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Review Article

# Hematopoietic stem cell gene therapy of neurometabolic lysosomal storage diseases

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ABSTRACT

Neurometabolic disorders are rare, inherited monogenic diseases arising from mutations in genes whose products are essential for brain functions and cause local accumulation of toxic substrates. Central nervous system involvement can be severe, is progressive and frequently appears early in life. Current treatment options for neurometabolic disorders are represented mainly by enzyme replacement therapy (ERT) and allogeneic hematopoietic stem cell transplantation (HSCT) which do not sufficiently address clinical manifestations and leave patients with a substantial residual disease burden. Given this unmet medical need, alternative strategies based on genetic manipulation of patient's cells have been developed. Hematopoietic stem progenitor cells-gene therapy (HSPC-GT) entails the harvest autologous HSPCs which are ex-vivo manipulated by means of viral vectors to express the therapeutic gene and infused back into the patient after chemotherapy-based preparation. Modified HSPCs engraft and differentiate into the various hematopoietic cell lineages, producing the functional enzyme at either normal or supranormal levels. The number of clinical trials with HSPC-GT in neurometabolic disorders is rapidly increasing and some HSPC-GT products have recently received market approval. This review focuses on HSPC-GT strategies summarizing the most recent developments in the field of neurometabolic disorders.

## 1. Introduction

Gene therapy (GT), which focuses on correcting genetic defects, has been widely researched in recent years and presents a promising alternative to conventional treatments, with the potential to overcome their limitations [1–3]. Gene transfer can be performed through either in-vivo or ex-vivo approaches (Fig. 1) [4].

Ex-vivo gene therapy (GT) entails harvesting hematopoietic stem progenitor cells (HSPCs) from the patient, then genetically modifying them in vitro using viral vectors to induce expression of the therapeutic gene at normal or supraphysiological levels—a process hereafter referred to as HSPC-GT. Afterward, the modified cells are infused into the patient, following a partial or fully myeloablative chemotherapy, where they engraft and differentiate into various hematopoietic cell lineages, producing the functional enzyme.

In contrast, in-vivo GT involves the direct administration of viral vectors carrying the therapeutic gene to the patient through different routes, including systemic intravenous injection or targeted delivery for example to the central nervous system (CNS), such as intracerebral, intracerebroventricular, or intracisternal injections.

While retroviral (RV) and lentiviral (LV) vectors are commonly used in ex-vivo HSPC-GT, adeno-associated viruses (AAV) are the preferred choice for in-vivo gene therapy applications. Currently, lentiviral vectors (LV) are favored for introducing multiple copies of the therapeutic gene into human HSPCs [5]. With proper vector design, LV transduction enables stable transgene expression in both committed and differentiated progeny of HSPCs, including the HSPC-derived myeloid cells that can repopulate the CNS following HSPC-GT. The therapeutic efficacy within the CNS depends on the ability of HSPCs to migrate to the brain and differentiate into microglia, which serve as a source of the therapeutic enzyme required for cross-correction of neighboring cells.

Neurometabolic lysosomal storage diseases (LSDs) are a group of rare, inherited monogenic disorders characterized by significant clinical and genetic heterogeneity. These conditions result from mutations in

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single genes that disrupt the function of specific enzymes or proteins, leading to a deficiency in critical metabolic products within the brain. The consequent impairment in substrate degradation or synthesis results in their pathological accumulation, ultimately causing cellular toxicity and death. CNS involvement is often profound, with pathological features including microglial activation, inflammatory demyelination, axonal degeneration, and neuronal loss. These processes contribute to progressive neurological deterioration driven by substrate accumulation, oxidative stress, and chronic neuroinflammation. [6].

Currently, treatment options for neurometabolic LSDs are limited. Available therapies include enzyme replacement therapy (ERT) and allogeneic hematopoietic stem cell transplantation (HSCT) [7], both directed toward the restoration of the equilibrium between substrate production and cleavage [8]. ERT is now considered the standard-of-care for some inherited metabolic disorders but, despite good results in slowing down disease progression, has many limitations: it is unable to reach the CNS and the skeleton; it can induce the production of antibodies [9]; and it is expensive and not widely available.

HSCT represents an alternative strategy for providing a sustained source of the deficient protein. The therapeutic mechanism of HSCT is based on the principle of cross-correction, wherein engrafted donor-derived myeloid cells continuously produce the missing enzyme, which is subsequently taken up by enzyme-deficient host cells [10]. Additionally, donor-derived HSPCs can migrate to the CNS and differentiate into microglia, enhancing neurocognitive outcomes [11]. However, HSCT carries risks such as graft rejection, graft-versus-host disease (GvHD), conditioning-related toxicity, and infections. Furthermore, the donor's delivered enzyme may not fully correct CNS deficits reaching only normal levels.

The unmet medical need and the monogenic nature of neurometabolic disorders make them promising candidates for cell- and gene-based therapies. Clinical trials are ongoing for several disorders, including mucopolysaccharidoses, X-linked adrenoleukodystrophy, Fabry and Pompe diseases, and metachromatic leukodystrophy (MLD), with recent market authorizations for X-ALD and MLD in the EU and USA(https://www.Ema.Europa.Eu/En/Medicines/Human/EPAR/Libmeldy; https://www.Fda.Gov/Vaccines-Blood-Biologics/Skysona).

This review focuses on HSPC-GT approaches for neurometabolic disorders (Table 1) summarizing the most recent developments in the field and touching upon future perspective.

## 2. Mucopolysaccharidoses (MPS)

MPS constitute a subset of rare, monogenic LSDs resulting from mutations in genes encoding lysosomal enzymes responsible for the catabolism of glycosaminoglycans (GAGs). Deficient enzymatic activity leads to the progressive accumulation of undegraded GAGs within lysosomes across multiple cell types, thereby affecting both the CNS and peripheral organs. The resultant multisystem pathology is characterized by hepatosplenomegaly, valvular cardiac disease, progressive pulmonary dysfunction, and skeletal dysplasia. Notably, primary CNS involvement is a hallmark of the severe phenotypes of MPS types I and II, all subtypes of type III, and type VII [10,12].

The severe form of MPS I (MPS IH), caused by a deficiency in alpha-L-iduronidase (IDUA), is characterized by skeletal abnormalities, hepatosplenomegaly, hearing and visual loss, and progressive cognitive decline. ERT is used adjunctively in the pre- and peri-transplant period [13–15]to mitigate the delay in engraftment of donor cells, which helps initiate detoxification of accumulated substrates [16–19]. While HSCT is currently established as the standard of care for MPSIH [20]and improves long-term survival, it does not fully address CNS involvement, skeletal dysplasia and quality of life in the patients, highlighting an

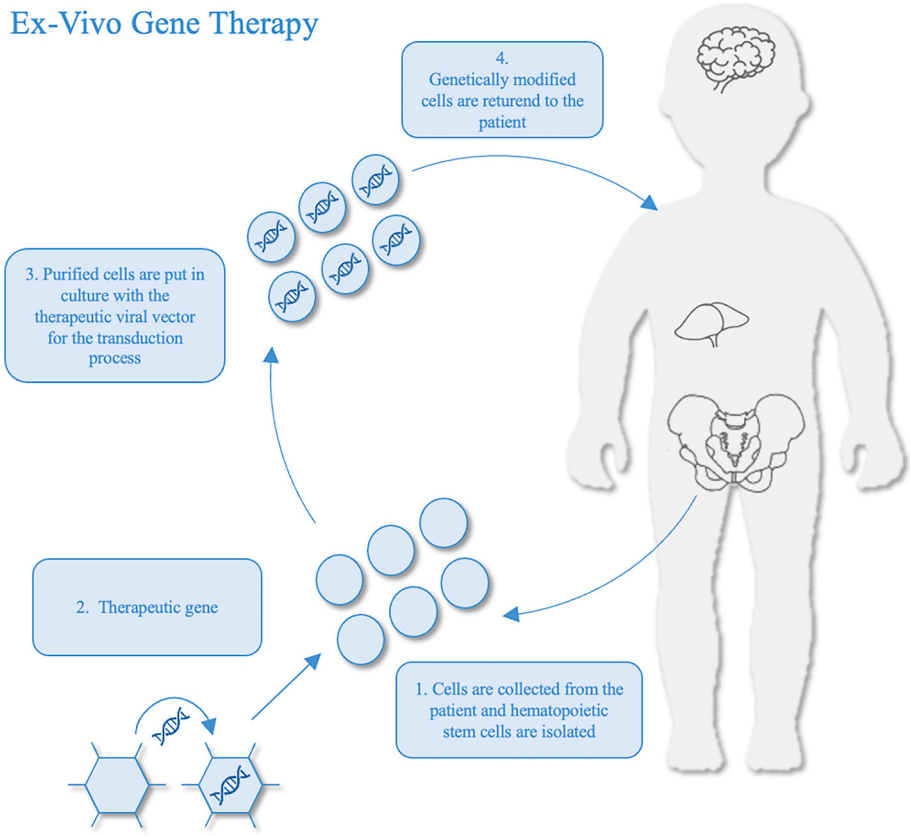


**Fig. 1.** Schematic representation of HSPC-GT. HSPC-GT requires patient's cell collection followed by $CD34^{+}$ cell isolation; subsequently, the purified cells are cultured with the therapeutic viral vector for gene delivery; finally, genetically modified stem cells are returned to the patient. This figure has been modified from one created in our previous study [4] with permission from Elsevier.

**Table 1**
Hematopoietic stem progenitor cells-gene therapy (HSPC-GT) clinical approaches for neurometabolic disorders.

| DISEASE | STUDY NAME/SPONSOR | VECTOR | ADMINISTRATION ROUTE | TRIAL ID | STATUS |
|---|---|---|---|---|---|
| MPSI | OTL-203<br>Orchard Therapeutics | LV-IDUA | Ex vivo CD34+ cells (IV) | NCT03488394 | Completed<br>(Phase I/II) |
| | OTL-203-02<br>Orchard Therapeutics | LV-IDUA | Ex vivo CD34+ cells (IV) | NCT06149403 | Active, recruiting<br>(Phase III) |
| MPSII | Manchester University, UK | LV-IDS<br>LV-IDS APOEII | Ex vivo CD34+ cells (IV) | NCT05665166 | Recruiting<br>(Phase I/II) |
| MPSIIIA | Orchard OTL-201<br>Manchester University | LVV-CD11b-SGSH | Ex vivo CD34+ cells (IV) | NCT04201405 | Active, not recruiting<br>(Phase I/II ongoing) |
| Fabry disease | University Health Network, Toronto and Ozmosis Research Inc. | LV-AGA | Ex-vivo CD34+ cells (IV) | NCT02800070 | Completed<br>(Phase I) |
| | Avrobio | LV-AGA | Ex-vivo CD34+ cells (IV) | NCT03454893 | Terminated<br>(Phase I/II) |
| MLD | OTL-200-f<br>(fresh formulation)<br>Orchard Therapeutics | LV-ARSA | Ex vivo CD34+ cells (IV) | NCT01560182 | Active, not recruiting<br>(Phase I/II) |
| | OTL-200-c<br>(cryopreserved)<br>Orchard Therapeutics | LV-ARSA | Ex vivo CD34+ cells (IV) | NCT03392987 | Active, not recruiting<br>(Phase II) |
| | OTL-200<br>(cryopreserved)<br>Orchard Therapeutics | LV-ARSA | Ex vivo CD34+ cells (IV) | NCT04283227 | Active, not recruiting<br>(Phase III) |
| MLD/<br>X-ALD | Shenzen Second People's Hospital, China | LV-ARSA/ABCD1 | Ex vivo CD34+ cells (IV) | NCT02559830 | Recruiting<br>(Phase I/II) |
| X-ALD | ALD-102<br>Bluebirdbio | Lenti-D LV-ABCD1 | Ex vivo CD34+ cells (IV) | NCT01896102 | Completed<br>(Phase II/III) |
| | ALD-104<br>Bluebirdbio | Lenti-D LV-ABCD1 | Ex vivo CD34+ cells (IV) | NCT03852498 | Active, not recruiting<br>(Phase III) |

MPS, mucopolysaccharidosys; X-ALD, X-linked adrenoleukodystrophy; MLD, metachromatic leukodystrophy; IDUA, alpha-L-iduronidase; IDS, iduronate-2-sulfatase; ARSA, arylsulfatase A; SGSH, N-sulfoglucosamine sulfohydrolase; AGA, alglucosidase alfa; IV, intravenous; LV, lentiviral.

unmet clinical need.

Preclinical studies in mouse models of MPSIH treated with LV-based HSPC-GT have demonstrated superior efficacy compared to HSCT [21,22]. This has supported the development of a clinical approach with IDUA-LV HSPC-GT in a Phase I/II clinical trial whose interim results showed supraphysiological blood IDUA activity and early normalization or near-normalization of GAG excretion in 8 patients. Following treatment, cerebrospinal fluid (CSF) IDUA activity became detectable and was associated with reduced local GAG accumulation. Clinically, patients demonstrated stabilization of cognitive and motor functions, enhanced joint mobility, and normal growth. [23,24].

A Phase III, multi-center, randomized trial sponsored by Orchard Therapeutics is underway to compare the safety and efficacy of autologous HSPC-GT (OTL-203) versus HSCT. The trial, which recently began in the USA and EU, aims to determine whether ex-vivo HSPC-GT offers a better treatment option for MPS IH compared to HSCT and could extend this approach to other ultra-rare LSDs with unmet medical need.

MPS II is an X-linked recessive LSD caused by a deficiency in iduronate-2-sulfatase (IDS), leading to the accumulation of GAGs in various cell types and organs. The application of HSCT in MPS II has been limited, with existing literature largely outdated and reporting variable outcomes, particularly with respect to its effects on the neurological manifestations of the disease. In MPS II mouse models, a brain-targeted HSPC-GT strategy, using a LV encoding IDS fused to ApoEII (LV.IDS.ApoEII) to enhance blood-brain barrier (BBB) crossing, showed superior efficacy compared to standard IDS expression or normal bone marrow transplant. The LV.IDS.ApoEII vector resulted in complete normalization of neuropathological and behavioral deficits, in contrast to the partial correction observed with the standard IDS. Moreover, LV.IDS.ApoEII significantly enhanced plasma enzyme activity, cellular uptake, and transcytosis across the blood-brain barrier, mediated by heparan sulfate/ApoE and mannose-6-phosphate receptor pathways [25,26]. Brain-targeted HSPC-GT thus represents a promising therapeutic approach for MPS II. A Phase I/II clinical trial is currently underway at the University of Manchester to evaluate its safety and efficacy. [26]

MPS III comprises four autosomal recessive subtypes, each resulting from defects in enzymes responsible for the degradation of heparan sulfate. Several reports on the neurological outcomes in children treated with HSCT have been published, yielding disappointing results, even when the transplantation was performed during the asymptomatic phase of the disease [27–31]. A phase I/II clinical trial of HSPC-GT is under investigation (NCT04201405) at Manchester University for MPSIIIA in patients between 3 and 24 months of age with preserved neurocognitive function. In this trial, autologous HSPCs, collected following mobilization, are transduced ex-vivo with a LV carrying the human SGSH gene under the control of the CD11b promoter. The modified cells are then cryopreserved and re-infused after myeloablative conditioning with busulfan. Safety and tolerability of the drug product and expression of SGSH activity in leukocytes at 12 months post-treatment are the primary endpoints, whereas neurocognitive outcome is a secondary endpoint. Although the study is still ongoing, preliminary data from the first patients recruited show supraphysiological enzyme expression in multiple lineages and substrate reduction in plasma, CSF, and urine. [32]

## 3. Fabry disease

Fabry disease is an X-linked condition caused by alpha-galacto-sidase A (Gal A) deficiency with consequent glycosphingolipids accumulation and neurological symptoms.

ERT with recombinant α-galactosidase A (r-αGAL A) has been used to treat Fabry disease for more than 15 years. While long-term treatment can help slow disease progression, cardiac, renal, and cerebral complications continue to emerge in the majority of patients. HSPC-GT has also been investigated for the treatment of Fabry disease [33]. Two clinical trials of HSPC-GT have been conducted with preliminary results showing efficient LV-mediated gene transfer, increased intracellular and circulating Gal A activity. Nevertheless, enzyme levels declined over time, underlying poor engraftment [34] and the company developing the product announced the deprioritization of the Fabry program, resulting in its removal from the development pipeline.

## 4. Pompe disease

Pompe disease is a rare autosomal recessive disorder caused by mutations in the acid alpha-1,4-glucosidase (GAA) gene, resulting in glycogen accumulation in various tissues, particularly muscles and the CNS, leading to progressive neurodegeneration. While early ERT can mitigate cardiomyopathy in infants, skeletal and smooth muscle dysfunction with associated weakness persist.

HSPC-GT has shown promise in preclinical studies, with long-term engraftment and continuous GAA supply after a single treatment in Gaa−/− mice, leading to improvements in cardiac and motor function. Liang et al. created a vector incorporating a codon-optimized GAA sequence fused to human IGF2 (LV-IGF2.GAAco) improving glycogen accumulation, autophagy, motor function, and brain glycogen content [35]. A similar approach has been used in other preclinical studies to create engineered GAA coding sequences, distinct peptide tags and codon optimizations. The use of this strategy with glycosylation-independent lysosomal targeting tags increased secretion and reduced glycogen, myofiber and CNS vacuolation in tissues, but maintained low GAA enzyme activity. [36]

## 5. Metachromatic leukodystrophy (MLD)

MLD is a rare inherited LSD caused by mutations in the arylsulfatase A (ARSA) gene, leading to sulfatide accumulation in the central and peripheral nervous systems, resulting in progressive demyelination and neurodegeneration. MLD is classified into three variants based on the age of symptom onset: late infantile (LI), juvenile (early [EJ] and late), and adult forms [37].

In MLD, intrathecal ERT with recombinant human ARSA (rhARSA) was evaluated in a Phase I/II multicenter trial. A 38-week treatment regimen led to normalization of CSF sulfatide levels at the highest dose (100 mg) in 24 MLD patients who exhibited symptom onset at or before 30 months of age. However, a general decline in motor function was observed, along with the development of antibodies against the recombinant enzyme, which reduced its therapeutic efficacy [38]. Moreover, one limitation of this approach was the development of antibodies directed against the recombinant enzyme, with consequent enzyme inactivation [39]. HSCT has demonstrated some benefit in patients with LJ and adult MLD, provided that it is performed at a presymptomatic stage or in patients with minimal symptoms, as well as in presymptomatic EJ children [40–42] by stabilizing cerebral demyelination. However, HSCT does not completely prevent the onset of neurological symptoms such as peripheral neuropathy, cerebellar dysfunction, and cognitive decline, highlighting the critical role of neurodegeneration in disease progression.

Preclinical studies in MLD mice showed superiority of HSPC-GT over HSCT from wild-type donors, underlying the relevance of over-expressing the target gene to improve cross-correction and control neurological manifestations. [43,44] Given these promising results, a phase I/II clinical trial based on.

HSPC transduced ex vivo with a LV encoding ARSA in 9 LI and EJ patients at presymptomatic or very early-symptomatic stage was conducted [45,46] achieving supranormal ARSA levels in circulating hematopoietic cells and normal enzyme in the CSF, preserving cognitive function and severe motor impairment [43]. Subsequently, a larger cohort of patients corroborated these findings, demonstrating consistent safety and efficacy outcomes up to 7.5 years following HSPC-GT [46,47]. In 2020, the European Medicine Agency granted marketing authorization for MLD HSPC-GT under the name of Libmeldy for LI pre-symptomatic and EJ pre- and early-symptomatic patients (https://www.Ema.Europa.Eu/En/Medicines/Human/EPAR/Libmeldy), followed by Food and Drug Administration (FDA) in 2024 (Lenmeldy) (https://www.fda.gov/vaccines-blood-biologics/skysona).

## 6. X-linked adrenoleukodystrophy (X-ALD)

X-ALD is caused by mutations in the ABCD1 gene (ATP-binding cassette, subfamily D, member 1), which encodes a peroxisomal transporter (ALDP), resulting in abnormal breakdown of very long-chain fatty acids with consequent damage in adrenal and nervous system tissues. [48]. This results in the accumulation of saturated very long-chain fatty acids (VLCFAs), primarily in the white matter of the brain, spinal cord, and adrenal cortex, causing adrenal insufficiency and multifocal demyelination of the CNS. By adulthood, approximately half of affected individuals develops cerebral adrenoleukodystrophy (CALD), a severe, inflammatory, demyelinating, and progressive disorder that leads to premature death [49].

For X-ALD, no ERT is available and over the years, numerous strategies have been used to modify the neurological progression of the disease, such as immunosuppressants to reduce CNS inflammation or special lipid diets with restricted intake of VLCFAs, but with no clinical benefit.

Allogeneic HSCT is considered as the standard of care for CALD [50–52]. When performed early, prior to significant brain demyelination and when clinical symptoms are minimal or absent, HSCT can halt the neuroinflammatory demyelinating process, stabilize neurological disease, and enhance long-term survival, while also ensuring a high quality of life in affected patients [53–55].

HSPC-GT was first tested in 2 boys with CALD and resulted in ABCD1 transgene expression in myeloid cells, metabolic correction, and clinical stabilization [56]. Thereafter, 2 clinical trials (ALD-102 and ALD-104) using Lenti-D LV-modified HSPC saw equivalent results, where patients remained free of major functional disabilities and had attenuated progression of brain lesions [49].

Although both HSPC-GT and HSCT appear to be similarly effective in preventing disease progression in patients with early-stage CALD, with HSC-GT being associated with fewer transplant-related complications, recent reports have highlighted cases of myelodysplasia (MDS) linked to lentiviral vector integration following HSPC-GT [55–58]. According to the current evidence, the development of MDS was mediated by Lenti-D LV insertion. Specific features of this vector, such as the presence of the MNDU3 promoter, have been recognized as a contributor factor for the development of MDS [55].

The long-term effect of HSPC-GT will have to be assessed, as well as the risks associated with possible insertional mutagenesis. The therapeutic product (Skysona®) developed by Bluebirdbio obtained FDA approval in September 2022 and is now available in the United States for boys of 4–17 years of age with early, active CALD. Skysona® also received marketing authorization from EMA in 2021, but Bluebirdbio decided in 2022 to withdraw from the European market for commercial reasons, precluding its use in Europe.

## 7. Advantages and limitations of ex-vivo HSPC-GT

So far, HSPC-GT for inherited neurometabolic disorders has demonstrated a favorable safety profile, with minimal transplant-related complications and prompt engraftment, leading to limited hospitalization [55]. Notably, autologous cell use avoids the risk of immunological complications typical of HSCT and eliminates the need for donor matching, making timely transplantation possible, which is crucial for long-term neurological outcomes [59]. Although the manufacturing and release of autologous CD34+ HSPCs typically requires 6–8 weeks, this timeframe may be shorter than the waiting period for an available donor for transplantation.

Given that HSPC require several weeks to engraft in the blood and brain with CNS enzyme delivery taking months in both HSCT and HSCT-GT, early recognition of these disorders through newborn screening (NBS) could enable presymptomatic diagnosis [60]and treatment, optimizing clinical outcomes with HSPC-GT, currently possible only for patients with a positive family history.

Furthermore, HSPC-GT presents advantages over conventional HSCT by enabling the expression of supraphysiological enzyme levels, potentially enhancing cross-correction of non-hematopoietic cells, including neurons. This mechanism has been proposed in MLD, where gene-modified myeloid cells replace microglia, offering a localized source of bioavailable enzyme that effectively clears accumulated sulfatides. However, patients may develop autoantibodies against the therapeutic enzyme, although these typically resolve without affecting clinical outcomes [47] [23].

Low-toxicity conditioning regimens, including monoclonal antibody-based strategies targeting HSPCs, could further reduce risks of the treatment and broaden HSPC-GT's application, especially in the youngest patients [61,62].

On the other hand, treating very young children presents a practical challenge, as the collection of mobilized autologous HSPCs is conducted via leukapheresis. This procedure is difficult to perform in children weighing less than 5–10 kg due to the necessity of central venous access and the requirement for extracorporeal circulation.

Moreover, risks related to vector-mediated insertional mutagenesis, which could lead to malignancies such as MDS or leukemia, are a concern, especially with gamma retroviral vectors [63]. LV have shown reduced genotoxicity thanks to the use of internal physiological promoter to drive the expression of the therapeutic transgene and the self-inactivating design; this being supported by clinical trial data. However, there have been instances of MDS in X-ALD patients treated with LV-based HSPC-GT, prompting regulatory caution [55].

Despite encouraging results, particularly for MLD, the long-term safety and efficacy of HSPC-GT across other neurometabolic diseases remain uncertain, necessitating further observation. Additionally, the high production costs and complex regulatory pathways limit widespread adoption of these strategies, contributing to recent disinvestment in HSPC-GT for some rare genetic defects [64].

## 8. Conclusions and future perspective

Encouraging results from clinical trials of HSPC-GT in neurometabolic disorders, including MLD, X-ALD, and, preliminarily, MPS IH and MPS III, have demonstrated metabolic correction and clinical efficacy [23,47,65] leading to marketing authorization for some of these therapies (https://www.ema.europa.eu/en/medicines/human/EPAR/libmeldy;https://www.Fda.Gov/Vaccines-Blood-Biologics/Skysona). However, recent cases of MDS in CALD patients underscore the need for further long-term safety evaluation. Additionally, limited follow-up in some diseases complicates direct comparisons between HSPC-GT and traditional treatments like enzyme ERT and HSCT.

The success of HSPC-GT in addressing neurological manifestations in certain disorders highlights its potential applicability to other neurometabolic diseases with unmet medical needs. A LV-based platform, building on the results observed in MLD, MPS I—H, and MPS III, could broaden the use of similar HSPC-GT strategies to a variety of diseases, including ultrarare conditions, thereby enhancing cost-effectiveness and accessibility. Although high costs and extended regulatory timelines remain significant challenges, this approach could help mitigate these issues and improve patient access to safe and effective treatments [64,66].

Overall, although data from HSPC-GT trials remain limited, the results are promising, showing favorable safety and efficacy compared to HSCT. These strategies warrant further clinical development for treating other rare neurometabolic diseases. The implementation of NBS strategies aimed at ensuring timely diagnosis and treatment will further optimize the clinical outcome of patients affected by neurometabolic disorders.

## Author contribution

All authors meet the ICMJE authorship criteria.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: *MEB is the PI of the Phase I/II clinical trial of HSC-GT for MPSIH since July 2020. GC, FT and MEB are investigators of the trial. MEB have acted as* ad hoc *consultant for an Orchard Therapeutics advisory board in 2020.* MEB and GC have received reimbursement for travel and registration costs related to conference presentations.

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