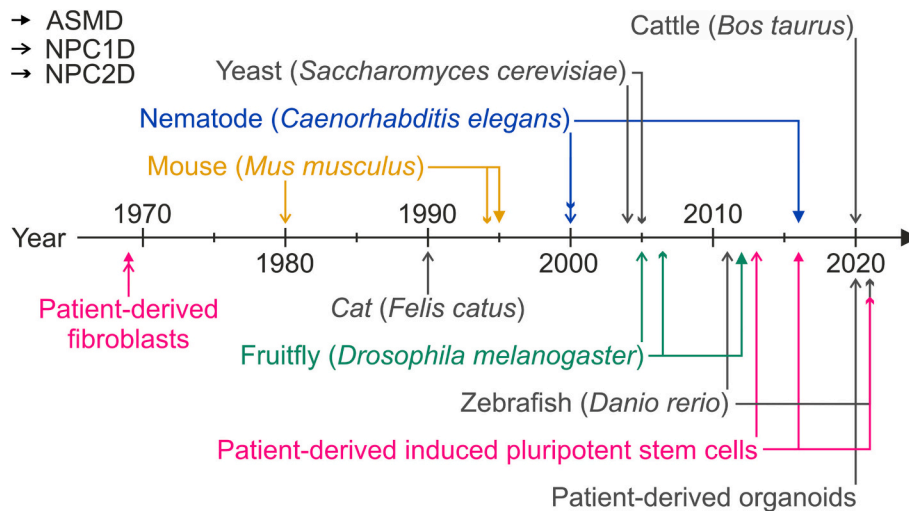
The identification of genes causing NPCD was delayed by several years compared to the breakthroughs on the ASMD front. The existence of distinct genetic culprits causing ASMD and NPCD was indicated by early observations that different genes complement the defects of fibroblasts from Niemann-Pick Type A and B compared to type C patients [103]. The first gene causing NPCD disease, named *NPC1*, was identified in 1997 [108,109]. Patients originally assigned to type D, the so-called "Nova Scotia type", carried a specific allele of *NPC1* [110]. Earlier studies had indicated the presence of a second gene provoking NPCD [111,112], which was subsequently identified as *NPC2* [113]. This gene was identical to *EPI-1* and *HE1* genes that were originally described in the 1990s as major components of epididymal fluid from chimpanzees [114] and humans [115], respectively. The functional collaboration between *NPC1* and *NPC2* in the lysosome was first indicated by experiments with genetically modified mice [116].

### 5. The proteins and their functions

The discovery of the defective proteins proceeded in parallel to the identification of the mutated genes. The enzyme defect causing ASMD was known since the 1960s, but the characterization of the protein, ASM, took off in the 1980s with its purification to homogeneity [117–119]. Further research revealed several processing steps generating different forms of the enzyme [120] that are targeted to the lysosome [121–124] or released to the extracellular space [125–127] upon external signals [128]. Other properties of the enzyme, which comprises 631 amino acids, were uncovered. This includes the presence of a saposin-like activator domain thus forgoing the need of co-activator proteins [129,130], and the dependence of its activity on zinc [126,131,132], post-translational modifications [133–135] and the cellular redox status [136–138]. The elucidation of the protein structure brought new insight with respect to conformations, binding sites, and the impact of mutations on protein structure and function [139–141]. Enzyme activity assays revealed that ASM is a promiscuous phosphodiesterase cleaving phospholipids other than sphingomyelin [142].

Starting in the 1980s, interest in ASM was propelled into new spheres by evidence that the enzyme and its product, ceramide, are implicated in different signaling pathways and cellular processes, notably apoptosis [143–150]. These findings provoked studies of ASM in the context of diverse pathologic conditions including atherosclerosis [151], bacterial or viral infections [152–154], dermatitis [155], emphysema [156], Wilson disease [157], cystic fibrosis [158], depression [159], and Alzheimer disease [160]. Evidence that specific variants of ASM enhance the risk for Parkinson disease have opened new avenues for research on this prevalent disorder [161–163].

Characterization of the proteins encoded by *NPC1* and *NPC2* took off after the identification of the genes. Human *NPC1* is a relatively large protein comprising 1278 amino acids and 13 transmembrane domains.



**Fig. 2.** Development of experimental models.

Timeline showing the development of experimental models for ASMD and NPCD. Model organisms used to study both diseases are indicated in colors, organisms in grey have been established for NPCD only.

Its smaller partner NPC2, made of 151 amino acids, is water-soluble and bears a hydrophobic pocket. Studies revealed the presence of NPC1 [164–167] and NPC2 [113,168–170] in late-endosomes/lysosomes, their glycosylation patterns [171–174], their binding of sterols [173,175–179], their interactions with lipids [180–183] and proteins [174,183–188], their critical domains [189,190], and the destiny of the frequent, disease-causing NPC1 variant I1061T [191–193]. Decisive insight in the molecular functions of NPC1 and NPC2 came from cryo-electron microscopic and x-ray diffraction analyses of their atomic structures [190,194–203]. A key finding was that binding pockets in NPC1 and NPC2 accommodate cholesterol in opposite directions. This insight inspired the "hydrophobic hand-off" model that explains how NPC2 transfers cholesterol to NPC1 [196,204]. The absence of NPC2 may explain the lack of NPC1-mediated cholesterol transport in an artificial system [205]. A next advance was the discovery of a tunnel inside the NPC1 protein, as shown for its distant relative PATCHED [206], enabling cholesterol to crawl through the protein [201–203]. The exact mechanisms how cholesterol exits the endosomal-lysosomal system and reaches other cellular organelles are under investigation. During the last decade, studies on generic cells such as cell lines or fibroblasts proposed several pathways including other carriers such as StARD proteins [207–209] and membrane contact sites [210–218]. The contribution of each pathway probably depends on the specific type of cell and the intracellular targets receiving recycled or imported cholesterol.

Similarly as interest in ASM was boosted in the 1990s by its newly discovered roles in cell signaling, interest in NPC1 was turbocharged during the last decade by its identification as cellular receptor for filovirus [219,220], which spawned an entire new branch of research [221] and incited the development of new tools [222]. In addition, specific NPC1 variants have been identified as risk factor for obesity [223,224].

## 6. Experimental models

Experimental models are essential to explore disease mechanisms and to develop therapeutic approaches. The first models for ASMD were cells from patient-derived skin and bone marrow biopsies [73] and immortalized lymphoid cells [225] with the more recent addition of induced pluripotent stem cells [226] (Fig. 2). Identification of the *SMPD1* gene enabled the generation of knock-out mice (Fig. 2). These animals show accumulation of lipids in visceral organs [227] and in different brain regions [228] and degeneration of cerebellar Purkinje cells [229], they develop neurologic symptoms between the third and

fourth month of age, and they die prematurely [230,231]. Heterozygous *Smpd1* mice also show changes including sperm abnormalities [232], reduced susceptibility to liver disease [233,234], and focal ischemia [235]. ASM-deficient mice are used to study a large variety of cellular processes given the above-mentioned roles of ASM and ceramide in diverse signaling pathways [149,236]. Transgenic mice have also been developed to study specific variants of ASM. Mice expressing a chimeric *SMPD1* targeted to the lysosome show a level of enzymatic activity that is high enough to avoid development of neurologic symptoms [237]. Other transgenic mice express specific human *SMPD1* variants on a *Smpd1*-deficient background [238] or variants that lack a caspase cleavage site [154]. With respect to other mammals, ASMD-like symptoms were described in a Balinese cat [239], a poodle dog [240], a Hereford calf [241], and a juvenile raccoon [242], but no breeding colonies were established. Eukaryotic orthologs of ASM and the outcome of their deficiency were described in the nematode *Caenorhabditis elegans* [243,244] and the fruit fly *Drosophila melanogaster* [245,246] (Fig. 2). Small-molecule inhibitors of ASM [247,248] can be used to interrogate the impact of reduced ASM activity on cells or tissues [249].

The arsenal to explore NPCD is well armed (Fig. 2). Here, selected advances on this front are highlighted, detailed overviews can be found elsewhere [250,251]. As for ASMD, the first models to study NPCD were primary cultures of patient-derived fibroblasts [73] followed by Chinese hamster ovary cell lines bearing defects in NPC1 [252], and neurons derived from embryonic stem cells [253,254]. Protocols to generate pluripotent stem cells from patient fibroblasts and to convert these cells to cell types of interest allowed to study how defects of NPC1 [255–259] and NPC2 [260] affect human neurons and other cell types in vitro [261]. New cell-based disease models allow to investigate the functional impact of NPC1 variants [262–264]. Organoid models help to assess the impact of NPC1 on brain cells and the efficacy of therapeutic approaches at a more integrated level than traditional two-dimensional cell cultures [265]. Pharmacologic induction of a NPCD-like phenotype in cells can be achieved by U186669A [266–268] and itraconazole [201,269,270], which inhibit NPC1 activity albeit through distinct binding sites [201,269].

The parade of animal models for NPCD started in the 1980s with mammals (Fig. 2). Mice of the BALB/C [271] and C57BL strains [272] and a cat [273–275] all bearing spontaneous mutations in the *Npc1* locus [109,276,277] recapitulate some of the neurologic symptoms seen in humans, and they die prematurely. Heterozygous individuals of the mouse strains also present changes such as increased caveolin-1 expression [278], reduced macrophage death due to atherosclerosis



[279], impaired glucose tolerance [280], reduced activity of the cytochrome P450 system [281], and delayed neurodegeneration [282]. The latter change recapitulates neurologic symptoms observed in feline [283] and human heterozygous *NPC1* carriers [284,285]. The mouse models with spontaneous mutations in *Npc1* were complemented by genetically modified mice bearing selected human *NPC1* variants or allowing for cell-specific analyses [286–291]. The latest arrival in the zoo of NPC1-deficient mammals are Angus cattle [292] (Fig. 2). The functions of NPC2 and its interactions with NPC1 in mammals have been studied in *Npc2* knock-down mice [116,181,293], which recapitulate neurovisceral symptoms.

Apart from mammals, a wide range of uni- and multicellular organisms is used to study the impact of NPC1 or NPC2 deficiency (Fig. 2), since NPC1 and NPC2 are "old inventions", and orthologs are present in many phyla [294–297]. This includes workhorses of biological sciences including the plant *Arabidopsis thaliana* (NPC1: [298]), the ciliate *Tetrahymena thermophila* (NPC1: [299]), yeast (NPC1: [300–305]; NPC2: [304,306]), the fruitfly *Drosophila melanogaster* (NPC1: [307–310]; NPC2: [311,312]), the nematode *Caenorhabditis elegans* (NPC1 [313,314]; NPC2 [313,315]), and the fish *Danio rerio* (NPC1: [316–318]; NPC2: [319,320]). Given the diverse functions of NPC1 and NPC2 orthologs, notably as odorant and pheromone carriers in arthropods [321,322], the "ancient" versions of these proteins are of increasing interest in diverse contexts including allergy [323,324], infectious diseases [325–331], and agricultural pest control [332–337].

## 7. Methods and tools for experimental research

Diverse methods and tools have been developed to study the biologic impact of the genetic variants on cells and to uncover disease mechanisms. The pioneers like Niemann and Pick relied on histologic staining methods and light microscopic inspection of biopsies and post-mortem samples. These techniques revealed a vacuolated appearance of cells due to the presence of "fat-like" substances ("lipids") [50,55]. Starting in the 1960s, electron microscopy showed very particular membranous structures named myelin figures, multilamellar bodies or polymorphous cytoplasmic inclusions, in cells from different tissues and organs of ASMD and NPCD patients [338–343] even before the accumulating lipids were identified. Enzymatic activity of ASM has been measured by radiometric [76,344], chromogenic [345], fluorometric [346–349], and mass spectrometric [350] assays, some of which were used for diagnosis and for newborn screens based on dried blood spots [351–357].

The intracellular accumulation of sphingomyelin due to defects in ASM can be tracked by light microscopy using fluorescent analogues [358,359] and by proteins such as lysenin [360,361] and actinoporins [362] that are produced by earth worms and sea anemones, respectively [363,364]. These proteins can be detected by light and electron microscopy after direct or indirect labeling [365]. At present, the intracellular transport activity of the NPC1/NPC2 team cannot be measured directly; cell-free assays were developed to study cholesterol transport by NPC2 between donors and acceptors [180,366]. The accumulation of unesterified cholesterol within cells due to NPC1 or NPC2 dysfunction can be visualized by filipin [83,367], a complex of several fluorescent polyenes secreted by *Staphylococcus filipinensis* [368–370]. Application of this cytochemical stain to patient-derived fibroblasts facilitated the notoriously protracted and difficult diagnosis of NPCD [371–373]. The presence of filipin-stained cholesterol in ultrastructurally defined lamellar inclusions was shown by correlative light and electron microscopic inspection [374]. Additional tools to visualize the distribution of cholesterol in cells are cholesterol-binding proteins derived from theta toxin (perfringolysin O), a cytolysin secreted by *Clostridium perfringens* [375–377], and fluorescent analogues or modified versions of cholesterol (for review see [378]). Other natural, protein-based toxins recognize sphingomyelin/cholesterol complexes [363,364,379]. Additional, indirect approaches to track ASMD- and NPCD-induced defects in cells are based on the accumulation of fluorescent lactosyl-ceramide

[380,381], and on the pathologic expansion of the acidic cellular compartment labeled by a pH-dependent fluorophore (LysoTracker). The size of this compartment in patient fibroblasts correlates with disease onset and severity [382–384]. These tools together with biochemical measurements of NPC1 protein levels were used to explore genotype-phenotype correlations for NPC1 [381,385–388] and NPC2 patients [389]. Further additions to the toolbox are functionalized sphingolipids and cholesterol for concentration-clamp, crosslinking and tracking [183,390–394], probes to monitor endosomal-lysosomal function and lipid accumulation in living cells [395–397], and new approaches to analyse the molecular content of lysosomes [398–400]. The latter are critical feats to study diseases affecting this organelle [12].

## 8. Clinical tests and measures

Clinical research and development require methods to identify and diagnose patients, to measure disease severity, to monitor its progression, and to gauge the efficacy of drug candidates in an objective and quantitative manner. A major breakthrough with respect to genetic tests was the advent of next-generation sequencing of DNA and RNA combined with advanced bioinformatic tools in the beginning of the 2000s. These techniques enabled the detection of new variants, facilitated the diagnosis of patients and led to a revision of carrier frequencies [28,401–408]. The genetic tools have also advanced experimental research as they help to track cell-specific reactions to NPC1 or NPC2 deficiency [320,374,409,410].

Clinical severity scales to quantify disease state and monitor its progression have been developed for ASMD [411] and for NPCD [412–417]. Natural history data summarizing the course of the diseases in individual patients were collected for ASMD [16,411,418–423] and for NPCD [424–434]. Clinical suspicion indices have been developed to identify NPCD patients [435–438]. Databases listing gene variants and patient information (registries) for ASMD [439] and NPCD [412,414,429,440–442] have been established facilitating preclinical and clinical research.

These developments were accompanied by the discovery of molecular biomarker candidates in body fluids of patients. Ideally, these molecules, produced in specific cells and tissues, should serve as surrogate markers of clinical endpoints allowing to monitor disease progression and to gauge the efficacy of therapeutic interventions in patients [443]. Biomarker candidates for ASMD measured in blood were cytokines [444,445], growth hormone and iron [446], 7-ketocholesterol [447], lysosphingomyelin/sphingosylphosphorylcholine [448,449], lysosphingomyelin-509 [450]. With respect to NPCD, blood-derived biomarkers were 7-ketocholesterol [451], oxysterols [451–453], 7-ketocholesterol [451], and bile acids [454–456], galectin-3 (LGALS3) and cathepsin D (CTSD) [457], different sphingolipids [458,459], lysosphingomyelin-509 [450], later identified as N-palmitoyl-O-phosphocholineserine (PPCS) [460,461], glycoprotein nonmetastatic melanoma protein B (GPNMB) [462–464], neurofilament light chain [465,466], and differences in metabolite profiles [467]. Biomarker candidates in cerebrospinal fluid were calbindin [468], fatty acid binding proteins [469], microglia-derived CD22 [470], neuropeptide Y [471] and neuroinflammation-related molecules [471–473]. In addition, cholesterol metabolites [474] and the small non-coding microRNAs miR-155 [475] may serve as markers in urine and tissues, respectively. Measures of sphingolipids and oxysterols were used to screen for ASMD and NPCD patients [476–480]. Recent studies show that the accuracy and specificity of biomarkers can be increased when several of them are detected in parallel and subjected to multivariate analyses [481,482]. Given the complexity of the Niemann-Pick diseases and the wide symptomatic variability among patients, diagnoses of ASMD and NPCD based on biomarkers must be validated by an ASM activity assay [483] and by genetic tests of NPC1 and NPC2, respectively [373,484,485]. Although non-specific, diverse methods have been proposed to evaluate and monitor disease state in ASMD [17,18] and NPCD patients [22].

**Table 3**  
Cell-specific changes in ASMD and NPCD.

Cell type (source*)	Disease	Change	References
Adipocytes, in vitro (h, m)	NPCD	Impaired differentiation and maintenance (NPC2-dependent)	[572]
Alveolar cells type II (m, c)	NPCD	Perturbation of autophagy and surfactant production	[573,574]
Astrocytes, microglial cells (h, m)	ASMD, NPCD	Different pathologic changes	ASMD: [563]; NPCD [409,470,502,550,563,565–567,575–584]
Generic cells: cell lines (m)	ASMD	Enhanced activator protein 1 (AP1) signaling	[585]
Generic cells: cell lines, fibroblasts (h, m)	ASMD	Impaired endocytosis and plasma membrane repair	[154,586]
Generic cells: cell lines, fibroblasts (h, m)	NPCD	Enhanced fluidity of plasma membrane	[587]
Generic cells: cell lines, fibroblasts (h, m)	NPCD	Impaired motility of endosomal-lysosomal compartments	[397,588–592]
Generic cells: fibroblasts (h)	NPCD	Production of oxysterols	[593]
Generic cells: cell lines, fibroblasts (h)	NPCD	Perturbed RAB9-dependent sorting of mannose 6-phosphate receptors	[594]
Generic cells: fibroblasts (h)	NPCD	Enhanced oxidative stress	[595]
Generic cells: fibroblasts (h)	NPCD	Perturbation of autophagy	[527,596]
Generic cells: cell lines, fibroblasts (h)	NPCD	Impaired lysosomal calcium release	[393,597]
Generic cells: cell lines, fibroblasts (h)	NPCD	Enhanced exosomal cholesterol release	[598]
Generic cells: cell lines, fibroblasts (h)	NPCD	Impaired lysosomal proteolysis	[527,599]
Generic cells: cell lines, fibroblasts (h)	NPCD	Hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1)	[185,599]
Generic cells: cell lines	NPCD	Changes in lysosomal glycocalyx	[600]
Generic cells: cell lines, fibroblasts (h)	ASMD, NPCD	Impaired cellular cholesterol efflux	[218,601,602]
Generic cells: cell lines, fibroblasts (h)	ASMD, NPCD	Increased permeability of lysosomal membranes	[599,603]
Generic cells: cell lines, fibroblasts (h)	ASMD, NPCD	Impaired biogenesis and function of mitochondria	[305,604]
Choroid plexus epithelial cells (m)	NPCD	Enhanced extracellular vesicle secretion	[605]
Coronary arterial smooth muscle cells (m)	ASMD	Perturbation of autophagy	[606]
Germline cells (m)	ASMD, NPCD	Impaired maturation of oocytes and spermatozoa	ASMD: [607]. NPCD: [608–610]
Hepatic stellate cells (m)	ASMD	Enhanced cathepsin activity	[611]
Hepatocytes, liver (m)	NPCD	Impaired peroxisome function	[612]
Hepatocytes, liver (h, m)	NPCD	Perturbation of metal homeostasis (zinc, copper and iron)	[613,614]
Hepatocytes (m)	NPCD	Impaired insulin signaling	[615]
Hepatocytes, liver (m)	NPCD	Impaired mitochondrial function	[604,616–619]
Hepatocytes (h)	NPCD	Perturbation of autophagy	[261]
Macrophages (m)	ASMD	Impaired killing of bacteria	[620,621]
Macrophages (m)	NPCD	Enhanced oxidative stress	[622]
Macrophages (h)	NPCD	Perturbation of autophagy	[623]
Lymphocytes, B type (h)	NPCD	Impaired lysosomal calcium release	[537]
Lymphocytes, B type (h)	ASMD	Perturbation of autophagy	[624]
Lymphocytes, T type (m)	ASMD	Impaired plasma membrane signaling and proliferation	[625]
Lymphocytes, T type (m)	ASMD	Cytotoxic granule secretion	[626]
Lymphocytes, T type (h)	NPCD	Impaired perforin activity	[627]
Lymphocytes, T type (Invariant natural killer cells) (h, m)	ASMD, NPCD	Loss of natural killer T cells; diminished lipid/antigen presentation	ASMD: [628]. NPCD: [181,629–631]
Microglial cells (m)	NPCD	Enhanced cathepsin levels and activity	[564,632]
Neurons, brain (m)	ASMD	Perturbed surface distribution of gangliosides and glycosyl phosphatidyl inositol-anchored proteins	[361]

(continued on next page)

Table 3 (continued)

Cell type (source*)	Disease	Change	References
Neurons, brain (m)	ASMD	Enhanced neutral sphingomyelinase and vitamin D receptor	[633]
Neurons, brain (h)	NPCD	Presence of neurofibrillary tangles	[634–637]
Neurons, in vitro (m)	NPCD	Impaired neurotrophin signaling	[638]
Neurons, brain (m)	NPCD	Modifications of cytoskeletal proteins including microtubulin-associated tau	[639–641]
Neurons, brain (h, m)	NPCD	Impaired amyloid precursor protein processing	[642–647]
Neurons, in vitro (m, r)	NPCD	Cholesterol depletion from axons	[525,648]
Neurons, brain (h, m)	NPCD	Enhanced tumor necrosis factor-alpha signaling	[649]
Neurons, brain (m)	NPCD	Impaired phosphatidylinositol-3 kinase signaling	[650]
Neurons, brain (m)	NPCD	Impaired self-renewal and differentiation of neural stem cells and neuronal precursor cells	[651,652]
Neurons, brain (m)	NPCD	Enhanced cytosolic proteolysis (cathepsin activity)	[560,632,653]
Neurons, brain (h, m)	NPCD	Impaired vascular epithelial growth factor / sphingosine kinase signaling	[654]
Neurons, brain (m)	NPCD	Impaired sonic hedgehog signaling	[652,655]
Neurons, brain (m)	NPCD	Enhanced synthesis of cholesterol	[374]
Neurons, brain (m)	NPCD	Hyperexcitability due to decreased expression of a voltage-gated potassium channel (Potassium Voltage-Gated Channel Subfamily Q Member 2/3, KCNQ2/3)	[656]
Neurons, in vitro (h)	NPCD	Impaired lysosomal proteolysis	[599]
Neurons, in vitro (h)	NPCD	Hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1)	[599]
Neurons, brain (m)	NPCD	Impaired transport of lysosomes along axons	[657]
Neurons, brain (m)	NPCD	Activation of the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway	[188]
Neurons, in vitro (r)	NPCD	Enhanced extracellular vesicle secretion	[658]
Neurons, brain (h, m)	ASMD, NPCD	Impaired mitochondrial function, mitophagy	ASMD: [604]. NPCD: [599,659–662]
Neurons, brain (m)	ASMD, NPCD	Defects in axons, dendrites and synapses	ASMD: [229,663,664]. NPCD: [525,543,581,583,665–676]
Neurons, brain (h, m)	ASMD, NPCD	Perturbation of autophagy	ASMD: [677]. NPCD: [261,286,495,527,596,632,662,678,679]
Neurons, brain (m)	ASMD, NPCD	Perturbation of calcium homeostasis	ASMD: [680]. NPCD: [676,681]
Neurons, brain (m)	ASMD, NPCD	Impaired ABL Proto-Oncogene 1, Non-Receptor Tyrosine Kinase (ABL1) signaling	ASMD: [682]. NPCD: [683,684]
Neurons, brain (m, r)	ASMD, NPCD	Enhanced oxidative stress	ASMD: [685]. NPCD: [686,687]
Neurons, brain (h, m)	ASMD, NPCD	Impaired endocannabinoid signaling	[688,689]
Oligodendroglial precursor cells, in vitro (m)	NPCD	Enhanced exosomal cholesterol release	[598]
Oligodendrocytes, Schwann cells, brain (h, m)	ASMD, NPCD	Impaired development and myelination	ASMD: [690]. NPCD: [277,491,567,576,583,674,691–702]
Pancreatic acinar cells (m)	NPCD	Impaired formation of secretory granules	[703]
Platelets (m)	ASMD	Degranulation and thrombus formation	[704]
Spleenocytes, spleen (h, m)	NPCD	Perturbation of metal homeostasis (zinc, copper and iron)	[613,614]
Umbilical vein endothelial cells (h)	NPCD	Inhibition of mechanistic target of rapamycin complex 1 (mTORC1) signaling	[705]

\* Source: h, human; m, mouse; r, rat.



**Table 4**  
Therapeutic targets and approaches tested for Niemann-Pick diseases.

Treatment	Model	References
<b>ASMD</b>		
Transplantation, liver	<i>Smpd1</i> <sup>-/-</sup> mice, patients	[747,784,785]
Transplantation, bone marrow cells	<i>Smpd1</i> <sup>-/-</sup> mice, patients	[786–789]
Transplantation, amniotic cells	Patients	[790,791]
Transplantation, bone marrow-derived stem cells, neural progenitor cells; intracerebral	<i>Smpd1</i> <sup>-/-</sup> mice	[530,748,749,792]
Gene therapy, viral vectors	Patient-derived fibroblasts, <i>Smpd1</i> <sup>-/-</sup> mice, healthy non-human primates	[750,793–797]
Enzyme replacement with rhASM (Olipudase alpha, Xenpozyme)	<i>Smpd1</i> <sup>-/-</sup> mice, patients	[752,754,761,762,798–804]
Neutral sphingomyelinase	<i>Smpd1</i> <sup>-/-</sup> mice	[664]
Phosphoinositide PI(4,5)P2 signaling	<i>Smpd1</i> <sup>-/-</sup> mice	[805]
Histone deacetylases, inhibition	<i>Smpd1</i> <sup>-/-</sup> mice	[685]
High density lipoprotein nanoparticles	<i>Smpd1</i> <sup>-/-</sup> mice	[806]
Endocannabinoid system, activation	<i>Smpd1</i> <sup>-/-</sup> mice	[689]
Apolipoprotein D (APOD)	Patient-derived fibroblasts	[722]
<b>NPCD</b>		
Cholesterol lowering drugs	Patients, <i>Npc1</i> <sup>-/-</sup> mice	[763,807,808]
Dietary restriction	<i>Npc1</i> <sup>-/-</sup> cats	[809]
Hydroxy-propyl-beta-cyclodextrin (VTS-270, Adrabetadex, Trappsol Cyclo)	<i>Npc1</i> <sup>-/-</sup> mice, cats, patients	[771,773–775,810–818]
N-butyl-deoxyojirimycin (OGT918, Miglustat, Zavesca)	<i>Npc1</i> <sup>-/-</sup> mice, cats, patients	[413,433,767,768,819–823]
Apoptosis, inhibition	<i>Npc1</i> <sup>-/-</sup> mice	[824]
RAB7/9 signaling	Patient-derived fibroblasts	[186,825]
Vitamin E	<i>Npc1</i> <sup>-/-</sup> mice	[257,826–828]
Allopregnanolone	<i>Npc1</i> <sup>-/-</sup> mice	[772,773,775]
Nuclear receptors, activation	<i>Npc1</i> <sup>-/-</sup> mice	[829,830]
High-density lipoprotein, release	Patient-derived fibroblasts	[831]
Histone deacetylases, inhibition	<i>Npc1</i> <sup>nmf164</sup> , <i>Npc1</i> <sup>-/-</sup> mice	[253,303,832,833]
Implantation of neural stem cells	<i>Npc1</i> <sup>-/-</sup> mice	[834]
Estradiol	<i>Npc1</i> <sup>-/-</sup> mice	[579]
Transplantation of mesenchymal stem cell	<i>Npc1</i> <sup>-/-</sup> mice	[835–837]
Mitogen-activated protein kinase, inhibition	<i>Npc1</i> <sup>-/-</sup> mice	[838]
Bis(monoacylglyceryl) phosphate / lysobisphosphatidic acid	Patient-derived fibroblasts	[839–841]
ABL proto-oncogene 1, non-receptor tyrosine kinase (ABL1), inhibition (Imatinib)	<i>Npc1</i> <sup>-/-</sup> mice	[684,842]
Curcumin	<i>Npc1</i> <sup>-/-</sup> mice	[537,843–845]
Vitamin C	<i>Npc1</i> <sup>-/-</sup> mice	[846]
Cyclin-dependent kinase-5 (CDK5), inhibition	<i>Npc1</i> <sup>-/-</sup> mice	[847]
Non-steroidal anti-inflammatory drugs	<i>Npc1</i> <sup>-/-</sup> mice	[582,846]

**Table 4 (continued)**

Treatment	Model	References
Drug-induced lysosomal exocytosis	Patient-derived fibroblasts, <i>Npc1</i> <sup>-/-</sup> mice	[374,684,827,848–853]
Protein replacement, NPC2	<i>Npc2</i> <sup>Gt(LST105)BygNya</sup> mice	[293]
UDP-glucose ceramide glucosyltransferase (UGCG), inhibition	<i>Npc1</i> <sup>-/-</sup> mice, cats	[769]
Autophagy, enhancers	Induced pluripotent stem cell-derived cells	[261,678,854]
N-acetyl-cysteine	<i>Npc1</i> <sup>-/-</sup> mice	[855]
Copper chelation	<i>Npc1</i> <sup>-/-</sup> mice	[856]
Acetylcholinesterase (ACHE), inhibition	<i>Npc1</i> <sup>-/-</sup> mice	[857]
Combination miglustat, curcumin, ibuprofen	<i>Npc1</i> <sup>-/-</sup> mice	[858]
N-acetyl-DL-leucine, N-acetyl-L-leucine (IB1001)	<i>Npc1</i> <sup>-/-</sup> mice, patients	[415,777,778,859]
Glucocerebrosidase (GBA2), inhibition	<i>Npc1</i> <sup>-/-</sup> mice	[546]
Cathepsins, inhibition	<i>Npc1</i> <sup>I1061T</sup>	[560,564]
Necroptosis, inhibition	<i>Npc1</i> <sup>-/-</sup> mice	[860,861]
Heat shock protein, activation (Arimoclomol)	<i>Npc1</i> <sup>-/-</sup> mice, patients	[783,862,863]
Gene therapy, viral vectors	<i>Npc1</i> <sup>-/-</sup> , <i>Npc2</i> <sup>tm1Plob</sup> , <i>Npc1</i> <sup>I1061T</sup> mice	[864–870]
Glutathione	<i>Npc1</i> <sup>-/-</sup> mice	[617]
Adenosine A2A receptor (ADORA2A), activation	<i>Npc1</i> <sup>-/-</sup> mice	[700,871,872]
Metabotropic glutamate receptor, activation	<i>Npc1</i> <sup>-/-</sup> mice	[873]
Polymeric beta-cyclodextrin	<i>Npc1</i> <sup>nmf164</sup> mice	[874]
Pneumococcal immunization	<i>Npc1</i> <sup>-/-</sup> mice	[875]
Histamine H3 receptor (HRH3), activation	<i>Npc1</i> <sup>-/-</sup> mice	[840]
6-O-alpha-maltosyl-beta-cyclodextrin	<i>Npc1</i> <sup>-/-</sup> mice	[876]
Implantation of VEGF-overexpressing neural stem cells	<i>Npc1</i> <sup>-/-</sup> mice	[877]
Cytochrome P450 family 46 subfamily A member 1 (CYP46A1), activation	<i>Npc1</i> <sup>nmf164</sup> mice, patients	[675,878]
High-density lipoprotein nanoparticles	<i>Npc1</i> <sup>I1061T</sup> mice	[806]
Endocannabinoid system, activation	<i>Npc1</i> <sup>-/-</sup> mice	[689]
Iron chelation	<i>Npc1</i> <sup>-/-</sup> mice	[879]
Gene therapy, Trojan horse liposomes	<i>Npc1</i> <sup>-/-</sup> mice	[880]
Transcription factor EB (TFEB), activation (Genistein)	Patient-derived fibroblasts	[852]
Lithium carbonate	Patients	[881]
Heat-shock protein 90 (HSP90), inhibition	Patient-derived fibroblasts	[882]
Extracellular vesicles	<i>Npc1</i> <sup>-/-</sup> mice	[883]
Graphene quantum dots	<i>Npc1</i> <sup>-/-</sup> mice	[884]
Acid ceramidase (ASAHL1), activation	Patient-derived fibroblasts	[619]
Two-pore channel 2 (TPC2), activation	Patient-derived fibroblasts	[885]
mRNA encoding NPC1	Patient-derived fibroblasts	[886]

This includes histologic analyses of biopsies [383,444,486–488], and non-invasive measurements to assess for example saccades [489], brain anatomy [490–494], structure and function of sensory organs [495–502], neuroinflammation [503], movement [504], swallowing [505] and cholesterol metabolism [506].

Starting in the 2000s, the development of innovative computational methods and the increase in computation power has opened new

directions for the fields. The use of *in silico* and molecular modeling approaches revealed dynamic properties of the proteins and provided new insight in structure-function and genotype-phenotype relations for *SMPD1* [439,507] and *NPC1/NPC2* [263,508–516]. Computer-based extraction of information from large sets of data or text (mining, machine/deep learning etc.) can help diagnosis [517] and suggest new candidates for biomarkers and therapeutic approaches [512,518–520].

## 9. Cell-specific changes and disease mechanisms

A pressing question is how pathogenic variants of *SMPD1*, *NPC1* or *NPC2* damage vulnerable cells and organs. By studying postmortem spleen and liver samples from his patient Irene, Niemann observed what became a cellular hallmark of the diseases, the accumulation of lipids within cells [50]. Later on, Bielschowsky and Epstein were the first to describe lipid aggregates in neuronal cell bodies, axons and dendrites in the neocortex and cerebellum of Niemann-Pick patients [521,522]. Obviously, prime suspects causing havoc in ASM- and *NPC1*- or *NPC2*-deficient cells are sphingomyelin and unesterified cholesterol, respectively. Depending on the cell type, these accumulating lipids may derive from lipoprotein uptake [83,523], but also from cell-intrinsic pools [374,524–526], for example due to impaired autophagy [527]. Notably, lipids other than the usual suspects accumulate due to defects in ASM, *NPC1* or *NPC2* as well. ASM deficiency enhances cholesterol levels in visceral organs [81], in macrophages [528], and in neurons [529,530], although absence of accumulation has also been reported [361,531]. Conversely, *NPC1*-deficiency elevates levels of sphingomyelin [81,532] and other sphingolipids, notably lactosyl- [533] and glycosylceramide [532], and sphingosine [183,393,458,534–538]. Moreover, accumulation of bis(monoacylglyceryl)phosphate (a.k.a. lysobisphosphatidic acid) [81,539] (for review see [540]), and gangliosides (ASM: [531]; NPCD: [374,458,541–543]) has been observed in both diseases. Why different lipids co-accumulate in the diseases is unclear. Some may accumulate as direct consequence of *NPC1* deficiency [183]. On the other hand, sphingolipids and cholesterol appear to mutually influence their processing in late endosomes *in vitro* [142,544–549] suggesting that the late-endosomal handling of different lipids by enzymes and carriers is interdependent and proceeds in a specific order depending on the cell type and the processed material. Whether and how the different lipids damage specialized cell types in ASM and NPCD, remains to be established.

Apart from lipid accumulation, numerous pathologic changes due to defects in ASM, *NPC1* or *NPC2* have been documented in generic and specialized cells from different tissues and organs during the last decades (Table 3). The thick catalogue comprises common defects such as impaired recycling of cellular components by autophagy, diminished energy conversion in mitochondria, and enhanced oxidative stress. Moreover, the catalogue lists cell type-specific changes including impaired phagocytosis in macrophages, defective secretion from immune cells, and defects in specialized neuronal structures (Table 3). Some changes observed in cells from animal models have been confirmed in human cells, and vice versa, but a large fraction of data remains to be cross-validated. The importance of this cross-validation is illustrated by recent evidence for differences among brain cells from *NPC1*-deficient mice and NPCD patients [550] and species-dependent trafficking of *NPC1* [193]. In addition, many signaling pathways and cellular processes affected by ASM, *NPC1* or *NPC2* deficiency were uncovered in generic cells (Table 3), and their contribution to dysfunction of specialized cells remains to be established. Direct comparisons of cells revealed that *NPC1* deficiency causes death of primary neurons, but not of cell lines [551], and impairs cholesterol efflux and cathepsin activity in macrophages, but not in hepatocytes [552]. Remarkably, cells differ with respect to their vulnerability to the gene variants. This is exemplified by the differential loss of Purkinje cells located in distinct cerebellar lobules of ASM- [229,529] and *NPC1*-deficient mice [553–555].

An important question is whether a given type of cell in an affected

organ degenerates autonomously or whether neighboring cells contribute to its demise. This applies in particular to neurodegenerative diseases, where the loss of neurons has been shown to depend on non-neuronal (glial) cells [556,557] (for review see [558]). Previous studies of ASM and NPCD models revealed pathologic changes in different types of glial cells and in the myelin sheath surrounding axons in the peripheral and central nervous system (Table 3). On the other hand, genetic experiments suggested that *NPC1* deficiency in neurons is sufficient to induce their death [286,287,559,560]. *In vitro* studies showed normal secretion of lipoproteins from *NPC1*-deficient glial cells [561]. However, these findings do not exclude a contribution of non-neuronal cells to neurodegeneration. Already in 1954, Paul Diezel suggested that storage material found in microglial cells of Niemann-Pick cases represents remnants of damaged neurons following their uptake by microglial phagocytosis [562]. Recent studies expose microglial cells as key players in neurodegeneration and as possible targets of therapeutic approaches for ASM [563] and NPCD [409,470,550,563–567]. An emerging question is how defects of ASM, *NPC1* or *NPC2* affect the complex lymphatic and neuroimmune systems that have been discovered in the meninges and skull bone marrow [568–570] (for review see [571]).

## 10. Tracking disease modifiers

A long-standing challenge is the identification of genetic [706], epigenetic [707] and environmental factors [708] that account for the substantial phenotypic variability in patients with different lysosomal disorders including ASM and NPCD. In both diseases, the involvement of protective and deleterious modifiers is indicated by studies of *NPC1* mutant mice showing an impact of genetic background on disease severity [289,709–712], and by clinical reports showing divergent symptoms in patients with identical variants [412,424,713–719]. In addition to modifiers that determine inter-individual variation of disease outcome, there are factors that determine the cell type-specific vulnerability to disease-causing gene variants as has been shown in many pathologic conditions [720].

Within the last decade, candidate modifiers have been identified for ASM and NPCD using a variety of approaches ranging from yeast screens to knock-outs of selected genes and single cell transcriptomics. Notably, some of these pathways may in fact be integral components of the disease mechanisms rather than modifiers. For ASM, sphingosine kinase has been suggested as modifier of Purkinje cell death based on its expression pattern in the cerebellum [721], whereas endocannabinoid signaling [689] and apolipoprotein D [722] have been shown to modify disease outcome in mice. For NPCD, the list of candidates is long and comprises sigma 2 receptor/TMEM97 [184], cathepsins [653], microtubule-associated protein tau [723,724], histone deacetylases [303], amyloid precursor protein [725], apolipoprotein E [726,727], GM3 synthase [728], non-lysosomal glucosylceramidase (GBA2) [546,729], cystatin B expression [560], heat-shock protein beta 1 (HSPB1) [730], alexidine-dependent signaling [731], endocannabinoid signaling [689], maternal immune activation [732], thrombospondin 1 and a glutamate transporter (SLC1A6) [733], F-box protein 2 [734], quantitative trait loci on mouse chromosomes 1 and 7 [291], annexin A6 [735], cholesterol esterification by corresponding enzymes (sterol O-acyltransferase 2, SOAT2 [736] and sterol o-acyltransferase 1 (ACAT1/SOAT1) [737]), and modulation of peroxisome proliferator-activated receptor-gamma activity [738]. With respect to Purkinje cell vulnerability, potential modifiers are Abelson Helper Integration Site 1 (AHI1), a serine-threonine kinase (ROCK2), a lysosomal cationic amino acid transporter (PQLC2) [388] and a glycosyl transferase (MGAT5) [739]. Other candidates are proteins that may shuttle cholesterol out of the endosomal-lysosomal system independently from *NPC1/NPC2* such as lysosomal associated membrane protein 2 (LAMP2) [740,741] and lysosomal integral membrane protein 2 / scavenger receptor class B member 2 (LIMP2/SCARB2) [742].

The long line of candidates implies that numerous modifiers interfere at different molecular and cellular levels ranging from the amount of ASM, NPC1 or NPC2 protein available per cell, to lysosomal function *per se* and the quality and extent of neuroinflammatory responses. Notably, genetic modifiers may act in a cell type-specific manner as shown recently by single-cell analyses of expression quantitative trait loci for autoimmune [743,744] and neurologic diseases [745].

## 11. Search for therapies

The faulty proteins that cause havoc in ASMD and NPCD differ fundamentally with respect to their location – luminal ASM versus transmembrane NPC1 – and function – enzyme activity versus transporter, respectively. Therefore, the search for therapies in each field has taken distinct paths and time courses [746]. For ASMD, the hunt began in the 1970s with transplantation of liver samples [747] and of mesenchymal cells from different sources (Table 4). These attempts yielded mixed outcomes and little to no effects on neurologic symptoms. Improvement of the latter required intracerebral injection of cells [748,749]. The feasibility of gene therapy was established first *in vitro* using patient-derived fibroblasts [750] and then *in vivo* using different approaches in animal models (Table 4). Enzyme replacement appeared as a promising approach for ASMD, and its preclinical development took off in the 1990s. Biologically active recombinant human ASM (rhASM) could be produced *in vitro* [751] and its systemic administration corrected pathologic changes in livers and spleens of ASM-deficient mice [752]. Intraparenchymal injection of rhASM reduced sphingomyelin accumulation in neurons [753] and its intracerebroventricular administration improved neurologic symptoms in ASM-deficient mice [754]. Better delivery of ASM was explored using nanocarriers coated with a cell adhesion molecule (ICAM1) [755–758] circumventing impaired uptake mechanisms in ASM-deficient macrophages [759] and fibroblasts [760]. However, systemic administration of ASM caused dose-dependent toxicity in ASM-deficient mice due to elevated ceramide levels following bulk cleavage of sphingomyelin. This obstacle was overcome by a debulking/dose escalating regimen in animals [761] and patients [762]. Several clinical trials proved short- and long-term safety and efficacy of rhASM (olipudase alpha/Xenpozyme) in ASMD patients showing significant improvement of visceral symptoms (Tables 4, 5; Fig. 3). These positive results led to its recent approval in several countries including the USA. In parallel to enzyme replacement, alternative therapeutic approaches have been tested for ASMD (Table 4).

The hunt for therapies to combat NPCD began with some delay compared to the efforts in the ASMD field. Starting in the 1990s, cholesterol-lowering drugs were the first approach explored in patients [763] and during the next decades, numerous targets and approaches have been tested preclinically (Table 4) [24]. Only few drug candidates have entered into industry-sponsored clinical development (Tables 4, 5; Fig. 3). The first drug was N-butyl-deoxyojirimycin (OGT918, Miglustat, Zavesca). The compound is a modified version of the bacteria- and plant-derived glucose mimetic nojirimycin. Discovered in Japan, it was shown to inhibit carbohydrate-splitting glucosidases [764]. N-butyl-deoxyojirimycin inhibits glucosylceramide synthase (UDP-glucose ceramide glucosyltransferase, UGCG) [765] and serves as substrate reduction therapy for Gaucher disease [766]. The drug was shown to slow down disease progression in NPC1-deficient mice [767] and cats [768] (Table 4). Several clinical trials proved that long-term treatment with the drug stabilizes neurologic disease progression in many NPCD patients (Tables 4, 5; Fig. 3). Its mechanism of action may involve concurrent inhibition of non-lysosomal glucosylceramidase (GBA2) [546,769,770]. N-butyl-deoxyojirimycin is currently the only drug approved for treatment of NPCD in many countries except for the USA.

Next in line was the cholesterol-binding compound hydroxypropyl-beta-cyclodextrin (HPBCD), which was tested beginning of the 2000s in mice [771] (Tables 4, 5; Fig. 3). Years later, it appeared again on the scene, after the revelation that positive effects on NPC1-deficient mice, originally ascribed to allopregnanolone [772], were mediated by HPBCD serving as vehicle [773–775]. Subsequent studies reported positive effects notably prolongation of life-span in NPC1-deficient mice and cats (Table 4). Clinical trials with HPBCD (named VTS-270, Adra-betadex), showed decelerated neurologic disease progression in patients following intrathecal administration of the compound (Tables 4, 5; Fig. 3).

A third candidate is the modified amino acid N-acetyl-L-leucine (IB1001) (Tables 4, 5; Fig. 3). The racemic version, N-acetyl-DL-leucine, sold in France as over-the-counter drug Tanganil, is used since more than 60 years to treat acute vertigo [776]. Positive effects of the racemic mixture in NPCD patients [777,778] and evidence that the L enantiomer is the active form slowing disease progression in NPC1-deficient mice [778] prompted clinical studies [779], which showed reduced neurologic disease progression after one year of treatment (Tables 4, 5; Fig. 3). With respect to the long-sought mechanism of action, N-acetyl-L-leucine appears to act as prodrug boosting L-leucine-dependent processes, notably energy metabolism, in those cells that can take up the acetylated molecule [780].

A fourth approach tested clinically was based on bimoclocholol or arimoclocholol, which represent small molecule enhancers of heat-shock protein expression (Tables 4, 5; Fig. 3). The drugs were first explored in preclinical models for diabetic neuropathy [781] and for amyotrophic lateral sclerosis [782]. Encouraging effects of arimoclocholol were observed in NPC1-deficient cells and mice [783] and a clinical trial showed decelerated disease progression notably in patients co-treated with arimoclocholol and N-butyl-deoxyojirimycin (Tables 4, 5; Fig. 3).

## 12. Summary and outlook

The Niemann-Pick diseases testify that defects in cellular lipid homeostasis cause dysfunction and death of cells in the brain and other organs, provoke progressive visceral, neurologic and psychiatric symptoms and premature death in animal models and humans. Research has tracked down the genetic culprit causing the "unknown clinical picture" noticed by Albert Niemann more than 100 years ago. Niemann's patient, Irene, most likely suffered from the uniformly fatal infantile neurovisceral form of ASMD invoking an enzymatic defect in sphingomyelin catabolism. Along a meandering path, a second nosologic entity, named Niemann-Pick Type C, was uncovered, where defects in NPC1 or NPC2 impair uptake and recycling of cholesterol and other components. Many candidate pathways and mechanisms have been uncovered yielding converging evidence for defects in lysosomes, autophagy and mitochondria in both diseases [888]. Still, the signal cascades linking the genetic variants with the progressive demise of vulnerable neurons and other specialized cells remain to be established. Further advances require continued efforts to uncover cell-specific reactions to variants of *SMPD1*, *NPC1* or *NPC2*. The identification of genetic, epigenetic, or environmental disease modifiers that determine the outcome of these variants in specific cell types and individual patients may help to reveal disease mechanisms and deliver new drug targets. From a biological point of view, it is curious that the defective culprits in Niemann-Pick diseases handle two lipids that are intimately linked in their natural habitat, the eukaryotic membrane. Therefore, it may be of value to join forces in the fields and explore whether and how primary defects in either protein impact the other. Integrated research efforts across the fields may help to define cell-specific pathologic pathways common to both diseases and suggest new therapeutic approaches.

**Table 5**  
Clinical studies exploring therapeutic approaches for Niemann-Pick diseases.

Code	Title	Period	Sponsor*	References <sup>#</sup>
<b>ASMD</b>				
NCT00410566	Safety Study of <b>rhASM</b> Enzyme Replacement Therapy in Adults With Acid Sphingomyelinase Deficiency (Niemann-Pick Disease)	12/2006 - 4/2009	Genzyme/Sanofi	–
NCT01722526	Tolerability and Safety Study of <b>Recombinant Human Acid Sphingomyelinase</b> in Acid Sphingomyelinase Deficiency Patients	03/2013 - 01/2014	Genzyme/Sanofi	[799,800,802]
NCT02004704	A Long-Term Study of <b>Olipudase Alfa</b> in Patients With Acid Sphingomyelinase Deficiency	12/2013 - 02/2024	Genzyme/Sanofi	[801–803]
EudraCT2013-000051-40	A Long-Term Study to Assess the Ongoing Safety and Efficacy of <b>Olipudase Alfa</b> in Patients With Acid Sphingomyelinase Deficiency	12/2013	Genzyme/Sanofi	–
EudraCT2010-023953-12	A Phase 2, Multi-Center, Randomized, Open-Label, Repeat Dose, Dose-Comparison Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of <b>Recombinant Human Acid Sphingomyelinase</b> in Patients	12/2013	Genzyme/Sanofi	–
EudraCT2014-003198-40	A phase 1/2, multi-center, open-label, ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of <b>olipudase alfa</b> in pediatric patients	02/2015	Genzyme/Sanofi	–
NCT02292654	Safety, Tolerability, PK, and Efficacy Evaluation of Repeat Ascending Doses of <b>Olipudase Alfa</b> in Pediatric Patients <18 Years of Age With Acid Sphingomyelinase Deficiency	05/2015 - 12/2019	Genzyme/Sanofi	[803,887]
EudraCT2015-000371-26	A Phase 2/3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Repeat Dose Study to Evaluate the Efficacy, Safety, Pharmacodynamics and Pharmacokinetics of <b>olipudase alfa</b> in Patients...	08/2015	Genzyme/Sanofi	[804]
NCT02004691	Efficacy, Safety, Pharmacodynamic, and Pharmacokinetics Study of <b>Olipudase Alfa</b> in Patients With Acid Sphingomyelinase Deficiency	12/2015 - 10/2023	Genzyme/Sanofi	[804]
NCT05359276	Data Analysis of Adult and Pediatric Participants With Acid Sphingomyelinase Deficiency (ASMD) on Early Access to <b>Olipudase Alfa</b> in France	06/2022 - 01/2025	Genzyme/Sanofi	–
<b>NPCD</b>				
NCT00517153	<b>Miglustat</b> in Niemann-Pick Type C Disease	01/2002–01/2008	Actelion	[819–821]
NCT00316498	Saccadic Eye Movements in Patients With Niemann-Pick Type C Disease	10/2002–08/2007	NEI, NIHCC	–
EudraCT2006-005842-35	Efficacy and safety of treatment with <b>N-butyl-deoxyojirimycin (NB-DNJ-miglustat)</b> in patients with Niemann-Pick disease type C	11/2006	Universita` di Napoli Federico II	[822]
NCT01760564	Application of <b>Miglustat</b> in Patients With Niemann-Pick Type C	01/2008–12/2010	National Taiwan University Hospital	–
NCT00975689	Biomarker Validation for Niemann-Pick Disease, Type C: Safety and Efficacy of <b>N-Acetyl Cysteine</b>	08/2009–11/2010	NICHD, UO, WUSM, NHGRI, NIHCC	–
NCT01747135	<b>Hydroxypropyl Beta Cyclodextrin</b> for Niemann-Pick Type C1 Disease	01/2013–03/2017	Vtesse/Mallinckrodt	[816]
NCT02124083	Phase 1/2 Study of <b>Vorinostat</b> Therapy in Niemann-Pick Disease, Type C1	04/2014–12/2016	NICHD, WU, WMCCU, NIHCC	–
NCT02534844	<b>VTS-270</b> to Treat Niemann-Pick Type C1 (NPC1) Disease	10/2015–10/2021	Mandos LLC	–
EudraCT2014-005194-37	A prospective non-therapeutic study in patients diagnosed with Niemann-Pick disease type C in order to characterise the individual patient disease profile and historic signo-symptomatology progress...	10/2015	Orphazyme ApS	–
NCT04958642	<b>Adrabetadex</b> to Treat Niemann-Pick Type C1 (NPC1) Disease	12/2015–11/2021	Mandos LLC	–
EudraCT2015-002548-15	A Phase 2b/3 Prospective, Randomized, Double-blind, Sham-controlled Trial of <b>VTS-270 (2-hydroxypropyl-β-cyclodextrin)</b> in Subjects with Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease	12/2015	Vtesse/Mallinckrodt	–
EudraCT2015-004438-93	<b>Arimoclomol</b> prospective double blind, randomised, placebo-controlled study in patients diagnosed with Niemann Pick disease type C	05/2016	Orphazyme ApS	–
NCT02612129	<b>Arimoclomol</b> Prospective Study in Patients Diagnosed With NiemannPick Disease Type C	06/2016–05/2022	KemPharm Denmark A/S	[416,863]
EudraCT2015-004846-25	<b>Immunization</b> against oxLDL in patients with lysosomal lipid diseases and associated metabolic disorders	07/2016	Maastricht University	–
EudraCT2015-005761-23	A Phase I/II study to evaluate the safety and pharmacokinetics of intravenous <b>Trappsol Cyclo (HP-β-CD)</b> in patients with Niemann-Pick disease type C (NPC-1) and the pharmacodynamic effects of treatm...	09/2016	Cyclo Therapeutics, Inc.	–
NCT02912793	Safety and Efficacy of Intravenous <b>Trappsol Cyclo (HPBCD)</b> in Niemann-Pick Type C Patients	03/2017–03/2021	Cyclo Therapeutics, Inc.	[817]

(continued on next page)

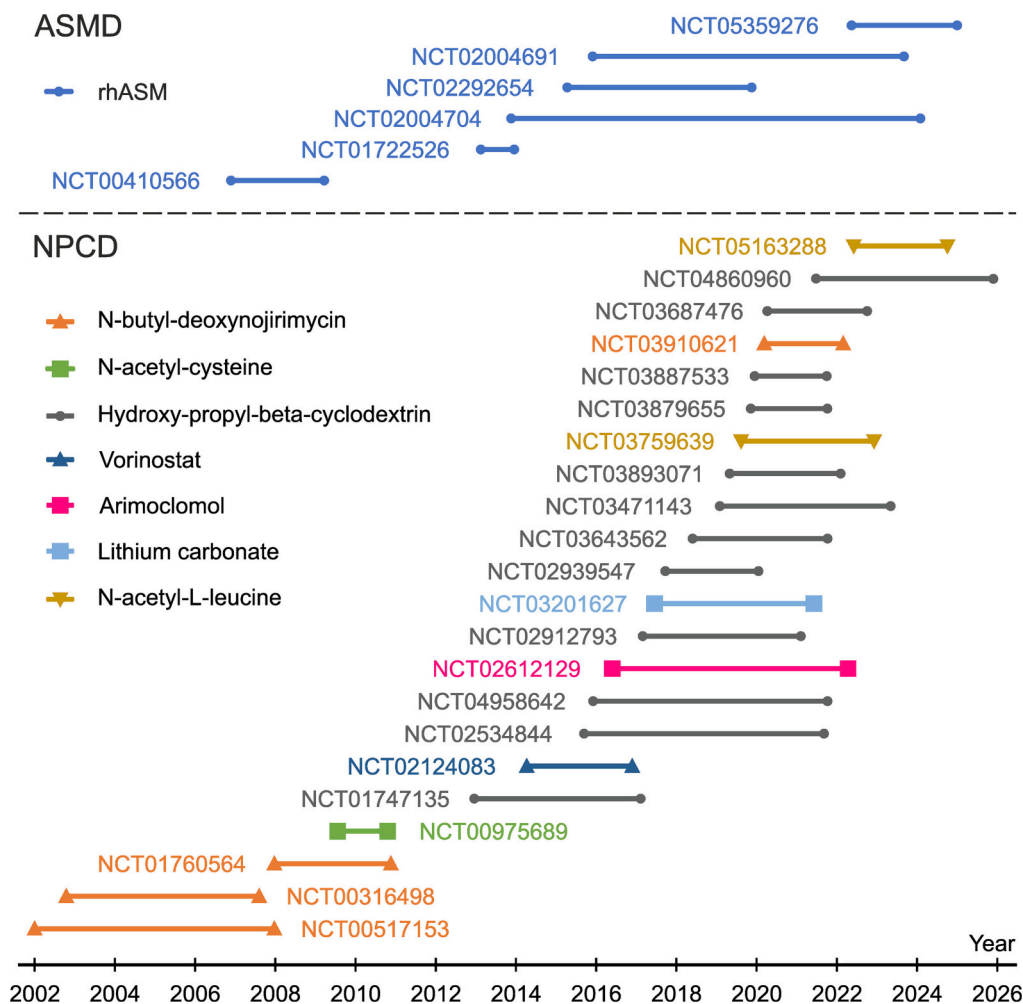
Table 5 (continued)

Code	Title	Period	Sponsor*	References <sup>#</sup>
NCT03201627	Study of <b>Lithium Carbonate</b> to Treat Niemann-Pick Type C1 Disease	07/2017–06/2021	XHSUSM	[881]
NCT02939547	Study of the Pharmacokinetics of <b>Trappsol</b> and Effects on Potential Biomarkers of Niemann-Pick C1 (NPC1)	10/2017–02/2020	Cyclo Therapeutics, Inc.	[818]
NCT03643562	Niemann-Pick Type C Treatment With <b>Adrabetadex</b> for Symptoms of Brain and Nervous System	06/2018–11/2021	Mandos LLC	–
NCT03471143	Study of IV <b>VTS-270</b> for Infantile Liver Disease Associated With Niemann-Pick Disease, Type C	02/2019–06/2023	WUSM, NICHD	–
NCT03893071	Open-Label Study of Long-Term Safety and Efficacy of Intravenous <b>Trappsol Cyclo (HPi<sup>2</sup>CD)</b> in Niemann-Pick Disease Type C	05/2019–03/2022	Cyclo Therapeutics, Inc.	[818]
EudraCT2018-004331-71	Effects of <b>N-Acetyl-L-Leucine</b> on Niemann-Pick type C Disease (NPC): A multinational, multi-center, open-label, rater-blinded Phase II study	05/2019	IntraBio, Inc.	[779]
NCT03759639	<b>N-Acetyl-L-Leucine</b> for Niemann-Pick Disease, Type C (NPC)	09/2019–01/2023	IntraBio, Inc.	[779,859]
NCT03879655	Open-label Study of <b>VTS-270</b> in Participants With Neurologic Manifestations of Niemann-Pick Type C1	12/2019–11/2021	Mandos LLC	–
NCT03887533	Combined Intrathecal and Intravenous <b>VTS-270</b> Therapy for Liver and Neurological Disease Associated With Niemann-Pick Disease, Type C1	01/2020–10/2021	NICHD, NIHCC	–
NCT03910621	Safety and Efficacy of <b>Miglustat</b> in Chinese NPC Patients	04/2020–03/2022	Actelion	–
NCT03687476	Safety and Tolerability Study of <b>VTS-270</b> in Pediatric Participants With Niemann-Pick Type C (NPC) Disease	05/2020–10/2022	Vtesse/Mallinckrodt	–
EudraCT2019-004498-18	EFFICACY AND SAFETY CLINICAL TRIAL WITH <b>EFAVIRENZ</b> IN PATIENTS DIAGNOSED WITH ADULT NIEMANN-PICK TYPE C WITH COGNITIVE IMPAIRMENT	06/2020	Drs. J. Gascón, Lola Ledesma	–
NCT04860960	Phase 3 Study to Evaluate Intravenous <b>Trappsol(R) Cyclo(TM)</b> in Pediatric and Adult Patients With Niemann-Pick Disease Type C1	07/2021–12/2025	Cyclo Therapeutics, Inc.	[818]
EudraCT2020-003136-25	A Phase 3, Double blind, Randomized, Placebo controlled, Parallel group, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of 2000 mg/kg of <b>Trappsol® Cyclo™</b> ...	10/2021	Cyclo Therapeutics, Inc.	–
EudraCT2021-005356-10	Effects of <b>N-Acetyl-L-Leucine</b> on Niemann-Pick disease type C (NPC): A Phase III, randomized, placebo-controlled, double-blind, crossover study	03/2022	IntraBio, Ltd.	–
NCT05163288	A Pivotal Study of <b>N-Acetyl-L-Leucine</b> on Niemann-Pick Disease Type C	06/2022–11/2024	IntraBio, Inc.	–
EudraCT2022-002514-16	A single-arm uncontrolled 12-month Clinical Study to evaluate the Safety and Efficacy of <b>miglustat (Zavesca®)</b> for the Treatment of Niemann-Pick Disease Type C (NPC) in Chinese subjects	07/2022	Actelion Pharmaceuticals Trading Co., Ltd	–

\* NEI, National Eye Institute; NIHCC, National Institutes of Health Clinical Center; NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; UO, University of Oxford; WUSM, Washington University School of Medicine; NHGRI, National Human Genome Research Institute; WMCCU, Weill Medical College of Cornell University; XHSUSM, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine.

<sup>#</sup> Articles citing the clinical trial (for further references see Table 4).





**Fig. 3.** Clinical trials in ASMD and NPCD. Timeline of clinical studies testing effects of drug candidates in ASMD (top) and NPCD patients (bottom). The legend indicates the specific drugs tested. Codes indicate clinical trial identification numbers (<https://clinicaltrials.gov/>). Only interventional studies are shown.

**Funding**

Subscription-based access to bibliographic information and scientific articles was provided through institutional accounts (University of Strasbourg; Centre National de la Recherche Scientifique). Research in the author’s laboratory has been supported by the Niemann-Pick Selbsthilfegruppe e.V. (Germany), the Ara Parseghian Medical Research Foundation (USA), Vaincre les maladies lysosomales (France), and BILD Hilft e.V. (Germany). Open access to this article was made possible by the Niemann-Pick Selbsthilfegruppe e.V. and NPSuisse (Switzerland).

**Declaration of Competing Interest**

The author declares no conflict of interest.

**Acknowledgements**

The author thanks Klaus Harzer, Ann-Kathrin Klewer, Valentina Pallottini, Konrad Sandhoff, and Marie T r se Vanier for valuable comments on earlier versions of the manuscript.

**Appendix**

Publications relevant to the fields were obtained by queries of a

bibliographic database (Web of Science; Clarivate Analytics) using the following terms for ASMD (**QT1**) and NPCD (**QT2**): **QT1:** ((TI=((niemann-pick AND disease AND ("type a" OR "type b" OR "type a/b")) OR ((ASMase OR acid sphingomyelinase OR sphingomyelin phosphodiesterase 1 OR smpd1 OR acidic smase) AND (deficiency OR deficient OR defect OR defective OR niemann-pick)) OR "niemann-pick A" OR "niemann-pick B" OR "niemann-pick A/B" OR "niemann-pick disease a" OR "niemann-pick disease b" OR "niemann-pick disease a/b") OR AB=((niemann-pick AND disease AND ("type a" OR "type b" OR "type a/b")) OR ((ASMase OR acid sphingomyelinase OR sphingomyelin phosphodiesterase 1 OR smpd1 OR acidic smase) AND (deficiency OR deficient OR defect OR defective OR niemann-pick)) OR "niemann-pick A" OR "niemann-pick B" OR "niemann-pick A/B" OR "niemann-pick disease a" OR "niemann-pick disease b" OR "niemann-pick disease a/b")) OR ((TI="niemann-pick" OR AB="Niemann-pick") AND PY=(1920-1969))) AND ((DT=="ARTICLE") NOT (DT=="REVIEW"))). **QT2:** ((TI=(niemann-pick AND (disease OR disorder) AND ("type c" OR "type c1" OR "type c2" OR "type d" OR "type e")) OR ((npc1 OR npc2) AND (deficiency OR deficient OR defect OR defective OR (niemann-pick AND disease))) OR "niemann-pick c" OR "niemann-pick d" OR "niemann-pick disease c" OR "niemann-pick disease d") OR AB=((niemann-pick AND (disease OR disorder) AND ("type c" OR "type c1" OR "type c2" OR "type d" OR "type e")) OR ((npc1 OR npc2) AND (deficiency OR deficient OR defect OR defective OR (niemann-pick AND disease))) OR "niemann-pick c" OR "niemann-pick d" OR "niemann-pick disease c" OR "niemann-

pick disease d")) OR ((TI="niemann-pick" OR AB="Niemann-pick") AND PY=(1920-1969)) AND ((DT=="ARTICLE") NOT (DT=="REVIEW"))). Additional queries were performed in MEDLINE using the freely accessible PubMed portal (<https://pubmed.ncbi.nlm.nih.gov/>). Bibliometric data were analysed and visualized using custom-made R scripts [889,890]. Information about clinical trials related to ASMD or NPCD was retrieved from publicly accessible registers using the terms "niemann-pick" or "sphingomyelinase" (<https://www.clinicaltrialsregister.eu/>, <https://clinicaltrials.gov/>).

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