

# The usage of enzyme replacement treatments, economic burden, and quality of life of patients with four lysosomal storage diseases in Shanghai, China

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**SUMMARY** Lysosomal storage diseases (LSDs) are a group of rare diseases that cause progressive physical dysfunction and organ failure, which significantly affected patients' quality of life. The objective of this study was to explore the characteristics and usage of Enzyme Replacement Treatments (ERTs), which is the only specific therapy for LSDs, of patients with the four different LSDs (Gaucher, Fabry, Pompe disease and Mucopolysaccharidosis) in Shanghai, and then evaluate the economic burden and quality of life of these patients. A total of 31 patients, involving 5, 14, 4 and 8 patients with Gaucher, Fabry, Pompe disease and Mucopolysaccharidosis, respectively, were included in analysis. The result showed that only five Gaucher disease (GD) patients in Shanghai used Imiglucerase in 2019, while the other 26 patients with the other three LSDs did not receive ERTs. The total health expenditure of GD patients was 2,273,000 CNY on average mainly resulted by the high cost of Imiglucerase. The total health expenditure of the other 26 patients was 37,765 CNY on average. Though the cost-sharing mechanism between basic medical insurance, charity fund and patients had been explored for Gaucher disease in Shanghai, the out-of-pocket part, which was 164,301 CNY, still laid a heavy economic burden on the patients and their families. The mean EQ-VAS score of GD patients was  $76.4 \pm 15.5$ , which was higher than that of the other three LSDs. It is recommended that the scope of drug reimbursement list and the reimbursement level should be further expanded and raised to help improve the living conditions of patients with LSDs.

**Keywords** Rare diseases, lysosomal storage diseases, enzyme replacement treatment, patient survey, quality of life, disease burden, Shanghai

## 1. Introduction

Lysosomal storage diseases (LSDs) are a group of diseases caused by defects in single genes. Enzyme defects cause nearly seventy percent of the LSDs, and the rest are defects in enzyme activator or associated proteins (1). A deficit in any of these enzymes will result in progressive accumulation of materials in affected organs and tissues, which will result in an increase in the size and number of these organelles and finally in cellular dysfunction and organ failure (2). Though as a group, LSDs are with an estimated incidence of 1/5,000 to 1/5,500, one single LSD is usually recognized as a rare disease with estimated incidences ranging from 1/50,000 to 1/250,000 live births (2). There is currently no systematic epidemiology study nor patient registry for LSDs in China.

There are 16 different approved therapies for 7

LSDs in the world (3), while there are only altogether 8 available therapies (seven of them are ERTs) in China for 5 LSDs, which are Gaucher disease (GD), Fabry Disease (FD), Mucopolysaccharidosis (MPS), Pompe Disease (PD), and Niemann-Pick disease (NP), according to the National Rare Diseases List (NRDL). However, only Miglustat for NP type C is now included in the National Drug Reimbursement List (NDRL), while the other seven ERTs are not. See Table 1 for the details. The newly updated NDRL (2020 version) did not contain these extremely expensive drugs for rare diseases (4). Theoretically, there are no healthcare security measures on the national level in China for patients with the mentioned four LSDs, which are GD, PD, FD and MPS.

Current studies regarding LSDs patients in China are mainly from the clinical aspect, while only few are not. Chen *et al.* introduced the demographic characteristics and distribution of all 322 diagnosed patients with

**Table 1. Marketed and reimbursed drugs for LSDs in China**

NRDL code	Disease	Approved name	Brand name	Approved date in China	Included in NDRL
27	Fabry disease	Agalsidase beta <sup>a</sup>	Fabra-zyme	2009/12	No
		Agalsidase alfa	Replagal	2020/8	No
31	Gaucher disease	Imiglucerase	Cerezyme	2008/11	No
		Velag-lucerase <sup>a</sup>	Vpriv	No	—
		Taliglucerase <sup>a</sup>	Elelyso	No	—
		Miglusta	Zavesca	No	—
		Eliglustat <sup>a</sup>	Cerdelga	No	—
35	Pompe disease	Alglucosidase alfa	Myozyme	2017/12	No
		Migalastat <sup>a</sup>	Galafpld	No	—
73	MPS				
	Type I	Laronidase <sup>a</sup>	Aldulra-zyme	2020/6	No
	Type II	Idursulfase <sup>a</sup>	Elapraxe	2020/9	No
	Type IVA	Elosulfase <sup>a</sup>	Vimizim	2019/6	No
	Type VI	Galsulfase	Naglazyme	No	—
82	Niemann-Pick disease type C	Miglustat	Zavesca	2017/9	Yes
	Wolman disease	Sebelipase	Kanuma	No	—
	Neuronal ceroid lipofuscinosis type 2 (CLN2)	Cerliponase	Brineura	No	—

<sup>a</sup>, Drugs included in the List of Urgently Needed New Drugs from Overseas for Clinical Use.

LSDs in Eastern China (5). Zhao *et al.* studied the characteristics of 59 Chinese PD patients from the Pompe Registry (6). Yang *et al.* described the cost-sharing mechanism for Imiglucerase in Qingdao, Shandong province (7). Except for the mentioned three literatures, there are some large-scale surveys focusing on living conditions of patients with rare disease in China. Some surveys on LSDs did report the cost of illness while health resources utilization and quality of life of those patients remained unknown (8-11).

In 2011, Shanghai Children's Hospitalization Assistance Fund, managed by the Red Cross Society of China Shanghai Branch decided to reimburse the ERTs for patients with the mentioned four LSDs, with a maximum reimbursement amount of 100,000CNY per patient per year (12). In 2013, Imiglucerase could be paid by the basic medical insurance in Shanghai and reimbursement level was ranging from 80%-85% depending on the dosage. In 2017, the Shanghai Foundation for Rare Disease established a special assistance fund for LSD patients supported by enterprises (13). The assistant amount was decided based on the income level of patients, ranging from 70% to 100% of the out-of-pocket (OOP) expenditure part, who were receiving ERTs treatments. The consequential outcomes of these policies on patients with LSDs in Shanghai are still little known.

Our study aimed to explore the characteristic and usage of ERTs of patients with GD, PD, FD and MPS in Shanghai and then evaluated the economic burden and quality of life (QoL) of these patients.

## 2. Materials and Methods

### 2.1. Study design

This study focusing on patients with 4 LSDs was based

on a large survey of living conditions of patients with rare diseases in Shanghai. The survey used a self-designed questionnaire based on a literature review and interviews with several doctors, health economists and government officials in the field of rare diseases. Snowballing sampling method was adopted due to that there was no epidemiological data nor patient registry of patients with rare diseases in Shanghai. The electronic questionnaire was administered using the Wenjuanxing software (Changsha Ranxing Information Technology Co. LTD) and filled out online by patients with rare diseases or their primary caregivers. The participants recruitment process was conducted through online and offline platforms and networks. The doctors from hospitals in Shanghai, which act as members of the National Rare Disease Diagnosis and Treatment Network, helped to invite their diagnosed patients with rare diseases to participate in the survey. Several patient organizations of rare diseases also called on patients to involve in the investigation. The whole process of data collection was done from April to August 2020.

### 2.2. Inclusion criteria

The patients would only be included in the survey when they met the following conditions: *i*) The disease they were diagnosed with was recognized as rare disease on the list of NRDL or Orphanet (14); *ii*) They paid their Basic Medical Insurance premium in Shanghai, including urban employee and urban resident basic medical insurance; *iii*) The patients or their primary caregivers were willing to participate in the survey and were able to complete the online questionnaire.

### 2.3. Quality control

The follow-up telephone calls of each participant

were made to ensure the quality of data. The follow-up interviews could correct the obvious mistakes participants made and refill in the blanks they left. The follow-up visits were performed by four postgraduates majoring in health policy or health management research, who had been strictly and systematically trained before.

#### 2.4. Data extraction

The information of patients diagnosed with GD, PD, FD and MPS were extracted from the whole dataset. A total of 31 patients were enrolled, including 5 GD patients, 4 PD patients, 14 FD patients and 8 MPS patients, in this study. 18 patients answered the questionnaire themselves and the rest 13 patients' conditions were reported by their caregivers due to reasons like "the patient cannot read".

Several important variables were chosen from the long questionnaire, including socio-demographic information (birthday, gender, education, marriage, occupation, personal annual income, annual household income, and *etc.*), economic burden caused by the disease (direct medical costs, direct non-medical costs and indirect cost in 2019), the treatments received (usage of drugs, numbers of outpatients visits and days of hospitalization) and health states (quality of life measured by EQ-5D-Y and EQ-5D-3L for different age groups).

#### 2.5. Data analysis

Since the included participants were too little ( $n = 31$ ), descriptive statistics were mainly used for the analysis. The economic burden is defined as the sum of direct medical costs, direct non-medical costs, and indirect costs from the patient's perspective (4). The EQ-5D Visual Analogue Scale (VAS) scores and problems reported in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were used to evaluate the patients' QoL. Statistical analysis was performed using SPSS 26.0 software.

#### 2.6. Ethical statements

Informed consents were attained by all the participants before the formal survey started. The participants' privacy, including any individual information they provided in the survey, would be protected. This study was approved by the Medical Ethics Committee of Shanghai Health Development Research Center (No. 2020004).

### 3. Results

#### 3.1. General characteristics

Table 2 demonstrates the characteristics of patients with

4 LSDs in Shanghai. Seventeen of the included patients were male (54.8%). Ten were non-adult among the 31 patients and eight of them were boys (80.0%). The mean age of the sample was  $29.8 \pm 14.4$  years. Five patients failed to complete their education as they suffered from the diseases. Only 12 of the 21 adult patients (57.1%) were employed in 2019. Thirteen of the 21 adult participants were married. Only 1 of the married adults had not given birth to a child. Altogether 16 participants had urban resident basic medical insurance and 15 participants had urban employee basic medical insurance. Additionally, two patients purchased commercial health insurances. The mean personal and household annual incomes were 57,218 CNY and 184,987 CNY (1 USD $\approx$ 6.8 CNY), respectively.

#### 3.2. Usage of ERTs and other medical services utilizations

The FD patients paid outpatient visits for the most times, which was 8.1 times on average in 2019, while the PD patients visited the outpatient clinics for 0.5 times on average, which was the least. The GD patients was hospitalized for the longest time on average, which took them 27.8 days on average. The patients with MPS were hospitalized for only 1.1 days on average. Only the 5 patients with GD were treated with ERTs in 2019. Each of them used 151 bottles of Imiglucerase on average. None of the other 26 patients with LSDs used ERTs in 2019. The details are shown in Table 3.

#### 3.3. Health expenditure

The mean total health expenditure of patients with GD was 2,273,100 CNY in 2019 while that of patients with the other 3 LSDs (PD, FD and MPS) was 37,765 CNY. The higher percent of OOP cost in outpatient expenditure among GD patients was caused by one GD patient who received a spine surgery and paid follow-up visits in outpatient clinics. The inpatient expenditure contributed 2,234,400 CNY, which was over 98.3% of the total cost of GD. Notably, the cost for Imiglucerase accounted for 99.9% of the total inpatient cost, and of which 79.0% could be covered by basic medical insurance and 15.6% was funded by Shanghai Foundation for Rare Disease. The GD patients also needed to pay the rest 5.4% by themselves, which was still 121,200 CNY in average. The medical cost of the other 3 LSDs, including 68.9% outpatient cost and 13.4% inpatient cost could be covered by basic medical insurance. The mean out-of-pocket expenditure for patients with the other 3 LSDs was 21,367 CNY in total. The mean cost happened outside of hospital (which includes cost for drugs and medical devices purchased from retail pharmacies) was similar for GD patients (4,300 CNY) and patients with the other 3 LSDs (4,700 CNY). However, expenditure happened outside of hospital should be self-paid. See Table 4 for details.

**Table 2. The socio-demographic characteristics of patients with 4 LSDs**

Characteristics	Overall (n = 31)		Non-adult (n = 10)		Adult (n = 21)	
	n	%	n	%	n	%
Gender						
Male	17	54.8	8	80.0	9	42.9
Female	14	45.2	2	20.0	12	57.1
Mean age (x ± S)	29.8 ± 14.4		12.4 ± 3.3		38.1 ± 9.5	
Educational level						
No education	4	12.9	4	40.0	0	0.0
Primary school	2	6.5	1	10.0	1	5.0
Middle school	7	22.6	5	50.0	2	9.5
High school	4	12.9	0	0.0	6	28.6
College or higher	14	45.2	0	0.0	12	57.1
Employment status						
Employed	—	—	—	—	12	57.1
Unemployed	—	—	—	—	8	38.1
Retired	—	—	—	—	1	4.8
Marriage						
Married	—	—	—	—	13	61.9
Single	—	—	—	—	6	28.6
Divorced	—	—	—	—	2	9.5
Fertility						
No	—	—	—	—	9	42.9
Yes	—	—	—	—	12	57.1
Medical Insurance						
Urban Employee Basic Medical Insurance	15	48.4	0	0.0	15	71.4
Urban Resident Basic Medical Insurance	16	51.6	10	100.0	6	28.6
Additional commercial insurance	2	6.5	0	0.0	2	9.5
Personal income per year(CNY, 1 USD≈6.8 CNY)						
0	—	—	—	—	4	19.0
10,000-49,999	—	—	—	—	5	23.8
50,000-99,999	—	—	—	—	2	9.5
100,000-199,999	—	—	—	—	8	38.1
200,000-299,999	—	—	—	—	2	9.5
Household annual income (CNY, 1 USD≈6.8 CNY)						
10,000-49,999	1	3.2	1	10.0	0	0.0
50,000-99,999	6	19.4	1	10.0	5	23.8
100,000-199,999	9	29.0	4	40.0	5	23.8
200,000-299,999	12	38.7	4	40.0	8	38.1
Above 300,000	3	9.7	0	0.0	3	14.2

**Table 3. Usage of ERTs and other medical services utilization among patients with 4 LSDs in 2019**

Health Resources Used	GD		PD		FD		MPS	
	Mean(SD)	Median	Mean(SD)	Median	Mean(SD)	Median	Mean(SD)	Median
Numbers of outpatient visits	6.6 (10.1)	0	0.5 (0.5)	0.5	8.1 (11.6)	5.5	7.9 (10.4)	0
Days of hospitalizations	27.8 (3.6)	26	3.5 (6.1)	0	5.1 (8.3)	0	1.1 (2.6)	0
Quantities of ERTs used	151 (47.7)*	130*	—	—	—	—	—	—

\*The strength of Imiglucerase is 400U/bottle.

### 3.4. Economic burden of patients

The average economic burden of patients caused by GD was 164,301 CNY, while the average economic burden of patients with PD, FD and MPS was 58,352 CNY in 2019. Direct medical cost was the majority of the disease burden, which contributed 97.1% and 60.5% of the total disease burden for GD patients and patients with the other three LSDs, respectively. The indirect cost of patients with PD, FD and MPS was 21,860

CNY, which was higher than that of GD patients. The details are shown in Table 5.

### 3.5. Quality of life

The QoL of patients with individual LSD was shown in Table 6. The mean EQ-VAS scores of patients with GD, FD, PD and MPS were 76.4, 55.0, 52.0, and 46.0, respectively. The mean EQ-VAS score of GD patients was the highest. Most patients with LSDs reported

**Table 4. Health expenditure of patients with 4 LSDs in 2019**

Cost (CNY)	GD (n = 5)		PD, FD and MPS (n = 26)	
	Mean (SD)	Median	Mean (SD)	Median
Total	2,273,000 (820,670)	1,648,000	37,765 (110,490)	4,700
Outpatient				
Total	34,400 (46,482)	4,000	13,088 (29,797)	2,450
Basic medical insurance	300 (600)	0	9,017 (24,931)	1,400
Out-of-pocket	34,100 (46,682)	2,500	4,071 (6,896)	750
Inpatient				
Total	2,234,400 (795,541)	1,612,000	19,977 (82,313)	0
Basic medical insurance	1,764,244 (593,872)	0	2,681 (5,516)	0
Charity	348,956 (135,764)	262,080	0 (0)	0
Out-of-pocket	121,200 (71,639)	100,000	17,296 (82,559)	0
Outside the hospital	4,300 (8,600)	0	4,700 (9,162)	1,000

**Table 5. Economic burden of patients with 4 LSDs in 2019**

Cost (CNY)	GD (n = 5)			PD, FD and MPS (n = 26)		
	Mean (SD)	Median	%	Mean (SD)	Median	%
Total economic burden	164,301 (113,267)	112,500	100.0	58,352 (113,675)	7,000	100.0
Direct medical cost	159,600 (111,062)	102,500	97.1	35,321 (92,353)	4,000	60.5
Direct non-medical cost	2,361 (2,212)	2,000	1.4	1,171 (2,218)	50	2.0
Indirect cost	2,340 (2,396)	2,200	1.4	21,860 (49,503)	0	37.5

**Table 6. The QoL of patients with 4 LSDs in 2019**

EQ-5D-3L Dimension	Problems	Total n (%)	GD n (%)	FD n (%)	PD n (%)	MPS n (%)
EQ-VAS(Mean ± SD)		31 (100)	76.4 ± 15.5	55.0 ± 19.7	52.0 ± 12.9	46.0 ± 28.6
Mobility	No	16 (51.6)	5 (100)	9 (64.3)	0 (0)	2 (25.0)
	Yes	15 (48.4)	0 (0)	5 (35.7)	4 (100)	6 (75.0)
Self-care	No	23 (74.2)	5 (100)	14 (100)	2 (50.0)	2 (25.0)
	Yes	8 (25.8)	0 (0)	0 (0)	2 (50.0)	6 (75.0)
Usual activities	No	13 (41.9)	4 (80.0)	7 (50.0)	1 (25.0)	1 (12.5)
	Yes	18 (58.1)	1 (20.0)	7 (50.0)	3 (75.0)	7 (87.5)
Pain/discomfort	No	6 (19.4)	2 (40.0)	1 (7.1)	1 (25.0)	2 (25.0)
	Yes	25 (80.6)	3 (60.0)	13 (92.9)	3 (75.0)	6 (75.0)
Anxiety/depression	No	8 (25.8)	3 (60.0)	2 (14.3)	1 (25.0)	2 (25.0)
	Yes	23 (74.2)	2 (40.0)	12 (85.7)	3 (75.0)	6 (75.0)

problems in Pain/discomfort and Anxiety/depression dimensions, accounts for 80.6% and 74.2%. All the GD patients reported no problems in Mobility, while 35.7%, 100% and 75% of patients with FD, PD, and MPS reported problems in such dimension. GD patients also had better performance than patients with PD and MPS in Self-care dimension.

**4. Discussion**

This is the first study focusing on the usage of all the available ERTs for LSDs in China, as well as the disease burden and QoL of patients with GD, FD, PD and MPS, respectively. The study revealed that the patients using ERTs in Shanghai were still the minority, which was 5 (16.1%) patients with GD, which might

be related to the high costs of available ERTs. Until now, there has been no healthcare security policies for patients with any LSDs on the national level in China, and Shanghai basic medical insurance only reimburses Imiglucerase for GD patients while ERTs for the other three LSDs are not reimbursed. Thus, in the absence of reimbursement, patients with LSDs rarely can afford the expensive cost of ERTs.

Based on foreign experience, a national policy framework, especially reimbursement policies, for patients with rare diseases is necessary (15-18). For instance, the Australian government developed the Life Saving Drug Plan to reimburse expensive and life-saving drugs for life threatening and rare diseases, including GD, FD, PD, MPS type I, type II, type IVA, type VI, and neuronal ceroid lipofuscinosis type 2



(CLN2), which are LSDs (19). In UK, Eliglustat and Migalastat for GD type1 and FD, respectively, was recommended to use in the National Health System *via* a health technology assessment process called Highly Specialized Technology appraisal for new and existing highly specialized medicines and treatments (20,21). Nevertheless, the National Healthcare Security Administration recently claimed that it had basically included all the drugs for rare diseases meeting certain criteria and could not further include orphan drugs with extremely high cost into the NRDL due to the poor affordability (22). Therefore, the current situation in China is that only some of ERTs are reimbursed in some areas, which to a certain extent increase the accessibility for ERTs, but this causes the inequities of healthcare among different areas and different diseases.

The premise is that ERTs are reimbursed, but our study found whether patients actually used ERTs also depended on the reimbursement level. Though the basic medical insurance in Shanghai started to reimburse Imiglucerase from 2013, our interviews with the 5 GD patients reported that none of them started to use it until the Shanghai Foundation for Rare Disease established the special assistance fund for LSD patients in 2017 (13). The reason was that, unlike common drugs, the OOP part after reimbursement remained still unaffordable to the patients. It was estimated to be 300,000-400,000 CNY per patient per year, while the annual disposable income per capital in Shanghai was 69,442CNY in 2019 (23). The Shanghai Foundation for Rare Disease reimbursed the patients depending on their personal income levels, which meant the lower their personal income is, the more reimbursement they would get. However, our study found that the average OOP health expenditure of the 5 patients with GD was still 121,200 CNY in 2019, which was almost 2 times of the annual disposable income per capital of Shanghai residents. The relatively low reimbursement rate in Shanghai also caused inadequate dosage among the patients with GD. Based on our interview, a few patients' dosage of Imiglucerase were lower than the dosage recommended by their physicians according to patients' age, weight, and disease severity. As a result, the economic burden of LSD patients in our study may be underestimated.

The OOP expenditure in Shanghai was found to be higher than that of GD patients from Qingdao City, Shangdong Province and Zhengjiang Province through comparison between different areas. The Qingdao government established a supplementary medical insurance to cover 80% of the cost for Imiglucerase. The donations from the enterprises and civil assistance for low-income families would cover some of the rest part as well (24). Another study reported 8 GD patients' average OOP expenditure for Imiglucerase was 82,700 CNY in Qingdao in 2017 (7). The Zhejiang government settled a special fund for rare diseases in 2020, especially for the expensive drugs. The fund reimburses three drugs for

LSDs, which are Imiglucerase for GD, Agalsidase alfa for PD, and Agalsidase beta for FD, respectively (25). These patients need to pay no more than 10,000 CNY per year by themselves in Zhejiang (26).

Regarding QoL, LSDs usually cause progressive damage in connective tissue, skeletal structure and various organs (27), pain and physical discomfort were the most frequently mentioned symptoms by patients, which was also reported in our study. The EQ-VAS scores of patients with all the four included LSDs were lower than the Chinese population norm of 80.4 (28), revealing the impaired QoL in patients with LSDs. Among the 4 LSDs, GD patients receiving ERTs had highest mean EQ-VAS score (76.4), which was quite close to the norm. The mobility and self-care ability of GD patients in our study were significantly better than patients with FD, PD and MPS as well. With the better health status, eighty percent of the GD patients worked as normal people did, while only 50% (8/16) of the adult patients with the other three LSDs could go to work. Most GD patients didn't need others to take care of them, which may be the reason why the indirect cost of GD patients (2,340 CNY) was much lower than that of the patients with the other three LSDs (21,860 CNY). Though previous study has confirmed that receiving ERTs is meaningful to the patients and could improve their QoL (29), the data analyzed in this study were cross-sectional, providing no evidence of a causal association between ERTs and QOL.

Our study has several limitations as well. Firstly, the sample size was notably small, but similar with other studies among the patients with LSDs and could be acceptable considering that the study was only conducted in a single city (30,31). Our study included around 50.8% (31/61) of the total samples based on our preliminary interviews with doctors and rare diseases organizations. It was believed altogether 61 alive patients with the four mentioned LSDs were in Shanghai right now. The treatment patterns of patients with LSDs, who did not participate in our study, were the same as that of patients included. Thus, we believe the results in our study could represent the actual situation that patients with LSDs in Shanghai are faced with. Secondly, the quality-of-life data could only be presented in the form of EQ-5D VAS scores rather than utility values as there are no EQ-5D-Y value set available in the world. Besides, our study only reported the current impaired QOL of patients with 4 LSDs. However, the causal relation between ERTs and the QOL of patients with LSDs could not be explained explicitly in the cross-sectional design, which needs to be further explored based on a randomized controlled trial, or panel data. Finally, with the inaccessibility of the hospital information systems, we adopted the online survey approach, which brought the general limitations of recall bias and preference bias. We added a round of quality control in the form of telephone interview to improve the quality.

## 5. Conclusions

Based on the current policies in Shanghai and our study on the patients with four LSDs, few patients with LSDs in Shanghai could have access to available ERTs without a high reimbursement level. Though the cost-sharing mechanism of basic medical insurance, charity fund and patients had been explored for Gaucher disease in Shanghai, the OOP part still laid a heavy economic burden on the patients and their families. The healthcare security system should pay more attention to LSDs patients, who need to be treated with extremely expensive ERTs. The scope of drug reimbursement list and the reimbursement level should be further expanded and raised to help improve the quality of life of patients with LSDs. Furthermore, considering the genetic background of LSDs and the high disease burden caused by LSDs, the preventive approach should be recommended by subsidizing the cost of gene tests during pregnancy.

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