

Enzyme reconstitution/replacement therapy for lysosomal storage diseases

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Purpose of review

Over the past 15 years, the lysosomal storage diseases have become paradigms for the specific treatment of monogenic disorders, particularly those affecting children. This review summarizes the phenotypes and recent literature regarding enzyme reconstitution (replacement) therapy and outcomes for such treatable lysosomal storage diseases: Gaucher disease, Fabry disease, Pompe disease and the mucopolysaccharidoses.

Recent findings

Recent clinical trials have shown that enzyme reconstitution therapy effectively treats many of the manifestations of the lysosomal storage diseases. When initiated early in the disease course, enzyme reconstitution therapy can reverse some disease manifestations, but may not completely alleviate the disease progression. Enzyme reconstitution therapy is generally well tolerated. Many adverse events are antibody-related, but can be managed without requiring cessation of enzyme reconstitution therapy. Documented IgE reactions, i.e. anaphylactoid, are quite rare (fewer than 1%).

Summary

Enzyme reconstitution therapy is a safe and effective treatment modality available for several of the lysosomal storage diseases. Owing to the short history of enzyme reconstitution therapy, the long-term outcomes of enzyme reconstitution therapy-treated individuals are unknown and require further investigation. Medical professionals must learn to identify patients likely to benefit from these life-changing therapies so as to prevent many of the devastating, irreversible complications of the lysosomal storage diseases.

Keywords

Fabry disease, Gaucher disease, glycosphingolipids, lysosomes, mucopolysaccharidoses, Pompe disease

Abbreviations

BMT	bone marrow transplantation
CNS	central nervous system
ERT	enzyme reconstitution therapy
FDA	Food and Drug Administration
GAA	acid α -glucosidase
GAG	glycosaminoglycan
GL3	globotriaosylceramide
LSD	lysosomal storage disease
MPS	mucopolysaccharidosis

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Introduction

Over the past 15 years, the lysosomal storage diseases (LSDs) have become paradigms for specific treatment of monogenic disorders, particularly those affecting children. Except for Fabry disease and Hunter syndrome [mucopolysaccharidosis (MPS) II] that are X-linked, the other around 40 LSDs are autosomal recessive traits. For currently treatable LSDs, a single gene is disrupted by various mutations (single substitutions to gene deletions) that lead to a defective encoded enzyme protein and/or activity. Lysosomal enzymes are synthesized on the rough endoplasmic reticulum, posttranslationally processed in the Golgi and targeted to the lysosomes [1]. The majority of such enzymes require the mannose-6-phosphate receptor system to direct newly synthesized or exogenously supplied enzymes to the lysosome; the Gaucher disease enzyme does not use this system. Other receptors (e.g. the mannose receptor) act as Trojan horses to deliver enzymes into lysosomes of cells. The LSDs lack sufficient enzyme activity to prevent pathologic cellular accumulation of specific macromolecules, i.e. glycosphingolipids, mucopolysaccharides or glycogen, that disrupt cell functions and perpetuate the disease by poorly defined mechanisms.

Clinical phenotypes within each LSD range from very severe infantile to attenuated variants in adolescence to adulthood. The nature of the mutation affects the amount of enzyme activity and is a major determinant of the phenotypes, i.e. the threshold hypothesis that small incremental changes in enzyme function in specific tissues lead to large variations in clinical course [2]. Many visceral tissues are accessible to intravenously supplied enzymes, whereas the brain is not.

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The term enzyme replacement therapy has been promulgated through the literature. A more accurate term is enzyme reconstitution therapy (ERT) in which the enzyme level within specific cellular compartments is raised above a threshold to prevent development or propagation of disease manifestations. Throughout this review the term ERT will be used in that sense. ERT is accomplished by the intravenous administration of purified human enzymes with requisite carbohydrate modifications for uptake into cells and intracellular delivery to the lysosomes. The attenuation of LSD phenotypes implies that early intervention could prevent or reverse disease progression. Even though some of the LSDs do not overtly manifest until adulthood, pediatricians are at the forefront of interventions to prevent long term clinical sequelae of these diseases.

Gaucher disease

Gaucher disease was described in 1882 by Philippe Gaucher in a 32-year-old woman with an enlarged spleen. Gaucher disease presentation can, however, vary from very severe central nervous system (CNS) abnormalities in infancy to asymptomatic nonagenarians (see [3,4] for detailed reviews). The disease results from the defective activity of acid β -glucosidase and the consequent accumulation of its substrate, glucosylceramide, in macrophage/monocyte cells of viscera, and in neurons and microglia of the brain. Classically, three clinical phenotypes of Gaucher disease are described; type 1 (non-neuronopathic), and types 2 and 3 (acute and subacute neuronopathic, respectively). Each type has several variants. The visceral manifestations of types 1 and 3 will be the focus here, since the CNS aspects of types 2 and 3 are not directly treated by intravenous ERT. Type 3 disease is variable, and has onset and progression of visceral and CNS disease in childhood. Predominant phenotypes can include myoclonic seizures and epilepsy or isolated, slowly progressive saccadic eye initiation defects. Type 1 has no primary CNS involvement. Visceral disease includes hepatosplenomegaly, cytopenias and bony disease. The pathogenesis of the bony disease is poorly understood, but osteopenia, frank osteoporosis and fractures can occur from bone marrow and architectural bone involvement.

The lack of CNS involvement has made Gaucher disease type 1 a paradigm for ERT. Over the past 15 years macrophage-targeted ERT has dramatically altered the disease by reversing manifestations [5,6]. Mannose-terminated acid β -glucosidase (imiglucerase, Cerezyme; Genzyme, Cambridge, Massachusetts, USA) for ERT has been sufficiently successful to provide for development of organ-specific therapeutic guidelines for responses and timelines for attainment [7]. Current research is clarifying correlations of organ-specific therapeutic guidelines with administered ERT dose.

The resolution of hepatosplenomegaly through the regular use of ERT generally occurs by 2 years, concomitant with improvements in anemia and thrombocytopenia. These improvements also may restore normal growth as children (around 35%) with untreated Gaucher disease have growth retardation. About 75–90% of untreated Gaucher disease patients manifest bony disease, including osteopenia, bone crises, bone pain, radiologic lytic lesions, fractures or bone marrow infiltration. Very painful bone crises from bone infarction occur in around 10% of patients and bone pain can occur in as many as 70% [4]. Like hepatosplenomegaly, bone crises and bone pain have prompt responses within 1 year to ERT, as does the osteopenia over 6–8 years; all these responses are dose-dependent [8,9]. Improvement in osteopenia and osteoporosis can be enhanced with bisphosphonates in adults and in some children with severe osteoporosis.

Regular ERT has completely altered the phenotypic manifestations of Gaucher disease, reconstituted health and reversed disease manifestations in many patients. Anecdotally, children may respond more completely and rapidly to ERT. Although ERT in affected children prevents the development and progression of bone disease, preexisting and secondary bone diseases in adults have been more difficult to treat. The successes of ERT in Gaucher disease established a viable medical and industrial model for the development of ERTs for other LSDs.

Fabry disease

Fabry disease results from the defective function of α -galactosidase-A, and the resultant storage of globotriaosylceramide (GL3) in lysosomes of the vascular endothelium, renal podocytes, myocardial and neural cells. A major consequence of GL3 accumulation in small vessel endothelium is hypoperfusion with subsequent organ damage [10–12]. GL3 storage begins in fetal life [13], but the age at overt manifestations is variable. The microvascular disease leads to fibrosis and sclerosis as the common pathway for organ damage that, with time, becomes irreversible.

Unlike other LSDs, Fabry patients show few physical signs, particularly in childhood, until they develop major organ dysfunction. Until recently, little had been published on the pediatric population [12,14–17]. These studies, limited by small numbers of patients and short follow-up, indicate appearance of first symptoms around 6 and 8 years in hemizygous boys and heterozygous girls, respectively. In childhood, Fabry disease manifestations include burning pain in the extremities (acroparesthesias) or gastrointestinal complications, e.g. nausea, diarrhea and abdominal pain [18–20]. Acroparesthesias respond poorly to narcotics, but neuroleptic medications (carbamazepine, gabapentin, phenytoin, etc.) can decrease

their severity. The gastrointestinal complaints may lead to frequent school absence. Anhydrosis and hypohidrosis are also common, and secondary exercise and heat intolerance interferes with participation in sports, play and employment opportunities. Adolescent affected males and young female heterozygotes can manifest angiokeratomas. Distinctive swirling corneal opacities may be visible with a slit lamp [21].

In childhood, cardiac, renal and CNS signs and symptoms are rare. In affected males the renal, cerebrovascular and cardiovascular systems become progressively involved during the second to fifth decades. Failure of these organs leads to early death. The average age of death for untreated males is 41–55 years [22,23]. Renal disease often presents with proteinuria, and progresses to renal insufficiency and renal failure over 2–3 decades; however, significant sclerosis is usually present before creatinine clearance becomes abnormal [24]. Bradycardia can be the earliest sign of cardiac involvement, but other arrhythmias and valvular dysfunction accompany hypertrophic cardiomyopathy, the most commonly reported cardiac finding [24]. Advanced cardiac hypertrophy is often accompanied by extensive fibrotic changes that fail to improve with treatment [25]. The underlying pathophysiology of the CNS disease is not well studied, but microvascular changes leading to dysregulation of blood flow eventually result in stroke; Fabry disease accounts for 4.9% (males) and 2.4% (females) of cryptogenic stroke [26].

In 2003, the Food and Drug Administration (FDA)-approved enzyme infusion therapy with α -galactosidase-A for treatment of Fabry disease. About 50% of female heterozygotes require treatment. Studies indicate that treatment before obvious organ dysfunction is needed for success [27]. A major goal of early treatment is to reduce the risk for severe potentially life-threatening complications later in life. Unlike ERT for other LSDs, Fabry disease does not produce immediate changes in either physical or laboratory findings. Validated biomarkers that correlate with disease activity in Fabry disease have not been firmly established. Serum and urine GL3 levels have not correlated well with risk for complications in adults, nor has serum α -galactosidase-A activity. Recent studies have identified several proteins that were significantly different between patients with Fabry disease and controls, and some of these normalized with ERT [28].

ERT for Fabry disease has provided a potentially life-saving intervention that can be offered to patients beginning early in life. ERT is safe and well tolerated in pediatric and adolescent patients [14,17]. Trends toward decreased pain and fewer pain crises were reported in uncontrolled pediatric studies. Some patients report

marked improvement in gastrointestinal symptoms [29]. For pediatric and adolescent patients with Fabry disease, more evidence is needed to guide decisions regarding initiation of therapy. No ERT studies are available in children under age 10. Pediatric patients with Fabry disease will benefit from further study of the early manifestations of the disease particularly with valid biomarkers.

Pompe disease

Pompe disease, the deficiency of acid α -glucosidase (GAA), is a cardioskeletal myopathy due to glycogen accumulation in lysosomes. Infantile Pompe disease presents with weakness, poor ventilatory effort and significant hypertrophic cardiomyopathy within the first months of life. The disease is rapidly fatal before age 2 years [30]. Later-onset patients have primarily skeletal muscle involvement and may become ventilator-dependent as the disease progresses [31,32]. Pompe disease was the first LSD in which ERT was attempted and provided 'proof of principle' of the ability to deplete liver tissue of accumulated glycogen. The larger amounts of recombinant human GAA produced in Chinese hamster ovary cells or milk of transgenic rabbits confirmed the potential to treat humans with Pompe disease [33,34]. ERT in animal models showed that recombinant GAA corrected the enzymatic defect in heart and skeletal muscle, depleted glycogen in these tissues, and improved strength.

Initial human trials with recombinant GAA were directed to infantile Pompe patients [35]. Preliminary results using GAA from Chinese hamster ovary cells or rabbit milk showed that a subset of treated patients achieved motor milestones unprecedented in infantile Pompe patients [36,37]. Based on these results, a pivotal trial was initiated in 18 infantile patients less than 6 months of age and before need for invasive ventilatory support. Significant improvement in overall survival, survival free of ventilatory support and achievement of improved motor milestones was observed in the majority of patients. Patients (seven of 18) were able to walk independently after 1 year of biweekly ERT. Reduction in left ventricular mass index was demonstrated in all patients [38]. ERT initiated before 6 months of age and before need for ventilatory assistance improved survival when compared with a natural history cohort [36,38].

The FDA approved the use of Myozyme (alglucosidase α ; Genzyme) for use in infantile Pompe disease in 2006. Studies in later-onset forms of Pompe disease are ongoing. Myozyme is administered by slow intravenous infusion (over 3–4 h) at 20–40 mg/kg/dose every 2 weeks. Infusion reactions were observed in half of the patients treated with Myozyme in clinical studies. Most of these reactions were easily managed, but anaphylaxis requiring life support measures has been reported. For these

reasons, and because many Pompe patients have preexisting compromise of respiratory and cardiac function, infusions in centers equipped to provide emergency care is recommended (Myozyme package insert). In addition to drug-related reactions, infantile Pompe patients may have difficulty with anesthesia for procedures related to placement of venous access devices [39]. The majority of patients developed IgG antibodies to Myozyme within the first 3 months of treatment. Some patients with high sustained IgG titers may have a poor clinical response to treatment (see below).

The relative resistance of skeletal muscle to effective glycogen depletion with administered GAA has been observed in animals and humans [40,41^{*}]. Type II muscle fibers appear to be quite resistant to therapy. From a clinical viewpoint, the failure of most ventilator-dependent patients to achieve independence from invasive ventilation is not surprising. Perhaps more disappointing is that five patients of the 18 infants treated before 6 months of age made no meaningful gains in motor function and six of 18 became dependent on ventilatory assistance after initiation of ERT. A variety of predictors of poor prognosis were observed, including increase in muscle glycogen during therapy, high IgG titers to GAA and complete absence of GAA. The relationship between GAA genotype and response to ERT is still under study [38]. Factors predicting poor response are incompletely known and therefore treatment effect for an individual patient may only be discovered by therapeutic trial. Concerns about the long-term effects of glycogen accumulation in anterior horn cells or brain, which are unlikely to respond to ERT administered intravenously, remain unanswered, but many treated patients show normal cognitive development despite their motor and speech delays.

Mucopolysaccharidoses

The MPS group of diseases is made up of LSDs that result from abnormal tissue accumulations of glycosaminoglycans (GAGs) or mucopolysaccharides. MPS types I–VII each result from a deficiency of enzymes that are involved in the stepwise degradation of the GAGs dermatan sulfate, keratan sulfate, heparan sulfate and chondroitin sulfate. The accumulations of specific GAGs in various tissues result in characteristic features with significant overlap between the various types (Table 1). Diagnosis is often suspected on clinical features and elevated urinary GAGs. Enzyme and DNA analyses are available to confirm diagnostic suspicion. Treatment has often been symptomatic, with selected role for bone marrow transplantation (BMT; see below). Since approval of Aldurazyme (MPS I), Elaprase (MPS II) and Naglazyme (MPS VI), ERT has become increasingly used to alleviate specific visceral manifestations of these disorders.

Table 1 Mucopolysaccharidoses treatable with enzyme reconstitution therapy

Type	Incidence [40,41 [*]]	Enzyme deficiency	Glycosaminoglycan stored	Mental retardation	Coarse facies	Corneal clouding	Deafness	Cardiac disease	Hepatosplenomegaly	Skeletal disease	Growth retardation
MPS I H (severe) Hurler syndrome	~1/100 000	α -L-iduronidase	dermatan sulfate, heparan sulfate	+	+	+	+	+	+	+	+
MPS I H/S (moderate) Hurler–Scheie syndrome	~1/100 000	α -L-iduronidase	dermatan sulfate, heparan sulfate	– to +	– to +	+	+	+	+	+	+
MPS I S (attenuated) Scheie syndrome	~1/100 000	α -L-iduronidase	dermatan sulfate, heparan sulfate	–	– to +	+	+	+	+	+	–
MPS II Hunter syndrome	~1/150 000	iduronate-2-sulfatase	dermatan sulfate, heparan sulfate	– to +	+	–	+	+	+	+	+
MPS VI Maroteaux–Lamy syndrome	1/248 000 – 1/667 000	N-acetylglucosaminase-4-sulfatase (arylsulfatase B)	dermatan sulfate	–	+	+	+	+	+	+	+

MPS, mucopolysaccharidoses.

BMT is often the mainstay of treatment in MPS I H, and, when successful, typically results in improvement of the coarse facial features, cardiac disease and upper airway obstruction [42,43]. The success of BMT is age and organ-dependent. Earlier BMT attenuates the progression of neurologic complications, but has little effect on the skeletal abnormalities [42–45]. BMT in MPS I H also continues to have high complication and mortality rates. ERT utilizing recombinant α -L-iduronidase (laronidase, Aldurazyme; Genzyme) was approved by the FDA in the US for clinical use in 2003, and was successful in improving the hepatosplenomegaly, respiratory functioning, and urinary GAG levels [46,47]. Patients were also found to have increased growth velocities, and improved range of motion in shoulder flexion and elbow extension [48^{*}]. ERT has been used pre-BMT in Hurler patients, and in symptomatic MPS I H/S and I S patients. Aldurazyme is administered weekly as 0.58 mg/kg (100 U/kg) by intravenous infusion over 3–4 h (Aldurazyme package insert).

In MPS II, BMT has limited, if any, clinical utility [49,50]. ERT with recombinant human enzyme (idursulfase, Elaprase; Shire TKT Pharmaceuticals, Cambridge, Massachusetts, USA) was approved by the FDA in 2006. ERT-treated patients had reductions in hepatosplenomegaly, improvements in cardiopulmonary function and decreases in urinary GAG levels in a randomized, double-blinded, placebo-controlled phase II/III clinical trial [51]. Elaprase is intravenously administered as a 0.5 mg/kg weekly infusion (Elaprase package insert).

The treatment of MPS VI (Maroteaux–Lamy syndrome) has been largely symptomatic. BMT has had a modicum of success, but has high morbidity and mortality [52,53]. Patients receiving recombinant arylsulfatase B (Naglazyme; Biomarin Pharmaceuticals, Novato, California, USA) had reduced hepatosplenomegaly, urinary GAG levels and decreased pain, as well as improvements in

joint and cardiopulmonary function [54,55]. Naglazyme is infused at a dose of 1 mg/kg dose/weekly (Naglazyme package insert) over several hours.

Adverse events/complications of enzyme reconstitution therapy and comments

Each ERT has its profile of adverse infusion-related events. Many of these are antibody-related, usually IgG-mediated, and have been managed by decreasing the rates of infusions (i.e. decreasing the protein mass administered per minute) together with antihistamines or occasionally corticosteroids. Except for Gaucher disease, the rate of antibody conversion ranges from around 50 to 90% for the various enzymes (Table 2). The documented IgE-mediated or anaphylactoid reactions have been very low (fewer than 1%) and several such patients have been able to resume ERT following desensitization or by using ramp-up infusion protocols. Since ERT has been available for only a few years, the long-term adverse sequelae of ERT have not been delineated. In Gaucher disease, a number of patients have received ERT for over 15–20 years without drug-related adverse outcomes.

Drug costs/insurance issues

The majority of patients receive benefit from ERT, but this comes with significant emotional and financial burdens. Access to physicians with relevant expertise in these rare diseases as well as to specialized healthcare/treatment centers (e.g. infusion centers who accept medically complex pediatric patients) may be difficult or unavailable in specific areas. Clearly, this posits emotional strain on the family and local healthcare providers. The financial burdens can be significant for the patient or insurance provider (public or private). These enzyme products are expensive with an average cost per year of \$300 000 for a 30 to 40-kg individual. This cost will vary with the individual's weight, the amount of drug prescribed and the average wholesale price of the individual drug (Table 3). Other fees, including markup on

Table 2 Current approved ERT for LSD

Enzyme	Disease	Brand name	Generic name	Year approved	Antibody ^a	
					Status (%)	Treatment effect
Acid β -glucosidase	Gaucher	Ceredase, Cerezyme	algucerase, imiglucerase	1991 1993	~12	none/rare
α -GAL A	Fabry	Fabrazyme, Replagal (not in US)	agalsidase β agalsidase α	2003 2003	>50–90	? dose-dependent
α -L-Iduronidase	MPS I	Aldurazyme	laronidase	2003	>59–90	?
Iduronate-2-sulfatase	MPS II	Elaprase	idursulfase	2006	>50	?
N-acetylgalactosamine 4-sulfatase	MPS VI	Naglazyme	galsulfase	2005	~90	?
Acid α -glucosidase	glycogen storage disease II, Pompe	Myozyme	alglucosidase α	2006	~50–90	+

MPS, mucopolysaccharidosis.

^a Status indicates antibody positivity rate. Treatment effect: + means that there is a significant effect on the efficacy of the ERT. For Myozyme, there is a significant effect to decrease efficacy in infantile Pompe patients. For the other drugs, the question mark indicates that the effect on efficacy is unknown. All of the drugs, except acid β -glucosidase, produce significant adverse effects in antibody-positive patients in addition to any other effects on efficacy.

Table 3 Cost of enzyme reconstitution therapy by disease^a

Disease	Product	Dose/kg	Drug average wholesale price (US\$/vial)	Annual cost (US\$)
Pompe disease	Myozyme 50 mg/vial (Genzyme)	20 mg/kg every 14 days	720.00	224 640.00
Gaucher disease	Cerezyme 200 U/vial (Genzyme)	60 U/kg every 14 days	790.00	184 860.00
MDS I	Aldurazyme 2.9 mg/vial (Genzyme)	0.58 mg/kg every 7 days	783.60	162 988.80
MDS II	Elaprase 6 mg/vial (Shire TKT Pharmaceuticals)	0.5 mg/kg every 7 days	3153.84	491 999.04
MDS VI	Naglazyme 5 mg/vial (Biomarin Pharmaceuticals)	1 mg/kg every 7 days	1812.00	565 344.00
Fabry disease	Fabrazyme 5 mg/vial (Genzyme)	1 mg/kg every 14 days	720.00	112 320.00
	Replagal ^b 3.5 mg/vial (Shire TKT Pharmaceuticals)	0.2 mg/kg every 14 days	2540.96	132 129.92

MPS, mucopolysaccharidosis.

^a Annual cost of enzyme reconstitution therapy based upon a 30-kg child receiving therapy according to dosing recommendations provided by the manufacturers in package inserts. Average wholesale prices of the drugs, except Replagal (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4118404) were obtained from the Red Book Database (<http://www.micromedex.com/products/redbook/database>). The annual cost calculation does not account for other fees, including markup on the drug from hospitals, private offices, and infusion centers, and cost of supplies, among others.

^b Replagal is licensed for use in Europe, Asia and Canada, but not the US.

the drug from hospitals, private offices and infusion centers, and for supplies are also incurred. The total cost of therapy also includes associated medications, physical therapy, surgery and other medical interventions needed for comprehensive care of these complex patients. Private individual insurance coverage presents a major issue for patients because the costs are not distributed over a large number of individuals, and the premiums may become unaffordable for the affected family member and all others covered by that policy. The lifetime maximums in many policies would be exceeded in 2–5 years given the drug and other ancillary costs. Recently, in the US, some pharmacy plans have set annual maximums on a subset of drugs at \$25 000–50 000, even though these policies do not appear to have lifetime maximums. For ERT, drug costs would be covered for only part of each year and for many patients at very suboptimal/subtherapeutic dosages. Some, but not all, of the makers of these drugs have developed programs to assist patients in understanding their policies, getting drug authorizations and obtaining insurance coverage after exceeding lifetime maximums. Genzyme's programs are the prototype and trendsetter for such programs. Its Charitable Access Program was developed over the last 15 years to provide ERT to patients who are uninsured and/or unable to afford ERTs developed by this company. Eligibility for this program is based upon financial and medical need, and physician's referral. Shire Pharmaceuticals has developed a Patient Assistance Program that offers financial assistance to qualified patients on a case-by-case basis and is based on financial need. Other companies in this rare disease field with current or developmental therapies should be encouraged to follow Genzyme and Shire's lead in assuring access to these therapies. Private organizations (e.g. the National Organization for Rare Disorders and support groups for each of these disorders such as the National Gaucher Foundation) also have programs that assist patients with financial

costs related to infusions and healthcare coverage. Thus, the development of effective therapies for this rare inherited disease has brought hope, health and a host of new challenges for affected families and individuals.

Conclusion

Importantly, ERT approaches are not cures, i.e. complete elimination of all signs and symptoms of the disease, but treatments with partial effects in specific body compartments, e.g. CNS and lungs, among others. In addition, the degree of preexisting disease in any particular organ could dictate the potential for reversibility of the disease process. These aspects of the longer-term outcomes and the development of unexpected disease manifestations remain to be delineated as new and/or alternative strategies are developed and evaluated for therapy of the LSDs. The pioneering work of Roscoe Brady to develop an effective ERT for Gaucher disease has fostered an environment of hope and promise for families and patients affected by the LSDs. Together with pediatricians, physicians with specialization in the LSDs need to learn optimal and cost-beneficial ways of bringing these life-changing therapies to affected individuals early enough to prevent many of the devastating, irreversible complications of the LSDs.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 737).

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