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Intrauterine enzyme replacement therapies for lysosomal storage disorders: Current developments and promising future prospects

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Abstract

Lysosomal storage disorders (LSDs) are a group of monogenic condition, with many characterized by an enzyme deficiency leading to the accumulation of an undegraded substrate within the lysosomes. For those LSDs, postnatal enzyme replacement therapy (ERT) represents the standard of care, but this treatment has limitations when administered only postnatally because, at that point, prenatal disease sequelae may be irreversible. Furthermore, most forms of ERT, specifically those administered systemically, are currently unable to access certain tissues, such as the central nervous system (CNS), and furthermore, may initiate an immune response. In utero enzyme replacement therapy (IUERT) is a novel approach to address these challenges evaluated in a first-in-human clinical trial for IUERT in LSDs (NCT04532047). IUERT has numerous advantages: in-utero intervention may prevent early pathology; the CNS can be accessed before the blood-brain barrier forms; and the unique fetal immune system enables exposure to new proteins with the potential to prevent an immune response and may induce sustained tolerance. However, there are challenges and limitations for any fetal procedure that involves two patients. This article reviews the current state of IUERT for LSDs, including its advantages, limitations, and potential future directions for definitive therapies.

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1 | INTRODUCTION

Lysosomal storage disorders (LSDs) are a group of rare genetic conditions characterized by the deficiency or malfunction of lysosomal enzymes, which are responsible for breaking down complex molecules in the cell necessary to maintain normal cellular function (Table 1). This deficiency leads to substrate accumulation in lysosomes, causing progressive cellular damage, organ dysfunction, and ultimately severe and often fatal clinical manifestations.[1] While LSDs primarily involve lysosomal dysfunction due to substrate accumulation, the impact of this can extend beyond lysosomes to affect other cellular organelles, including the endoplasmic reticulum, the Golgi apparatus, and mitochondria.[2] The disruption of subcellular homeostasis as a secondary phenomenon in LSDs is a consequence of the complex interplay between organelles and key processes essential for maintaining cellular function[3] (Figure 1). This includes the impairment of autophagy,[4–6] mitochondrial DNA damage,[7] lipid metabolism dysfunction,[8] altered calcium homeostasis,[9] and cellular energy imbalance.[3] Mitochondrial dysfunction, for example, and the subsequent oxidative stress, the altered calcium signaling, as well as ATP deprivation are all involved in lysosomal alkalinization[2] and neurodegeneration,[10,11] which are components of several LSDs. The postnatal diagnosis of LSDs is based on enzymatic testing of neonatal blood samples. The specific enzyme being tested for will vary depending on the suspected LSD. In some cases, confirmatory tests, such as genetic testing or additional biochemical tests, may be required for a definitive diagnosis. In regions with newborn screening programs, certain LSDs might be included in the neonatal screening panel, allowing for early diagnosis and potential therapeutic intervention. However, not all LSDs are routinely screened for at birth, and the number of included diseases varies by country and region.

2 | PRENATAL DIAGNOSIS

Prenatal diagnosis of LSDs is available by genetic or enzymatic testing of chorionic villus or amniotic fluid samples. Earlier treatment is associated with improved outcomes,[12,13] and as such, prenatal detection of LSDs is crucial for the success of eventual intrauterine enzyme replacement therapy (IUERT). This can be challenging because:

1. Many LSDs are not included in carrier screening panels, likely because their design is based on the prevalence of the condition and not on the actionability of the resulting diagnosis.[14] The Recommended Uniform Screening Panel lists MPS I (2015), MPS II (2022), and Pompe (2013). As such, states are offering or developing assays to screen newborns for these conditions. The availability in various states is, however, not uniform.
2. Routine prenatal screening currently involves ultrasound scans, and while some LSDs may present as nonimmune hydrops fetalis (NIHF)[15–18] during pregnancy (Table 1), most LSDs do not have prenatal ultrasound manifestations. Nevertheless, inborn errors of metabolism cause up to 15% of NIHF[20,21] and LSDs are the most common inborn error of metabolism, responsible for 15%–29% of unexplained NIHF[22]: Mucopolysaccharidosis (MPS) VII, followed by Gaucher disease and GM1-gangliosidosis, seem to be among the most common

LSDs diagnosed in NIHF.[17,22,23] Although LSDs are rare disorders as a group, they should be considered as a possible cause of NIHF, even in the absence of consanguinity or of a previous family history.[19] Suspected cases of NIHF should be confirmed with further genetic/biochemical testing.

3. Although non-invasive prenatal testing is becoming more prevalent, the advances in this field have yet to reach these conditions.

4. Chromosomal microarray (CMA) is particularly useful for identifying chromosomal causes of developmental delays. However, LSDs are typically caused by point mutations, small insertions/deletions at the single gene level, that may involve only a few nucleotides, which affect the function of specific enzymes in the lysosome. As such, they cannot be diagnosed with CMA.

As more prenatal and early postnatal therapies become available, early diagnosis and a clear understanding of the genotype-phenotype correlation, ideally in the prenatal period, will be critical. Even if fetal therapy is not desired/available, a prenatal diagnosis enables planning for the initiation of timely postnatal therapy.

3 | POSTNATAL ENZYME REPLACEMENT THERAPY

Enzyme replacement therapy (ERT) after birth is a well-established therapeutic strategy for many LSDs in which patients receive a recombinant version of the missing or deficient enzyme. When administered systemically, the ERT binds to either Mannose-6-Phosphate receptors or Mannose receptors,[19] depending on the disease, and is trafficked to lysosomes (during a process called *"cross correction"*), where it contributes to normal function.[1] Despite promising outcomes, ERT has several limitations, such as (1) the inability to cross the Blood-Brain Barrier (BBB) and access other sanctuary sites such as the bone or cornea; (2) the potential for triggering the development of neutralizing anti-drug antibodies (ADAB) that limit effectiveness and (3) the limited efficacy in curbing the disease sequelae that develop in the prenatal period.

4 | RATIONALE FOR INTRAUTERINE ENZYME REPLACEMENT THERAPY IN LSDs

IUERT could potentially address the above mentioned challenges of ERT, by taking advantage of (1) the unique characteristics of the fetal environment, such as a more permissive BBB,[24,25] (2) a tolerogenic immune system, (3) by acting before irreversible damages occur,[26] and possibly allowing for a phenotypic rescue. As the enzyme is dosed for the fetus, IUERT also allows for (4) low initial drug doses at lower costs and (5) an improved drug-target ratio.

4.1 | Potential to penetrate affected tissues

The active BBB limits the access of ERT to the central nervous system (CNS), which curbs the uptake of systemically administered ERT into the brain. During fetal development, the relative immaturity of the BBB may facilitate the passage of the recombinant enzymes to the CNS. As such, IUERT has the potential to enable better penetration of affected tissues,

such as the CNS[12] and other.[13] Additionally, fetal cells in developing organs have a higher capacity to proliferate than adult cells,[27,28] which may increase the uptake and utilization of the therapeutic enzyme, achieving higher enzyme activity levels in those tissues.

4.2 | Early treatment

In many LSDs, the pathological process begins before birth.[29] IUERT can potentially prevent the onset or progression of irreversible damage to the developing organs. In a mouse model of MPS VIII,[12] IUERT prevented fetal demise, and continued postnatal doses resulted in the prevention of multi-organ pathology (Figure 2). Similarly, IUERT in a human patient with infantile-onset Pompe disease (IOPD) treated per the University of California, San Francisco (UCSF) protocol prevented the development of cardiac hypertrophy in-utero in a family in which the parents are carriers, and two previous siblings had died from the disease.[13]

4.3 | Fetal immune system

Postnatal ERT can lead to the development of ADAB, which can reduce the therapeutic benefit and increase the risk of adverse events. In humans, naïve fetal T-cells are more likely to become regulatory T cells upon antigen exposure, whereas adult naïve T cells are more likely to become effector T cells.[30,31] As such, preventing/limiting the formation of ADAB is paramount, and is particularly relevant for the cross-reactive immunological material (CRIM) negative IOPD. Although ADAB titers above 1:12,800 are considered clinically significant for Pompe Disease,[32] for other LSDs there are no clearly defined thresholds. Given the capacity of the fetal immune system to develop tolerance to foreign antigens, the risk of developing ADAB[33] in response to IUERT may be lower compared to ERT given postnatally, even when compared to ERT given in the first weeks of life.[34] Our group has shown that in murine models, IUERT may result in induction of tolerance to the recombinant protein even after repeated postnatal doses[12] (Figure 3).

5 | CURRENT APPROACHES IN IUERT FOR LSDs

For a disease to be considered for prenatal molecular therapies, icl. IUERT,[35] (1) the benefits of the offered treatment should outweigh the risks compared to the standard of care, (2) there should be an accurate prenatal molecular diagnosis of the condition, (3) since, the treatment is given before the onset of the phenotypic disease, there should be a clear genotype-phenotype correlation, with a severe phenotype based on prior reports or family history, (4) there needs to be a multidisciplinary team experienced with all aspects of the specific condition and associated therapies (e.g., immune tolerance induction, IUERT administration, laboratory surveillance studies, follow-up).

5.1 | Preclinical studies

Preclinical investigations have provided valuable insights into the feasibility and efficacy of IUERT for LSDs. In a murine model of MPS VII,[12] we demonstrated multiple advantages of IUERT versus ERT. We chose the MPS VII mouse model because this disease leads to hydrops in utero,[29] and many patients do not survive to birth.[36] Even though in the mouse model, the survival of affected fetuses was below the rate predicted by the breeding

scheme, it was restored to normal after IUERT.[12] We showed that in fetal mice treated with IUERT at mid-gestation, followed by postnatal ERT, lysosomal deposits decreased in multiple organs, and bone length increased compared to untreated controls and those treated only postnatally (Figure 2). We also demonstrated that the humoral immune response after ERT was robust in naïve mice versus slightly attenuated in mice exposed to ERT starting at age 3 weeks, findings which demonstrate that although neonatal mice have some ability to develop tolerance, fetal mice exposed to IUERT had a notable lack of immune response when compared to untreated and postnatally only treated mice (Figure 3).

Lastly, we showed that the enzyme administered in utero when crossed the BBB and entered the microglia, which are the usual storehouses of the enzyme; this was not seen in postnatally only-treated controls. An additional experiment demonstrated green fluorescent protein-positive (GFP^+) hematopoietic stem cells from a reporter mouse donor transplanted into a mid-gestation fetal mouse liver went into the CNS, where they became microglia-like cells. This is a significant advantage, as the closure of the BBB often precludes therapies from acting in the CNS after postnatal systemic administration. Behavioral testing further highlighted neuron targeting by showing increased grip strength in treated mice. The combined in-utero and postnatal treatment attenuated the degree of inflammation in the brain, as evidenced by CD68 staining. Collectively, these results were encouraging for the future use of IUERT in patients with severe LSDs.[12] This study also demonstrated that IUERT might provide an improved clinical head start for individuals receiving postnatal ERT or more definitive postnatal therapies.

5.2 | Clinical trials of IUERT

Based on the available preclinical data,[12] we applied to the United States Food and Drug Administration for an investigational new drug (IND) approval for a Phase 1 clinical trial testing the safety and efficacy of infusing disease-specific ERT before birth. The IND was approved in September 2020, and the clinical trial was launched in 2021 (NCT04532047). Since various LSDs share a similar pathophysiology and treatment type, the study included eight disorders under a single IND: MPS I, II, IVa, VI, VII, IOPD, Neuronopathic Gaucher (types II and III), and Wolman Disease. Each disorder has a severe, early onset phenotype and has an FDA-approved recombinant ERT available in the postnatal setting.

Affected fetuses are typically identified in families with a history of the genetic disease, and the diagnosis is confirmed with genetic testing during pregnancy through chorionic villous sampling or amniocentesis. Inclusion criteria for enrollment in this clinical trial are (1) fetuses with a confirmed diagnosis of one of the eight diseases, (2) gestational age between 18 and 35 weeks of gestation (GW), and (3) lack of any concurrent severe fetal genetic or structural anomalies, or maternal comorbidities that could increase morbidity of the intervention. The primary objectives are safety and feasibility, and the secondary objectives are tolerance to the enzyme, improved biomarker levels, and improved functional outcomes. Participation in this trial does not prevent patients from participating in other postnatal clinical trials. An Enrollment Advisory Board consisting of an independent group of experts advises on patient inclusion, typically limited to early onset and severe phenotypes. The

treatment regimen comprises IUERT every 2 weeks through umbilical vein injection. The injected compounds are weight-adjusted doses of FDA-approved drugs for postnatal use.

Regarding safety, the enzymatic activity (trough level) is evaluated in fetal and maternal blood before every injection to gather data on appropriate dosing. To evaluate efficacy, disease-specific biomarkers are checked in the fetal blood, amniotic fluid throughout pregnancy and in neonatal blood and urine postnatally. After delivery, patients continue standard-of-care ERT (+/− Immune tolerance induction—ITI) while awaiting other possibly definitive therapeutic options, such as gene therapy. Fresh placental tissues are obtained at the time of delivery for electron microscopy (EM) evaluation and spatially resolved comparative analysis. Annual follow-up visits are coordinated through 5 years of age.

We recently published the results of our first patient treated using this protocol[13] in a family where two prior children were homozygous for a pathogenic variant associated with IOPD (*c.525_526del*;*p.Asn177*fs) and succumbed to the disease (Figure 4A). This genotype correlates to a severe phenotype known as CRIM-negative IOPD due to the absence of residual GAA enzyme activity in the affected individual. The mother was referred during her fourth affected pregnancy, and after non-directive counseling of all pregnancy options, IUERT was initiated at 24 + 5 GW, every two weeks for a total of 6 doses and was delivered vaginally at 37 + 4 GW. In this patient, IUERT prevented the development of cardiac hypertrophy: a fetal echocardiogram at 34 + 3 GW demonstrated a normal heart, compared to the sibling's prenatal echocardiogram at the same time point (34 + 4 GW), which showed severe thickening of the interventricular septum with a Z-score of 7 (Figure 4B). Unlike in late-onset Pompe disease, there appears to be minimal phenotypic and lifespan variation among siblings with IOPD, who demonstrate significant concordance in clinical phenotype.[39,40]

In this case, the EM of the placenta showed a lack of substrate accumulation when compared to untreated, affected controls—historic samples (Figure 4C).

Postnatally, this patient had been receiving ERT with alglucosidase-alfa at 20 mg/kg, initially every 2 weeks until 9.6 months of age, and is now receiving 40 mg/kg weekly. When compared to a cohort of four patients with the same condition (CRIM-negative IOPD) diagnosed on newborn screening and treated early after birth, this prenatally treated patient had lower creatine kinase levels than the age-matched patients, also demonstrated normal muscle function and had been meeting all developmental milestones at 11 months of age (Figures 5A,B).

Patients with CRIM-negative IOPD are prone to a marked development of ADABs and, therefore, typically receive ITI with methotrexate, rituximab, and IVIG concurrent with ERT initiation.[26,32,42] When compared to postnatally treated patients, our patient had a milder ADAB response that decreased rapidly after postnatal ITI. Since we did not administer immune modulation inutero, we systematically tracked ADAB response during pregnancy by collecting fetal blood samples with each in-utero infusion. The patient developed low antibody titer levels after the third infusion of IUERT; the highest level in utero reaching 1:3200 at the time of the sixth in utero infusion. The individual's ADAB level then peaked at

the time of the second postnatal infusion (1:6400) and rapidly resolved with typical postnatal ITI and a continued course of rituximab at intermittent dosing intervals. The patient is currently negative for ADAB, whereas the patient's sibling, who was treated with typical ITI initiated at the time of the first postnatal ERT dose and following a clinical diagnosis at 6.6 months of age, eventually developed ADAB titers to a peak level of 1:6400. Sustained titers at this level required a second round of ITI. The rapid resolution after the initial course of postnatal ITI in the prenatally treated patient demonstrates the possible benefit of the IUERT in CRIM-negative patients but also the importance of IUERT being done by a multidisciplinary team where ADAB titers can be monitored and discussed during the fetal period to optimize prenatal treatment (e.g., dose adjustment), if necessary, and to determine optimal postnatal management, including early ITI. Although IUERT did not result in tolerance induction, it is important to note that the patient tolerated six doses of the prenatally administrated enzyme without developing clinically significant (1:12,800 or greater) ADAB titers (Figure 6).

6 | CHALLENGES AND LIMITATIONS OF IUERT

6.1 | Risk-benefit ratio

Novel therapies inherently carry known and unknown risks, and with prenatal therapies such as IUERT, the risk-benefit analysis for both the fetus and the mother must be considered. The benefit to the fetus is essential, which suggests that the disorder should be sufficiently severe, and the therapy should have the prospect of improved outcomes, even in a phase 1 clinical trial. It should improve multiorgan pathology, and potentially induce immune tolerance given the unique properties of the fetal immune system. Risks and benefits should be openly discussed with the family as part of non-directive counseling.

6.2 | Enzyme delivery

IUERT is administered directly into the umbilical vein using the standard fetal blood transfusion technique.[43–45] The risk of preterm labor is low in expert hands.[45] While early administration (<20 weeks) is technically more challenging,[46] after 20 weeks, the procedure-related complication (infection, premature rupture of membranes, fetal death) rate has been <1,6%.[43,47] Challenges such as placenta insertion on the posterior wall or oligohydramnios can also add technical difficulties.

6.3 | Patient engagement

The involvement of patients and patient advocacy group is essential when planning a clinical trial for in-utero therapies[48] to inform study design and implementation with patient and family interests at the core. These stakeholders can provide critical insights into the experience of living LSDs and the associated burden, driving the priorities for research and ensuring a patient-centered approach with outcomes that are meaningful to those affected by the disease. To improve understanding of patient and parent attitudes towards fetal therapy for LSDs, we surveyed parents and patients about the prospective management of a future affected pregnancy. Respondents were asked about their likelihood of ending a future-affected pregnancy; over half (54.4%) indicated they were unlikely to terminate. In addition, 60.1% were likely to enroll in a phase 1 clinical trial of IUERT, and 71% would

opt for IUERT if it were an established therapy (Figure 7).[48] Despite this survey being limited to mostly white respondents, it suggests that the LSD community is interested in and supportive of IUERT.

7 | ETHICAL IMPLICATIONS OF IUERT FOR LSDS

The requirements for optimal safety assessment for in-utero interventions are becoming clear through discussions of clinical trial protocols with regulatory and ethical authorities.[35,49] Safety evaluations must consider the risks to the mother and fetus during the administration of the injected agent, as well as ensuring local access to prenatal care and pregnancy management should complications arise. While IUERT has been shown to be safe and effective in an animal study[12] and in a single patient,[13] there might still be a potential risk of harm. Consequently, monitoring strategies have been developed to detect potential adverse events for enrolled patients, such as the Maternal and Fetal Adverse Event Terminology.[50]

Other ethical concerns include access issues: IUERT for LSDs is currently limited to a single site via the Phase 1 clinical trial at UCSF. As novel fetal molecular therapies emerge, health systems costs for these interventions will rise, posing unique challenges for providers and payers. While dosing a fetus might render (initially) lower enzyme costs, concerns about variable insurance coverage limiting access to new therapies are raising discussions worldwide.[35]

8 | IUERT AS A BRIDGE TOWARDS MORE DEFINITIVE THERAPIES

IUERT for LSDs has the potential to function as a bridge toward more definitive or curative therapies, such as fusion protein and BBB transporter molecule ERT able to cross the BBB, gene replacement (ex-chromosomal/non-integrating), splice-modifying approaches, gene editing (in-vivo or ex-vivo), and small molecule substrate inhibition. By delivering the missing enzyme early in development, IUERT can prevent or reduce the buildup of the substrate and provide an improved clinical environment for gene therapy or other definitive therapies, potentially rendering them more effective in the infant and child. By preventing or reducing organ damage, IUERT could improve the chances that a severely affected individual will be considered a candidate for definitive therapies and may improve the chance of an overall positive outcome. Clinical trials are currently evaluating gene therapies for LSDs in the postnatal setting (Table 2). The emergence of postnatal gene therapy and other novel endeavors are paving the way toward definitive therapeutic applications in the prenatal setting.

9 | CONCLUSION

IUERT is a promising approach for managing LSDs with several potential advantages over postnatal ERT or hematopoietic stem cell transplantation alone: preventing irreversible in-utero damage to the developing organs, improving CNS tissue penetration prenatally, and enhancing tolerance to foreign antigens such as the recombinant enzyme. The field is still developing, and some challenges, such as the need for improved prenatal diagnosis,

still have to be addressed. Collaborative efforts involving researchers, clinicians, ethicists, patients, advocacy groups, and policymakers are essential to establish comprehensive bioethical frameworks and regulatory guidelines for IUERT.

Our phase 1, first in human clinical trial, evaluates the safety and efficacy of IUERT and serves as proof of principle (NCT04532047). The results from a limited number of participants are encouraging, warranting the enrollment completion of 10 patients with grant funding available for additional domestic/international participants. In addition, a registry for diagnosed individuals is simultaneously enrolling (NCT05619900) new patients. While this trial demonstrates the potential benefit of prenatal therapy for early onset diseases, it is not a cure. As such, it is essential to focus on bridging these patients toward definitive/curative therapies and to promote the advancement of definitive therapies, such as gene therapies, in the pre and postnatal context.

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DATA AVAILABILITY STATEMENT

Data for the preclinical research and the clinical trial is available by request.

REFERENCES

1. Platt FM, d'Azzo A, Davidson BL, Neufeld EF, Tifft CJ. Lysosomal storage diseases. Nat Rev Dis Primers. 2018;4(1):27. 10.1038/s41572-018-0025-4 [PubMed: 30275469]

2. Stepien KM, Roncaroli F, Turton N, et al. Mechanisms of mitochondrial dysfunction in lysosomal storage disorders: a review. J Clin Med. 2020;9(8):2596. 10.3390/jcm9082596 [PubMed: 32796538]
3. Wong YC, Kim S, Peng W, Krainc D. Regulation and function of mitochondria-lysosome membrane contact sites in cellular homeostasis. Trends Cell Biol. 2019;29(6):500–513. 10.1016/j.tcb.2019.02.004 [PubMed: 30898429]
4. Platt FM. Sphingolipid lysosomal storage disorders. Nature. 2014; 510(7503):68–75. 10.1038/nature13476 [PubMed: 24899306]
5. Raben N, Baum R, Schreiner C, et al. When more is less: excess and deficiency of autophagy coexist in skeletal muscle in Pompe disease. Autophagy. 2009;5(1):111–113. 10.4161/auto.5.1.7293 [PubMed: 19001870]
6. Kohler L, Puertollano R, Raben N. Pompe disease: from basic science to therapy. Neurotherapeutics. 2018;15(4):928–942. 10.1007/s13311-018-0655-y [PubMed: 30117059]
7. Pivtoraiko VN, Stone SL, Roth KA, Shacka JJ. Oxidative stress and autophagy in the regulation of lysosome-dependent neuron death. Antioxidants Redox Signal. 2009;11(3):481–496. 10.1089/ars.2008.2263
8. Samie MA, Xu H. Lysosomal exocytosis and lipid storage disorders. J Lipid Res. 2014;55(6):995–1009. 10.1194/jlr.r046896 [PubMed: 24668941]
9. Feng X, Yang J. Lysosomal calcium in neurodegeneration. Messenger (Los Angel). 2016;5(1-2):56–66. 10.1166/msr.2016.1055 [PubMed: 29082116]
10. Wang Y, Xu E, Musich PR, Lin F. Mitochondrial dysfunction in neurodegenerative diseases and the potential countermeasure. CNS Neurosci Ther. 2019;25(7):816–824. 10.1111/cns.13116 [PubMed: 30889315]
11. Parenti G, Medina DL, Ballabio A. The rapidly evolving view of lysosomal storage diseases. EMBO Mol Med. 2021;13(2):e12836. 10.15252/emmm.202012836 [PubMed: 33459519]
12. Nguyen QH, Witt RG, Wang B, et al. Tolerance induction and microglial engraftment after fetal therapy without conditioning in mice with Mucopolysaccharidosis type VII. Sci Transl Med. 2020; 12(532). 10.1126/scitranslmed.aay8980
13. Cohen JL, Chakraborty P, Fung-Kee-Fung K, et al. In utero enzymereplacement therapy for infantile-onset Pompe's disease. N Engl J Med. 2022;387(23):2150–2158. 10.1056/nejmoa2200587 [PubMed: 36351280]
14. Gelb MH, Lukacs Z, Ranieri E, Schielen P. Newborn screening for lysosomal storage disorders: methodologies for measurement of enzymatic activities in dried blood spots. Int J Neonatal Screen. 2019; 5(1):1. 10.3390/ijns5010001 [PubMed: 30957052]
15. Norton ME, Chauhan SP, Dashe JS. Society for maternal-fetal medicine (SMFM) clinical guideline #7: nonimmune hydrops fetalis. Am J Obstet Gynecol. 2015;212(2):127–139. 10.1016/j.ajog.2014.12.018 [PubMed: 25557883]
16. Iyer NS, Gimovsky AC, Ferreira CR, Critchlow E, Al-Kouatly HB. Lysosomal storage disorders as an etiology of nonimmune hydrops fetalis: a systematic review. Clin Genet. 2021;100(5):493–503. 10.1111/cge.14005 [PubMed: 34057202]
17. Gimovsky AC, Luzi P, Berghella V. Lysosomal storage disease as an etiology of nonimmune hydrops. Am J Obstet Gynecol. 2015;212(3): 281–290. 10.1016/j.ajog.2014.10.007 [PubMed: 25305402]
18. Lee K, Fisher R, Quinonez SC, Ahmad A. Infantile onset Pompe disease presenting with non-immune hydrops fetalis. Mol Genet Metab Rep. 2019;21:100503. 10.1016/j.ymgmr.2019.100503 [PubMed: 31467850]
19. Burin MG, Scholz AP, Gus R, et al. Investigation of lysosomal storage diseases in nonimmune hydrops fetalis. Prenat Diagn. 2004;24(8): 653–657. 10.1002/pd.967 [PubMed: 15305357]
20. Bellini C, Donarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: an update. Am J Med Genet. 2015;167a(5):10821088. 10.1002/ajmg.a.36988
21. Sohan K, Carroll SG, De La Fuente S, Soothill P, Kyle P. Analysis of outcome in hydrops fetalis in relation to gestational age at diagnosis, cause and treatment. Acta Obstet Gynecol Scand. 2001; 80(8):726–730. 10.1034/j.1600-0412.2001.080008726.x [PubMed: 11531615]

22. Al-Kouatly HB, Felder L, Makhamreh MM, et al. Lysosomal storage disease spectrum in nonimmune hydrops fetalis: a retrospective case control study. Prenat Diagn. 2020;40(6):738–745. 10.1002/pd.5678 [PubMed: 32134517]
23. Sheth J, Mistri M, Shah K, Chaudhary M, Godbole K, Sheth F. Lysosomal storage disorders in nonimmune hydrops fetalis (NIHF): an Indian experience. JIMD Rep. 2017;35:47–52. [PubMed: 27928775]
24. Haddad-Tóvolli R, Dragano NRV, Ramalho AFS, Velloso LA. Development and function of the blood-brain barrier in the context of metabolic control. Front Neurosci. 2017;11:224. 10.3389/fnins.2017.00224 [PubMed: 28484368]
25. Goasdoué K, Miller SM, Colditz PB, Björkman ST. Review: the bloodbrain barrier; protecting the developing fetal brain. Placenta. 2017;54:111–116. 10.1016/j.placenta.2016.12.005 [PubMed: 27939102]
26. Kazi ZB, Desai AK, Berrier KL, et al. Sustained immune tolerance induction in enzyme replacement therapy-treated CRIM-negative patients with infantile Pompe disease. JCI Insight. 2017;2(16). 10.1172/jci.insight.94328
27. Fauza DO. Tissue engineering and transplantation in the fetus. In: Robert Lanza RL, ed. Principles of Tissue Engineering; 2014:511–529.
28. Alexander V, Chalphin DOF. Fetal tissue. In: Reis RL, ed. Encyclopedia of Tissue Engineering and Regenerative Medicine. Academic Press; 2019:299–313.
29. Derderian SC, Jeanty C, Fleck SR, et al. The many faces of hydrops. J Pediatr Surg. 2015;50(1):50–54. discussion 4. 10.1016/j.jpedsurg.2014.10.027 [PubMed: 25598092]
30. Mold JE, Michaëlsson J, Burt TD, et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science. 2008;322(5907):1562–1565. 10.1126/science.1164511 [PubMed: 19056990]
31. Mold JE, McCune JM. Immunological tolerance during fetal development: from mouse to man. Adv Immunol. 2012;115:73–111. [PubMed: 22608256]
32. Desai AK, Baloh CH, Sleasman JW, Rosenberg AS, Kishnani PS. Benefits of prophylactic short-course immune tolerance induction in patients with infantile Pompe disease: demonstration of long-term safety and efficacy in an expanded cohort. Front Immunol. 2020;11: 1727. 10.3389/fimmu.2020.01727 [PubMed: 32849613]
33. Kishnani PS, Dickson PI, Muldowney L, et al. Immune response to enzyme replacement therapies in lysosomal storage diseases and the role of immune tolerance induction. Mol Genet Metabol. 2016;117(2): 66–83. 10.1016/j.ymgme.2015.11.001
34. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline. Genet Med. 2006;8(5):267–288. 10.1097/01.gim.0000218152.87434.f3 [PubMed: 16702877]
35. Herzeg A, Almeida-Porada G, Charo RA, et al. Prenatal somatic cell gene therapies: charting a path toward clinical applications (proceedings of the CERSI-FDA meeting). J Clin Pharmacol. 2022;62((Suppl 1)):S36–s52. 10.1002/jcph.2127 [PubMed: 36106778]
36. Sparks TN, Lianoglou BR, Adami RR, et al. Exome sequencing for prenatal diagnosis in nonimmune hydrops fetalis. N Engl J Med. 2020;383(18):1746–1756. 10.1056/nejmoa2023643 [PubMed: 33027564]
37. Firpo C, Hoffman JI, Silverman NH. Evaluation of fetal heart dimensions from 12 weeks to term. Am J Cardiol. 2001;87(5):594–600. 10.1016/s0002-9149(00)01437-5 [PubMed: 11230845]
38. Bendon RW, Hug G. Morphologic characteristics of the placenta in glycogen storage disease type II (alpha-1,4-glucosidase deficiency). Am J Obstet Gynecol. 1985;152(8):1021–1026. 10.1016/0002-9378(85)90551-4 [PubMed: 2411138]
39. Smith WE, Sullivan-Saarela JA, Li JS, et al. Sibling phenotype concordance in classical infantile Pompe disease. Am J Med Genet. 2007;143a(21):2493–2501. 10.1002/ajmg.a.31936 [PubMed: 17853454]
40. Stenger EO, Kazi Z, Lisi E, Gambello MJ, Kishnani P. Immune tolerance strategies in siblings with infantile Pompe disease-advantages for a preemptive approach to high-sustained antibody titers. Mol Genet Metab Rep. 2015;4:30–34. 10.1016/j.ymgmr.2015.05.004 [PubMed: 26167453]
41. Li C, Desai AK, Gupta P, et al. Transforming the clinical outcome in CRIM-negative infantile Pompe disease identified via newborn screening: the benefits of early treatment with enzyme

replacement therapy and immune tolerance induction. Genet Med. 2021;23(5): 845–855. 10.1038/s41436-020-01080-y [PubMed: 33495531]

42. Kishnani PS, Goldenberg PC, DeArmey SL, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. Mol Genet Metabol. 2010;99(1):26–33. 10.1016/j.ymgme.2009.08.003
43. Pasman SA, Claes L, Lewi L, et al. Intrauterine transfusion for fetal anemia due to red blood cell alloimmunization: 14 years experience in Leuven. Facts Views Vis Obgyn. 2015;7(2):129–136. [PubMed: 26175890]
44. Yang YJ, Wei X, Zou G, Zhou FH, Sun LM. [Feasibility and safety of fetal intravascular transfusion via the intrahepatic vein in the treatment of fetal anemia]. Zhonghua Fu Chan Ke Za Zhi. 2021;56(4):244–250. [PubMed: 33902235]
45. Lindenburg IT, van Kamp IL, Oepkes D. Intrauterine blood transfusion: current indications and associated risks. Fetal Diagn Ther. 2014;36(4):263–271. 10.1159/000362812 [PubMed: 24903741]
46. Zwiers C, Lindenburg ITM, Klumper FJ, de Haas M, Oepkes D, van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. Ultrasound Obstet Gynecol. 2017;50(2):180–186. 10.1002/uog.17319 [PubMed: 27706858]
47. Van Kamp IL, Klumper FJ, Oepkes D, et al. Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. Am J Obstet Gynecol. 2005;192(1):171177. 10.1016/j.ajog.2004.06.063
48. Schwab ME, Brown JEH, Lianoglou B, et al. Fetal therapies and trials for lysosomal storage diseases: a survey of attitudes of parents and patients. Orphanet J Rare Dis. 2022;17(1):25. 10.1186/s13023-022-02178-z [PubMed: 35093147]
49. Sagar R, Almeida-Porada G, Blakemore K, et al. Fetal and maternal safety considerations for in utero therapy clinical trials: iFeTiS consensus statement. Mol Ther. 2020;28(11):2316–2319. 10.1016/j.ymthe.2020.10.012 [PubMed: 33069884]
50. David A 2023. https://www.ucl.ac.uk/womenshealth/research/maternal-and-fetal-medicine/prenataltherapy/current-projects-professor-anna-david-0

Key points

- Postnatal treatment of lysosomal diseases is well-known and well-accepted as a standard of care for Lysosomal storage disorders (LSDs).
- This current review evaluates the safety and feasibility of intrauterine enzyme replacement therapy (IUERT) as a novel approach to treating LSDs.

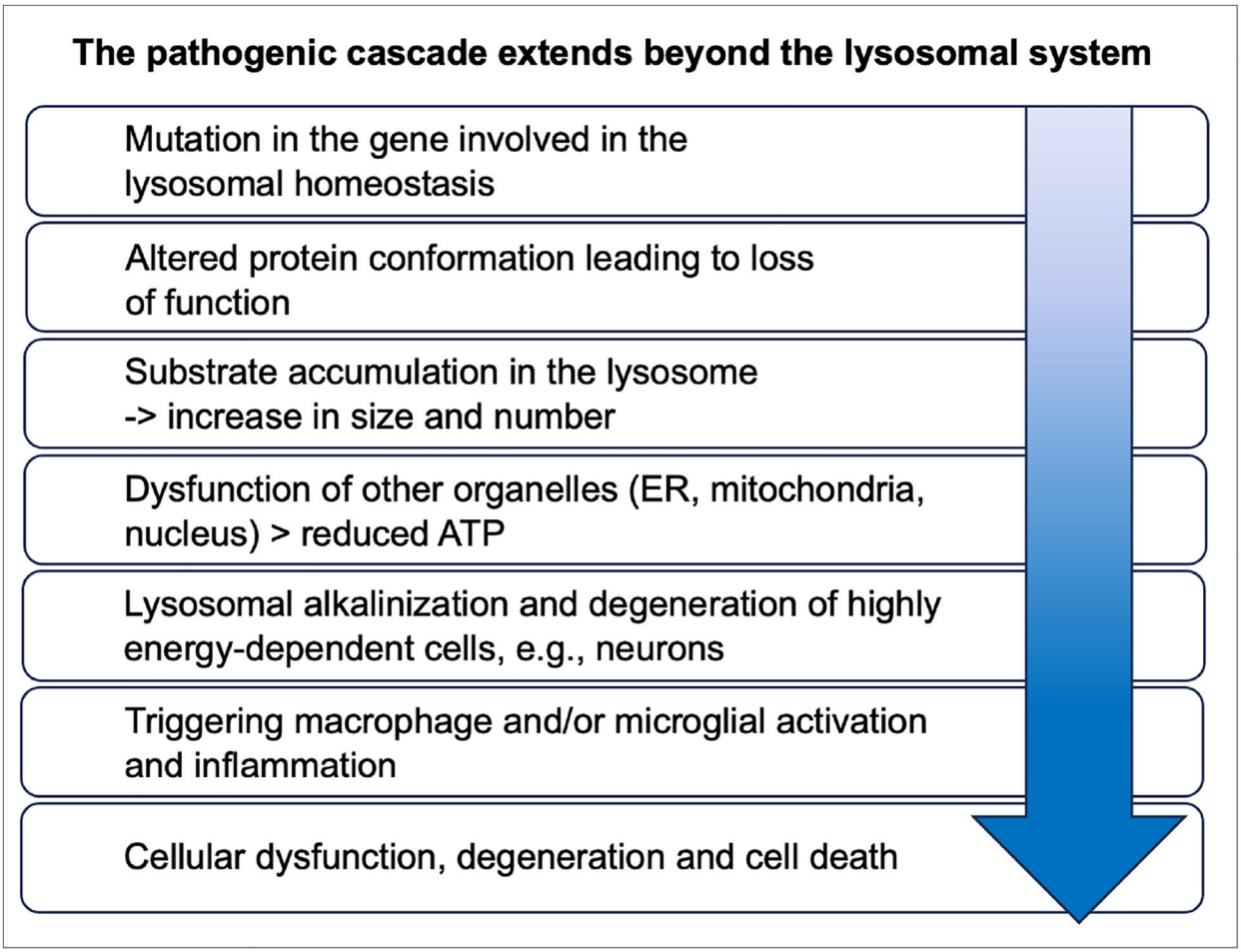


FIGURE 1.
The pathogenic cascade of lysosomal storage disorders (LSDs) extends beyond the lysosomal system. Adapted from Platt, F., Sphingolipid LSDs (2014) and LSDs (2018).[2,4]

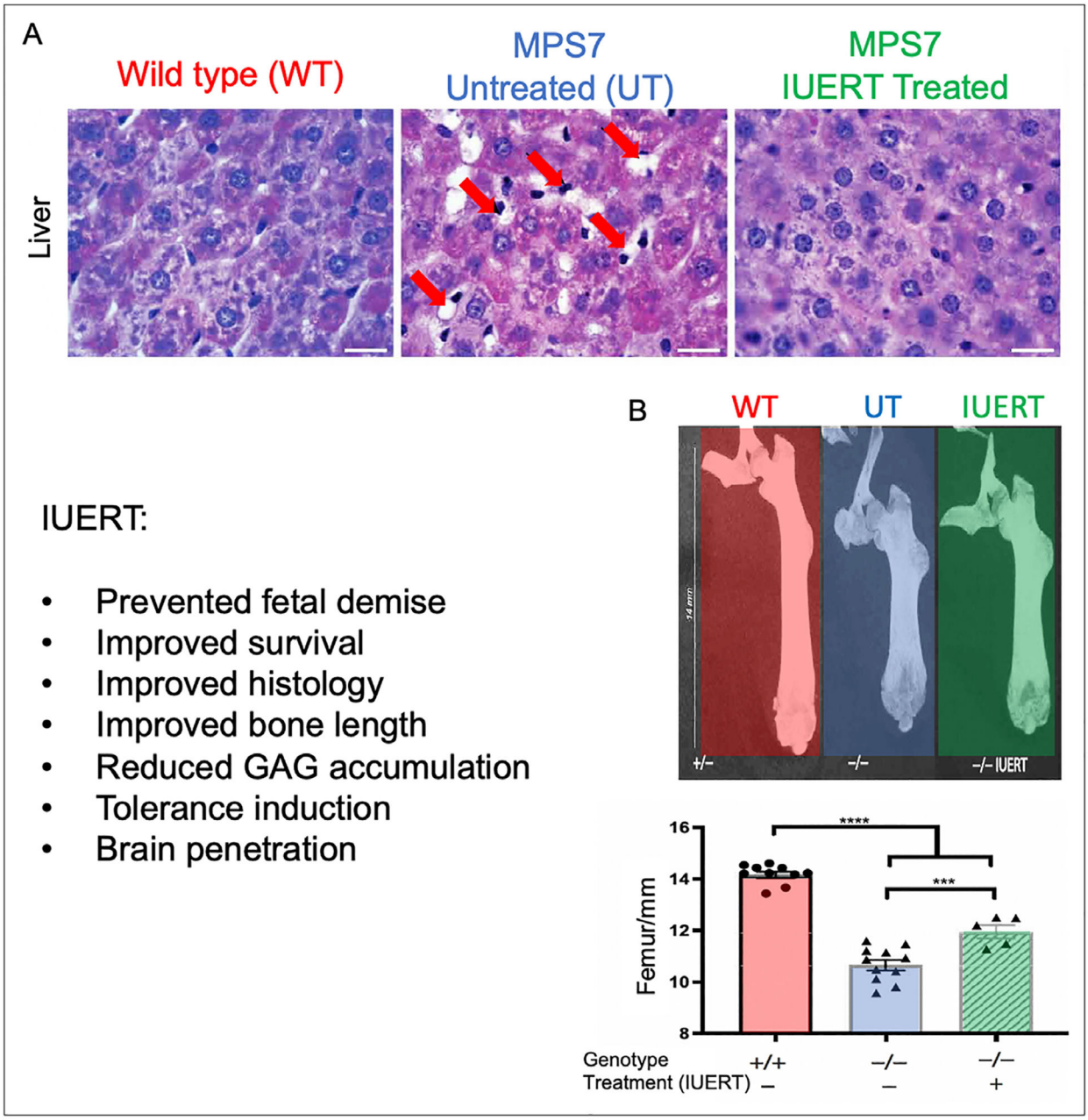


FIGURE 2.

Combination of in utero and postnatal enzyme replacement therapy (ERT) improves pathologic lysosomal accumulations of glycosaminoglycans (GAGs) as well as bone length. Mice were harvested at 8 weeks of age, and their livers, spleens, and kidneys were examined with a PAS stain. (A), Representative images from the liver (scale bars, 20 μm) demonstrating intracellular accumulations (vacuolated cells, solid arrows) of GAGs. (B), Representative CT images of femurs in unaffected, MPS7$^{-/-}$-untreated, and MPS7$^{-/-}$treated mice harvested at 8–10 weeks of age. Compiled data for femurs $n \geq 5$ per group. *$p <$ 0.05, ***$p < 0.001$, and ****$p < 0.0001$ (ANOVA with Tukey's multiple comparisons test). Adapted with permission from Nguyen et al., 2020(24).

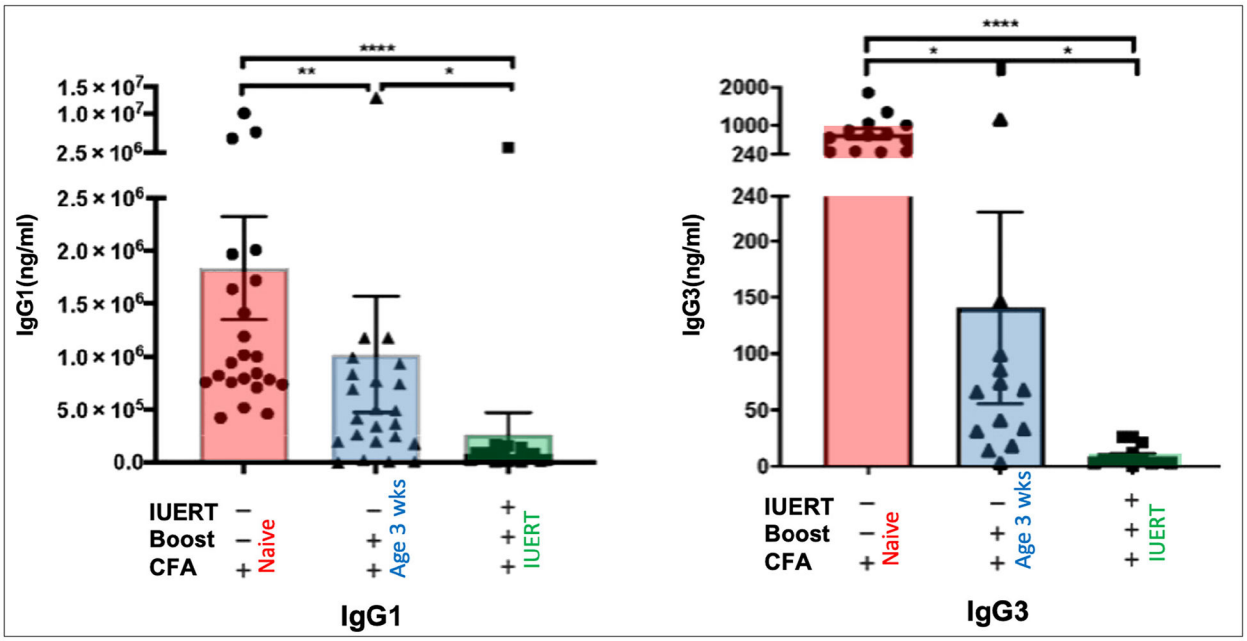


FIGURE 3.

In utero enzyme replacement therapy (ERT) results regarding tolerance to rhGUS. Mice underwent in-utero injection with either rhGUS enzyme or PBS followed by postnatal boosting starting at 3 weeks and continuing every other week. At 6 weeks of age, mice underwent intraperitoneal (IP) injection of rhGUS with complete Freund's adjuvant (CFA). Plasma concentrations of antibodies against rhGUS were measured by ELISA at 8 weeks. Amounts of IgG1 (left graph) and IgG3 (right graph) antibodies against rhGUS. $N \geq 10$ per group. Data are means ± SEM. *$p < 0.05$, **$p < 0.01$, and ****$p < 0.0001$ (Kruskal-Wallis with Dunn's multiple comparisons test). Adapted with permission from Nguyen et al., 2020(24).

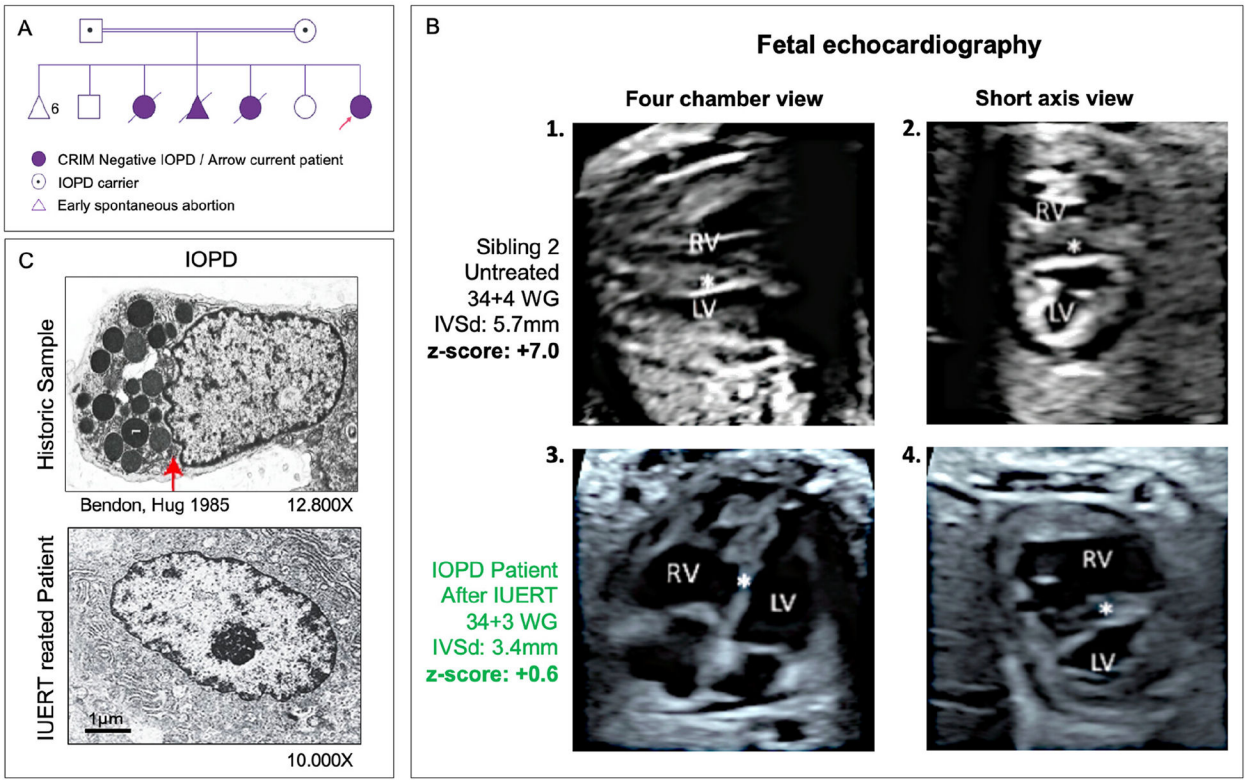
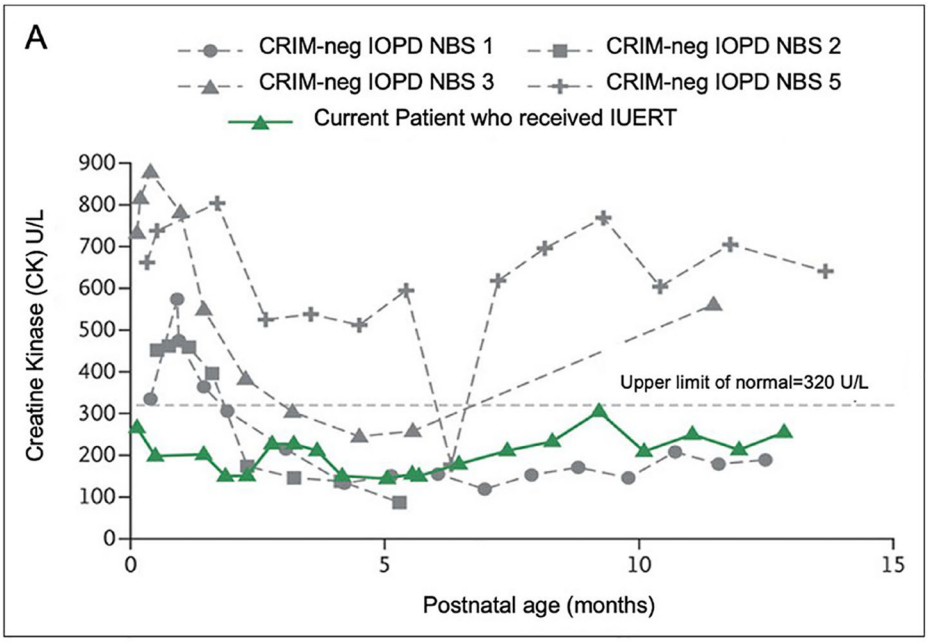


FIGURE 4.

(A), Family pedigree. Squares indicate male family members, circles female family members, triangles pregnancies not carried to term, double bars consanguinity, open symbols unaffected, filled black symbols affected, diagonal slashes deceased, single dot in center carrier. The arrow denotes IUERT-treated patient. Cross-reactive immunological material (CRIM) denotes cross-reactive immunologic material, infantile-onset Pompe disease (IOPD) IOPD. (B). Fetal echocardiogram performed at 34 weeks of gestation shows the affected untreated sibling in the top two panels (1 and 2) with thickened and hyperechogenic ventricular walls, with a diastolic interventricular septum z score of 7 compared to the normal findings of the prenatally treated patient in the lower panel (3 and 4). The ventricular-wall thickness, quantified as the diastolic measurement of the interventricular septum (IVSd) (asterisk), was 5.7 mm (z score, 7.0) in Sibling 2, whereas it remained normal in Sibling 3 (3.4 mm; z score, 0.6) during fetal therapy. The z scores were calculated according to the methods of Firpo et al.,[37] LV denotes left ventricle, and RV right ventricle. (C), Electron microscopic images from previously studied patient with IOPD who did not receive IUERT (top panel)[38] and from the patient who received IUERT (lower panel). The top panel shows numerous membrane-bound glycogen lobules (L) in a stromal cell in the untreated patient, which are not present in the patient who received IUERT in the bottom panel. Red arrow showing lysosomal substrate accumulation. Adapted with permission from JL Cohen et al., 2022(25).



B

Motor skills trajectory

Patient	Motor assessments	Age	Corrected gestational age
CRIM neg IOPD NBS1	Central hypotonia	1m14d	1m
CRIM neg IOPD NBS2	Age-appropriate gross motor skill development	25d	4d
CRIM neg IOPD NBS3	AIMS<5th percentile and delayed milestones	1m	21d
CRIM neg IOPD NBS4	AIMS<10-25th percentile	1m6d	29d
IUERT treated IOPD Patient	**AIMS 25-50th percentile CHOP-Intend 53/64** Normal motor Function Independent walking at 11.5 months	**2m4d**	**1m17d**

FIGURE 5.

(A), Skeletal-muscle outcomes: shows creatine kinase levels at 4 days or more of life in patients with CRIM-negative infantile-onset Pompe disease (IOPD) (gray dashed curves) treated with enzyme replacement therapy (ERT) after newborn screening (NBS) (treated at ≤4 weeks of age)[41] as compared with the levels in the IUERT-treated patient (green). In utero enzyme replacement therapy (IUERT) denotes in-utero enzyme-replacement therapy; neg denotes negative. (B), Motor skills assessment: the patient treated with IUERT (green) in comparison to previously published CRIM-negative newborn screening (NBS) IOPD cohort.[41] m: months; d: days; AIMS: Alberta Infant Motor Scale; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders Adapted with permission from JL Cohen et al., 2022(25).

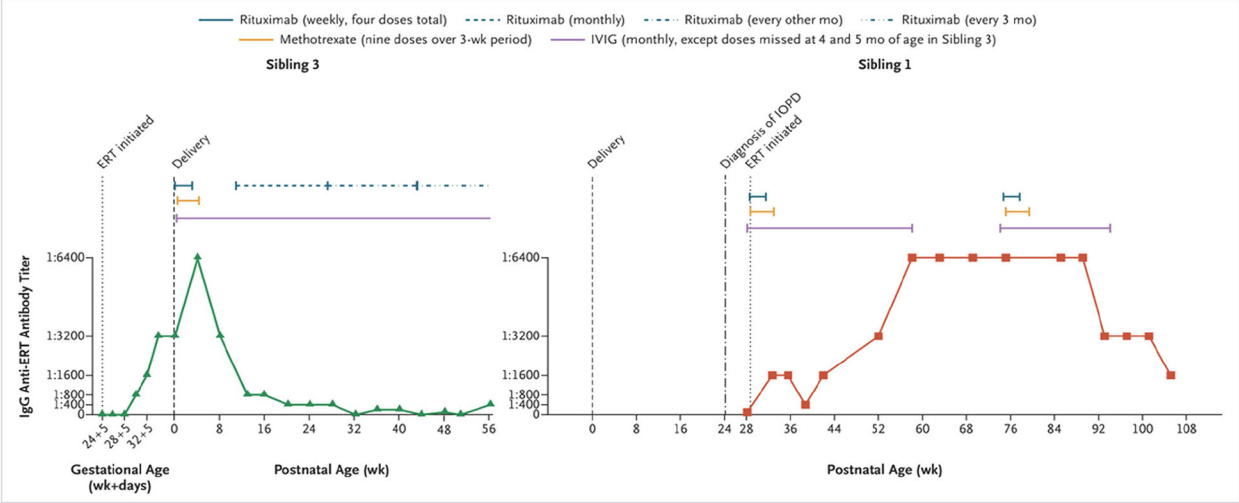


FIGURE 6.

Anti-Drug Antibody Monitoring: shows the time course for antidrug antibody levels and immune tolerance induction in the IUERT-treated patient (Sibling 3, green; left graph) and the proband (Sibling 1, red; right graph). The antidrug antibody levels of Siblings 1 and 3 reached the same peak, with Sibling 1 having a longer duration of titers at this level. Sibling 3 received postnatal immune tolerance induction as previously published,[26] followed by monthly rituximab alone, then rituximab alone every other month, and later every 3 months; Sibling 1 received immune tolerance induction as previously published,[26] followed by a repetition of a full course of immune tolerance induction (three medications), owing to her persistent titers at 1:6400. Pharmacokinetic and clinical concerns are present when titers reach a level of 1:12,800 or greater[32] [Lumizyme (alglucosidase alfa), Cambridge, MA: Genzyme, 2016 (package insert)], IVIG denotes intravenous immune globulin. Adapted with permission from JL Cohen et al., 2022(25).

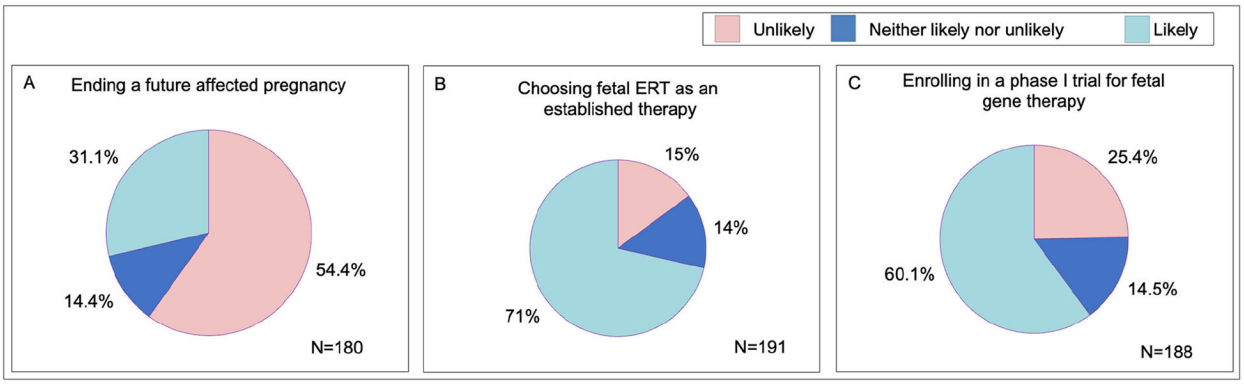


FIGURE 7.

Attitudes towards managing and treating pregnancies with Lysosomal storage disorder (LSD). (A), Attitudes toward continuation of a future pregnancy affected with an LSD. Respondents were asked the question, "If you or your partner were to become pregnant and the fetus was diagnosed with an MPS, how likely would you be to end the pregnancy?" All respondents (n = 180). (B), Attitudes toward choosing an approved fetal enzyme replacement therapy (ERT). Respondents were asked the question, "If you or your partner were to become pregnant and the fetus was diagnosed with an MPS, would you choose fetal enzyme replacement as an FDA-approved therapy?" All respondents (n = 191). (C). Attitudes toward participation in a clinical trial for fetal gene therapy. Respondents were asked the question, "If you or your partner were to become pregnant and the fetus was diagnosed with an MPS, would you enroll in a phase I clinical trial (to determine safety) for fetal gene therapy?" all respondents (n = 138). Adapted with permission from M. Schwab et al., 2022(44).

TABLE 1

Commonly diagnosed lysosomal storage disorders.

Disease	Prevalence at birth	Inheritance	Median age of survival	Hydrops fetalis[b]
Cystinosis	1:100,000–200.000	AR	Infantile form: 10 years	No
Fabry disease	1:40,000–50,000	XLD/XLR	5th to 7th decade	No
Galactosialidosis	<1:200,000	AR	Infantile form: early childhood	Yes
Gaucher disease	**<1:100,000**/1:450[a]	**AR**	Type I: Normal life expectancy	No
			Type II: 2–4 years	**Yes**
			Type III: Teenage	**No**
GM1 gangliosidosis	1:100,000–200,000	AR	Infantile form: early childhood	Yes
Infantile free sialic acid storage disease	<1:1,000,000	AR	Early childhood	Yes
Pompe disease	**1:40,000**	**AR**	**Infantile onset: 1–2 years w/o ERT**	**Yes**
			Late onset: Adulthood	
Krabbe disease	1:100,000–250,000	AR	Infantile onset: 2 years	No
			Late onset: Adulthood	
Metachromatic leukodystrophy	1:40,000–160,000	AR	Infantile form: early teens	No
	1:2500 (Navajo)	AR	Juvenile: Up to 30 years	
			Adult form: mid adulthood	
MPS I	**1:100,000 (severe)**	**AR**	**6–10 years**	**Yes**
	1:500,000 (attenuated)		**Normal life expectancy**	
MPS II	**1:100,000–150,000**	**XLR**	**20 years (severe form)**	**Yes**
MPS III	1:70,000	AR	10–20 years	No
MPS IVA	**1:40,000–200,000**	**AR**	**Early adulthood**	**Yes**
MPS VI	**1:250,000–600,000**	**AR**	**Varies/Adulthood**	**Yes**
MPS VII	**1:250,000**	**AR**	**Pre-/Neo-natal**	**Yes**
Niemann pick A + B	1: 250,000	AR	2–3 years (A)	Yes (A)
			Adulthood (B)	No (B)
Niemann pick C	1:120,000	AR	Up to adulthood	No
Sialic acid storage disease	<1:1,000,000	AR		No
Tay sachs disease	1:320,000	AR	5–10 Years	**No**
Lysosomal acid lipase deficiency (wolman)	**1:500,000**	**AR**	**6–12 Months**	**No**

Note: In Bold: diseases currently (2023) included in the NCT04532047 clinical trial. Data source: National Organization of Rare Diseases (rarediseases.org), Last updated: September 05, 2019, and orpha.net. These figures can vary based on geographic region, specific populations, diagnostic criteria, and others.[19]

Abbreviations: AR, autosomal recessive; MPS, Mucopolysaccharidosis; XLD, X-linked dominant; XLR, X-linked recessive.

[a] In people of Ashkenazi Jewish descent.

[b] Conditions marked with "Yes" are associated with a higher risk NIHF. If there's suspicion of any of these conditions in a fetus, molecular and/or enzymatic testing should be pursued

TABLE 2

Clinical trials of definitive/curative therapies for the lysosomal storage disorders included in the IUERT.

Route	Agent	Disease
Intradiaphragmatic	Gene therapy with AAV1 mediated alpha-glucosidase (rAAV1-CMV-hGAA)	Pompe disease[42]
Intracisternal or intraventricular	Gene therapy with AAV9 vector	MPS I (NCT03580083)/MPS II (NCT03566043, NCT04571970 and NCT04597385) Sponsor: RegenXbio
Intracisternal	Phase 1/2, multicenter study to evaluate the safety and efficacy of single-dose LY3884961/ AAV9	Gaucher type II (NCT04411654) Sponsor: Prevail
Intracisternal	Phase 1/2 clinical trial of PR001 (PROVIDE)	Gaucher type I, (NCT04411654) Sponsor: Prevail therapeutics
Intravenous	Gene therapy GC301 adeno-associated virus vector expressing codon-optimized human acid alpha-glucosidase (GAA)	IOPD (NCT05567627 and NCT05793307) Sponsor: PLA general Hospital, Beijing, China
Cisterna magna or intraventricular	Gene therapy with AAV9 vector	MPS I (NCT03580083) MPS 2 (NCT03566043, NCT04571970) (Sponsor RegenXbio)
Intravenous	Phase I/II study evaluating safety and efficacy of autologous hematopoietic stem and progenitor cells genetically modified with IDUA lentiviral vector encoding for the human α-L-iduronidase gene	MPS I (NCT03488394) Sponsor: IRCCS san Raffaele, Milan, Italy
Intravenous	Phase 1, first-in-human, open-label, single-arm study using autologous plasmablasts engineered to express α-L-iduronidase (IDUA) using the sleeping beauty transposon	MPS I (NCT05682144) Sponsor: Immusoft of CA
Intravenous	DNL310 (investigational fusion protein engineered to cross the BBB) compared with idursulfase.	Neuronopathic and non-neuronopathic MPS II (NCT05371613) Sponsor: Denali therapeutics
Intravenous	A global phase III multicenter, randomized, assessor-blinded, active-controlled designed to evaluate safety and efficacy of JR-141	MPS II (NCT04573023) Sponsor: JCR Pharmaceuticals Co., Ltd.
Intravenous	Extension study of JR-141 to evaluate the long-term safety and efficacy	MPS II (NCT05594992)Sponsor: JCR Pharmaceuticals Co., Ltd.
Intravenous	Autologous ex-vivo gene modified HSCT in MPSII - designed to penetrate BBB	MPS II (NCT05665166) Sponsor: University of manchester

Route	Agent	Disease
Intracisternal	Phase 1/2 clinical trial of administering PR001 (PROVIDE)	Gaucher type I (NCT04411654) Sponsor: Prevail therapeutics