

# Newborn Screening for Inherited Metabolic Diseases Using Tandem Mass Spectrometry in China: outcome and cost-utility analysis

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## Research article

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# Abstract

## Background

Few studies in China have focused on economic evaluation of newborn screening (NBS) for inherited metabolic diseases (IMDs) by tandem mass spectrometry (MS/MS). This study assessed the total costs, benefits, benefit-cost ratio (BCR), cost-utility ratio (CUR) and incremental cost-utility ratio (ICUR) of NBS using MS/MS compared to non-screening group for the first time.

## Methods

This study was conducted as a retrospective piece. Newborns who underwent MS/MS screening for IMDs from 2009 to 2018 were included. All records were extracted from a screening management system in NBS Center of Zhejiang province. All costs, including indirect cost, were discounted at a rate of 5% for the whole life-time. The putative benefit of clinical outcomes related to early-diagnosis through screening was assumed as improvements in quality of life and potential life expectancy in screening group.

## Results

Of the 3,040,815 newborns screened, 26,297 (0.86%) newborns were suspected positive after first-round screening and called back to take another MS/MS screening. 25,670 (97.62%) of them followed the latter procedures and finally 735 (2.86%) cases were diagnosed through gene sequence analysis. The most frequent cause of IMD was amino acid diseases (n=276), in most cases fatty acid oxidation disorders (n=248), followed by organic acidemias (n=211). The difference of QALYs ranged from 0.78-15.4. The CUR was CNY¥86,155.80/QALY in screening group and CNY¥303,9517.32/QALY in non-screening group. The ICUR was CNY¥-795,686.47/QALY, and the BCR was 1:8.11.

## Conclusions

NBS using MS/MS can be considered as cost-effective. Nationwide promotion of NBS using MS/MS deserves priority consideration and sufficient publicity.

## Key Points

The most frequent cause of IMD in China was amino acid diseases, in most cases fatty acid oxidation disorders, followed by organic acidemias.

NBS using MS/MS can be considered as cost-effective, as it provides a BCR of 1:8.11, compares favorably with some screening programs for single disease.

The cost-utility analysis suggests MS/MS screening program could gain QALYs and save costs at the same time.

## Background

Newborn screening (NBS) programs are widely recognized as secondary prevention interventions in the “field of Public Health” around the world (1), and encompass an abundance of aspects. The program for the Early Detection of Inherited Metabolic Diseases (IMD) is part of the NBS program. IMD refers to a group of diseases with a series of clinical symptoms caused by enzyme defect, abnormal cell membrane function or receptor defect caused by gene mutation, resulting in collective biochemical metabolism disorder, and accumulation of intermediate or bypass metabolites or lack of final metabolites (2). The screening aims to detect asymptomatic infants before onset of clinical symptoms caused by abnormal biochemical metabolism and provide proper treatment to prevent the occurrence of body dysfunction and irreversible damage, so as to reduce the morbidity, mortality and potential disabilities associated with IMD. The history of

NBS began in the early 1960s, dominant with single disease screening for a long time. Methods such as gas chromatography mass spectrometry and liquid chromatography mass spectrometry also demonstrate obvious flaws, mainly have long analysis cycle, low sample flux and high false-positive rate, thus cannot meet the needs of mass application for NBS. Tandem Mass Spectrometry (MS/MS) emerges as a rapid analysis technology with high sensitivity and specificity, which can test a variety of IMD including amino acids diseases, organic acidemias and fatty acid oxidation disorders through one experiment (3). The introduction of MS/MS makes possible the simultaneous measurement of several metabolites and, consequently, the detection of several diseases in one blood spot and in a unique analysis.

In China, exploratory NBS programs for IMD began with the screening of phenylketonuria (PKU) in the 1980s in Beijing and Shanghai. In 1994, the "Maternal and Infant Health Care Law of the People's Republic of China" was promulgated. For the first time, the law proposed "gradually carry out newborn screening", which provided a fundamental legal guarantee for the work of NBS. The management measures for NBS was issued in 2009, which clearly defined the responsibilities of health administrative departments, all levels' NBS centers and medical institutions (4). According to the data of the national maternal and child health monitoring office in 2013, there are 211 NBS centers in China. So far, Shanghai, Zhejiang, Guangzhou and other NBS centers had gradually started to use MS/MS to carry out mass screening, and have demonstrated good application effects. As for the NBS center of Zhejiang province, as the largest NBS center in China, 40 + newborn genetic and metabolic diseases could be detected by MS/MS. In Zhejiang province, MS/MS has been used for NBS for nearly 10 years, with a total of 3 million newborns screened. And by 2018, approximately 90% of the newborns in Zhejiang province were screened by MS/MS.

However, as the expensive screening expenses and high false-positive rates, an argument has emerged that MS/MS may not be cost-effective for NBS, but should be only used as a clinical diagnostic tool for suspected positive infants. Hence, the cost-utility of using MS/MS in NBS remains to be investigated. This study first assessed the costs, benefits, BCR, CUR and ICUR of NBS program using MS/MS in China.

## Methods

### *Study design*

This study conducted the cost-utility analysis using a decision model. As a decision node (□), a screening or non-screening option must be selected and at a chance node (●), a variety of outcomes may occur, each one with some degree of probability. The clinical outcomes were assumed to have a difference between patients diagnosed early and late. And the costs were calculated for screening and non-screening group as the schematic diagram displayed (Fig. 1). As the false-negative rate of MS/MS cannot be obtained in the management system, we adopted a false-negative rate of 0 in this study. We took a societal perspective in the calculation of costs and benefits.

Fig.1 Schematic diagram of decision model

### *Source of data*

Incidence rate, false-positive rate and internal cost data were obtained from the NBS Management Information System of Zhejiang province, an automated system, which currently manages metabolic disorders in more than 10,000 children. Apart from that, our research team also included 1 pediatricians for the estimation on the frequency of follow-up and hospitalizations.

Calculations were based on average costs of medical procedures in 3,040,815 newborns who underwent MS/MS screening for IMDs in NBS center of Zhejiang province from 2009 to 2018. For the infants participated the MS/MS screening, they were asked to take the first-round screening using dried blood spot(DBS) no sooner than age 72 hours and for premature babies, no later than age 30 days after birth, those who had positive test results were called back to take another MS/MS

test. If someone had two positive test results, the confirmatory test was required to be done. Positive results from MS/MS tests would be confirmed with gene sequence analysis, genetic counselling and disease-specified tests for diagnosis.

### ***IMD incidence and false-positive rates***

The diseases incidence and false-positive rates were obtained from the NBS management information system of Zhejiang province, which covered the whole medical procedures of each NBS participant. For all the disorders can be detected, 28 diseases were found in the 3,040,815 newborns who underwent MS/MS screening. For costs calculation, we assumed the incidence rates and false-positive rates as the NBS management information system provided.

### ***Estimated costs***

The direct medical cost (e.g. screening tests, confirmatory tests, etc.), direct non-medical costs (e.g. special care, transportation) and indirect costs (e.g. wage loss of family member for screening) are specified in Table 1. On the basis of our two pediatricians' experience and Khneisser's work (5), the cost of dietary treatments and pharmaceutical treatments were not included, as they are supposed to be equally incurred once diagnosed. The cost data for screening tests, confirmatory tests, pediatrician consult, hospitalizations were extracted from the medical department.

We assumed that every newborn takes their first-round screening in 72 hours after birth, so the first-round MS/MS requires no extra transportation cost and wage loss. Once having a positive result, these newborns are called back to take the second-round MS/MS, which obviously need the relatives accompanied. We assumed that each newborn has two accompanying relatives and the screening make them to have a half-day away from work. Wage loss of accompanying relative was calculated by per capital income of Zhejiang province (6). In line with Zhejiang practice, the confirmatory test is required when someone gets two positive results. The normal procedure for confirmatory test necessitates a specified test for amino acid diseases(CNY¥60), specified tests for fatty acid oxidation disorders / organic acidemias (CNY¥115), a pediatrician counselling (CNY¥14), a genetic counselling(CNY¥80), and for some highly suspected cases a gene sequence test(CNY¥3,120). Most of the time, the false-positive results engender a pediatrician counselling and a specified test for diseases, costing as much as CNY¥74 to CNY¥129 total.

As the complications and severity are varied in different patients, some of them may have hospitalization cost. Expert opinion combined with medical records were used to estimate the hospitalization frequency of different disease. We assumed that patients with VLCAD, CPTII, OTCD, ASA, ARG, MMA, PA, IVA or Ga- $\beta$  may become symptomatic within the first week of life and may require hospitalizations due to metabolic disorders in the first 5 years. Due to less intensive hospital stays, the cost of each hospitalization for the early-diagnosed infants is CNY¥5,000. We assumed an initial hospitalization cost savings of CNY¥5,000 for early-diagnosed infants versus diagnosis made after symptoms manifested. Number of hospitalizations was calculated based on three hospitalizations (early diagnosed) and four hospitalizations (late diagnosed) per year in the 20% of diagnosed patients with VLCAD. For CPT  $\beta$ , we use three (early diagnosed) and four hospitalizations (late diagnosed) per year in the 80% of patients. Data used on OTCD patients was three (early diagnosed) and four hospitalizations (late diagnosed) per year in the 60% of patients. Patients with ASA or ARG may require three (early diagnosed) and four hospitalizations (late diagnosed) per year in the 20% of patients. Two (early diagnosed) and three hospitalizations (late diagnosed) per year in the 50% of MMA patients and 10% of IVA patients. Hospitalization calculation was based on two (early diagnosed) and three (late diagnosed) hospitalizations per year in the 30% of diagnosed patients with PA/Ga  $\beta$ .

To calculate the cost of treatment, expert opinion was adopted to estimate the follow-up frequency and what tests need to be done each time. Estimated follow-up tests included 17 categories, namely MS/MS (CNY¥390), blood gas assay (CNY¥91), blood ammonia assay (CNY¥25), blood homocysteine assay (CNY¥48), liver function test(CNY¥60), phenylalanine determination (CNY¥30), alpha-fetoprotein determination(CNY¥25) urinary gas chromatography(CNY¥300), blood routine test(CNY¥15), blood biochemistry(CNY¥181), microelement test(CNY¥39), echocardiography(CNY¥130),

electrocardiography(CNY¥20), magnetic resonance imaging(CNY¥689.6), Ages and Stages Questionnaires(CNY¥119), Wechsler Intelligence Scale(CNY¥184) and Bayley Scales of Infant development(CNY¥184). These tests were divided into different combinations to suit each disease, costing CNY¥810 (SCADD) to CNY¥4481(MMA) per year. For most of the IMDs, we assumed an extra 2 times annual follow-up for patients diagnosed late.

Estimation of transportation cost during the life years of IMD patients was based on a survey conducted on 307 patients both from local and non-local regions. As the first round MS/MS screening was tested in the local hospital, the transportation cost for this section was calculated using CNY¥18 per case. The proportion of the local and non-local confirmed cases was adopted to estimate the distributions of the newborns who were recalled. CNY¥338 per visit was used to estimate the transportation cost of non-local patients.

We use per capita basic rehabilitative services subsidy to calculate the cost of rehabilitative services (7), and the data of per capita compulsory education expenditure of disabled children to calculate the cost of special education (8).

For indirect cost, wage loss of accompanying relative /family member was calculated by per capita income of Zhejiang province. Among handicapped children, 70% can be regarded as total loss of labor force, and 30% of them can be regarded as partial loss of labor force (9). We use the gap between capital minimum income and per capita income to calculate the partial wage loss of disabled patients. For cases total loss of labor force, per capita income of Zhejiang province was used for calculation. We also assumed a 50% wage loss of one family member for each disabled patient, for in china, most of the disabled people were cared at home by the family caregivers (10,11).

As lack of discount could encourage policymakers to delay implementing health programs indefinitely (12,13). In this study, all the costs and benefits were discounted at 5% during the life years of patients with IMDs, a commonly used figure that recommended by China Guidelines for Pharmacoeconomic Evaluations (14).

### ***Estimated life expectancy and QALYs***

Based on facts and clinical experience, the onset of complications of the primary metabolic disease in both screening patients and non-screening patients depends on the integrate operation of many factors, the putative benefit of diagnosed early through MS/MS screening was assumed as a difference in the life expectancy and QALYs after treatment. As the severity and responsiveness to treatment are varied by different disease, some even would not necessarily be detected without MS/MS screening (15), so specified life expectancy for each IMDs was used for calculation. We assumed a 0.5-55years difference in life expectancy between patients diagnosed late and those diagnosed early by screening. Meanwhile, the patient's burden of having an IMD had also been described by impairment in utilities (16,17). Though in some studies (18,19), adults IMD patients had similar QoL scores as normal. However, as the research design and sampling method ruled, only patients who could finish the questionnaires or reply the emails (which apparently indicates a higher cognitive level) were included leading to inevitable bias in the results. Hence, utility scores of patients with IMDs in this paper were estimated to have a 0.3-0.7 difference between early and late diagnosed patients varied by different clinical outcomes and severity of disorders. Also, a rate of 5% was adopted to calculate the total discounted QALYs as well.

## **Results**

### ***Incidence of IMDs***

As infants with IMDs may die without clear diagnoses, we assumed that the incidence rates in non-screening group was similar to those in screening group. A total of 3,040,815 newborns were screened between 2009 and 2018, 26,297 of them were suspected positive after first-round screening and called back to take another MS/MS test. 25,670 of them followed the latter procedures and finally 735 cases were diagnosed through confirmatory tests. The most frequent cause of IMDs is

amino acid oxidation disorders, in most cases fatty acid diseases, followed by organic acidemias. The number of diagnosed cases and incidence rates of 28 IMDs are specified in Table 2 respectively.

### **Costs**

Based on the medical records from MS/MS management system in NBS center of Zhejiang province, the number of false-positive test results and the costs were presented in a cohort of 100,000 newborns. Mean per-patient cost of false-positive test results was CNY¥23,905.00. Life-time discounted treatment cost for each disease ranged from CNY¥2,753.33(GA- $\beta$ ) to CNY¥82,920.62(HMG) for early diagnosed patients and CNY¥4,578.62(GA- $\beta$ ) to CNY¥108,993.5 (CPT  $\beta$ ) for late diagnosed patients in per 100,000 newborns. However, the life-time discounted treatment cost for early diagnosed patients are not always lower than those of late diagnosed patients. For BKD, HCS, CPT $\beta$ , CIT $\beta$  and TYR, little life years gained by screening and expensive treatment cost led to higher total discounted treatment costs (Table 3). The cost of total direct medical was CNY¥80,739.88 per patient diagnosed, with the biggest cost factor of treatment costs(CNY¥49,745.77). Comparing with non-screening group, most savings in all the costs was realized in wage loss savings because of decreased follow-up frequency, disabled and mortality rates. Wage loss of accompanying relative per patient was CNY¥160,420.19 and CNY¥232,917.86 respectively, for early and late diagnosed patients. Cost of disabled patients' special care, including rehabilitative services in 0-6 years old and special education in 7-15 years old were CNY¥246,640.21 and CNY¥1,651,432.05 per patient, respectively. The average cost of transportation was CNY¥7,622.68 in screening group, and CNY¥10,220.98 in non-screening group. Overall, the total cost per patient in screening group was CNY¥1,427,601.59, and CNY¥1,580,560.99 in non-screening group (Table 4).

### **Utilities**

In addition to, the prolongation of life years and improvement of utilities resulted in total discounted QALYs difference ranging from 0.78 to 15.40. Among them, patients with BKD and HCS seems to benefit a lot due to diagnosed early by screening. By contrast, GA- $\beta$  and PA could only save little QALYs by screening. The estimated life expectancy and QALYs for patients diagnosed early and diagnosed late are specified in Table 5 (20-

### **Cost-utility analysis**

Results of cost-utility analysis are presented in Table 6. The CUR was CNY¥86,155.80/QALY and CNY¥303,9517.32/QALY in screening and non-screening group. The ICUR for screening group was CNY¥795,686.47/QALY compared to non-screening group. The costs and benefits per patient diagnosed were CNY¥1,427,601.59 and CNY¥11,580,560.99, and the BCR was 1:8.11.

## **Discussion**

The spectrum and incidences of IMDs differ among populations, which has been well characterized in Caucasians but much less so in Chinese (30). Several studies have been carried out in other countries (31-36), while a growing number of studies of IMDs in Chinese population are emerging (37-41), mostly conducted by screening program. This study reported incidence rates of IMDs in east Chinese population using the data from NBS center of Zhejiang province during 2008Q1-2019Q4, with a total of 3 million newborns screened. The collective incidence rate of 28 IMDs included in the screening program is 1/4,137, which was lower than the reported incidence of a pilot study conducted in Mainland China (1/3795) (39) and in many other countries, e.g. 1/2500 in Canada (31), 1/2900 in Germany (32), 1/1944 in Egypt (33), 1/2916 in Malaysia (34), 1/2800 in South Korea (35), and 1/3165 in Singapore (36). Compare to other regions in China (40-43), the incidence rate of IMDs in Zhejiang province also remained relatively low, excluding Taiwan (1/5882).

In this study, the most frequent cause of IMDs was amino acid oxidation disorders, in which PKU accounted for 58.33% suggesting PKU was the most common amino acid oxidation disorder and IMD in Zhejiang province. The second most

common disorder was PCD, which accounted for 136 patients in this study, with its incidence rate of 1/22,359. Meanwhile, the incidence of BKD, HMG, HCS, CPS1, ASA, HCY, TYR were relatively rare, even lower than 1/1,000,000.

Early diagnosis and regular follow-up is important to improve quality of life and long-term survival of IMD, and to prevent the occurrence of body dysfunction and irreversible damage. NBS for these disorders could lighten the social burden related to incapacitating symptoms of these diseases. Though MS/MS has been conducted in China for over 10 years, study focused on the economic evaluation of this technique is still lacked, with more efforts devoted to studies on screening for single disease (e.g. CH, PKU) (44-45).

In this study, the total cost for per early-diagnosed patient was CNY¥1,427,601.59, saving CNY¥10,152,959.41 compared to late-diagnosed patient. Savings are primarily attributed to wage loss of family members and patients (86.03%), and to avoided costs of special care (13.84%), which both benefit from the mortality and severity reduction of IMDs. The treatment cost savings only accounted for 0.08% of all the cost savings, indicating the direct medical cost would not show a substantial decrease because of MS/MS screening. Some diseases will continue to have high mortality and poor clinical outcome even detected by MS/MS before symptoms onset and well-managed since then. Table 3 presented the life-time discounted treatment cost savings of each disorder both per patient and per 100,000 newborns, the latter taking the incidence rate into consideration. It seems that MCCC, MMA, MET could each get a treatment cost saving of more than CNY¥10,000 per 100,000 newborns screened. While not considering the incidence rate, HMG,OTCD and CPT could each save more than CNY¥20,000 treatment cost per early diagnosed patient. Like some studies, we quantified the monetary value of expectancy life years saved and the wage loss of caregivers due to sick children as indirect cost. Failure to add indirect cost in a cost-utility analysis might make the results more likely to be not cost-effective.

The estimated cost per QALY (CUR) was CNY¥86,155.80 (for screening group) and CNY¥303,9517.32 (for non-screening group), saving CNY¥2,953,361.52 per QALY. The incremental cost per QALY (ICUR) was CNY¥-795,686.47 compared to non-screening group, indicating NBS program could both gain QALYs and save costs at the same time.

NBS has been found to be cost-effective by other research groups in China (42-45), although the estimated BCR varied widely. In their 2011 study (45), Zhang et al. reported that the estimated BCR of screening for PKU and CH in china was 1:6.9, whereas the BCRs were estimated ranging from 1:1.17 to 1:141.96 in studies carried out in each specific disorder (43,44,46). While our study included cost-utility estimates of screening for most of the disorder categories detected by MS/MS, it did not include analyses for CH, CAH and G6PD. Inclusion of CH may have influenced the results of the study because it is a much more prevalent condition as compared with many other disorders (47). Meanwhile, some of the benefits of early detection of IMDs cannot be estimated through a monetary analysis, such as improved psychosocial development both in patients themselves and the caregivers. The results still showed that MS/MS screening for IMDs may be considered to be economically beneficial, which consistent with the studies carried out in other countries (5,31,47-48).

Despite MS/MS has been used in China for many years, its application is mainly concentrated in Shanghai, Zhejiang, Guangdong and other developed areas and high-end laboratories (49). Neither corresponding technical specifications in China nor NBS data from less-developed areas has been reported, where might have a rate of consanguineous marriages and could lead to high incidence of IMDs. From early 2015, the NHS Newborn Blood Spot Screening Program in England started to offer screening for a total of nine disorders, six of which were IMDs. The UK screening program was regulated by the Department of Health through the National Screening Committee (UK NSC) and clear recommendations exist regarding management and follow-up of positive screen results (50). Similar technical specifications or recommendations need to be built in China, so does the reimbursement policy related to NBS expenses nationwide.

The major limitation of this study referred to not applying a Markov model-based analysis to evaluate the costs and health benefits for MS/MS screening in China. Moreover, this study did not consider the poor adherence of patients follow up, assuming that all patients would treat their disease for life. However, actually a substantial part of patients discontinued treatment as a result of economic problems by their parents (49).

## Conclusions

In conclusion, NBS using MS/MS can be considered as cost-effective, as it provides a BCR of 1:8.11, compares favorably with some screening programs for single disease. The CUR and ICUR for screening group is CNY¥86,155.80/QALY and CNY¥795,686.47/QALY, suggesting MS/MS screening program could gain QALYs and save costs at the same time. The results prompt that there needs to have sufficient publicity and priority consideration towards nationwide promotion of NBS using MS/MS in China.

## Abbreviations

NBS, Newborn screening; IMD, Inherited metabolic diseases; MS/MS, Tandem Mass Spectrometry; BCR, benefit-cost ratio; CUR, cost-utility ratio; ICUR, incremental cost-utility ratio; PKU, phenylketonuria; CH, hypothyroidism; MMA, Methylmalonic acidemia; PA, Propionic acidemia; IVA, Isovaleric acidemia; MCCD, 3-methylcrotonyl-CoA carboxylase deficiency; BKD,  $\beta$ -ketothiolase deficiency; HMG, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; HCS, Holocarboxylase synthetase deficiency; Ga-II, Glutaric acidemia type II; IBD, isobutyryl-CoA dehydrogenase deficiency; 2-MBD, 2-methylbutyryl-CoA dehydrogenase deficiency; PCD, primary carnitine deficiency; SCADD, Short-chain acyl-CoA dehydrogenase deficiency; MCADD, Medium chain acyl-CoA dehydrogenase deficiency; VLCADD, Very long chain acyl-CoA dehydrogenase deficiency; CPT-I, Carnitine palmitoyl transferase deficiency type I; CPT-II, Carnitine palmitoyl transferase II deficiency type II; GA-II, Glutaric acidemia type II; NICCD, Neonatal intrahepatic cholestasis caused by citrin deficiency; CIT-I, Citrullinemia type I; OTCD, Ornithine transcarbamylase deficiency; CPS I, Carbamoyl phosphate synthetase type I; ARG, Argininemia; ASA, Arginosuccinic aciduria; HCY, Homocystinuria; MET, Hypermethioninemia; MSUD, maple syrup urine disease; TYR, Tyrosinemia; QALY, quality-adjusted life-years.

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## Tables

Table 1 Costs of screening related items

	Item	Unit value(RMB)
Direct cost		
Direct medical cost	Screening tests	
	First-round MS/MS	175
	Second-round MS/MS	390
	Confirmatory tests	
	Gene sequence test	3,120
	Genetic counselling	80
	Specified tests for amino acid diseases	60
	Specified tests for fatty acid oxidation disorders / organic acidemias	116
	Pediatrician consult	14
	Treatment (per year)	810-4,481
	Hospitalizations	
	Early diagnosed	5,000
	Late diagnosed	10,000
	Direct non-medical cost	Rehabilitative services(0-6 years old)
Special education(7-15 years old)		6,000
Transportation cost		
Local		18
Non-local		338
Indirect cost	Wage loss of accompanying relative (per day)	263
	Wage loss of family member (per year)	32,949
	Wage loss of patient	
	Total loss of labor force(per year)	65,898
	Partial loss of labor force(per year)	47,898

Table 2 Incidence rates of 28 inherited metabolic diseases

Diseases	Number of cases	Incidence rate(*10 <sup>-5</sup> )
Organic acidemias	211	7.7
MMA	78	3
PA	11	0.4
IVA	18	0.6
MCCD	48	2
BKD	3	0
HMG	1	0
HCS	2	0
Ga- $\xi$	16	0.5
IBD	29	1
2-MBD	5	0.2
Fatty acid oxidation disorders	248	8.1
PCD	136	4.5
SCADD	55	1.8
MCADD	15	0.5
VLCADD	16	0.5
CPT $\xi$	10	0.3
CPT $\xi$	4	0.1
GA- $\xi$	12	0.4
Amino acidemias	276	8.7
NICCD	42	1.4
CIT-I	9	0.3
OTCD	4	0.1
CPS1	2	0
ARG	9	0.3
ASA	3	0
HCY	2	0
MET	28	0.9
MSUD	13	0.4
TYR	3	0
PKU	161	5.3
Total	735	24.5

Table 3 Costs of Treatment and of False-Positive Results of MS/MS screening

Condition	Incidence*	No. of False-Positive Test Results*	Cost of False-Positive Test Results*	Life-time Discounted Treatment Cost			Treatment Cost Savings*
				IMD Diagnosed Early	IMD Diagnosed Late	Difference	
Organic acidemias							
MMA	3	92	64,093	63,739.98	67,712.74	3972.76	11,918.28
PA	0.4	13	9,039	46,037.03	51,563.24	5526.22	2,210.49
IVA	0.6	21	14,791	62,060.10	63,380.79	1320.70	792.42
MCCD	2	57	39,442	40,685.35	51,792.17	11,106.81	22,213.63
BKD	0	4	2,465	32,734.75	28,348.11	-4,386.64	0
HMG	0	1	822	82,920.62	105,557.40	22,636.74	0
HCS	0	2	1,643	27,473.81	23,792.16	-3,681.65	0
Ga-III	0.5	19	13,147	66,326.26	79,225.79	12,899.53	6449.77
IBD	1	34	23,830	27,473.81	35,847.14	8,373.33	8,373.33
2-MBD	0.2	6	4,109	43,998.30	56,009.53	12,011.23	2,402.25
Fatty acid oxidation disorders							
PCD	4.5	161	111,752	19,067.58	21,629.28	2,561.70	11,527.66
SCADD	1.8	65	45,194	15,782.83	20,593.04	4,810.21	8,658.38
MCADD	0.5	18	12,326	19,101.82	25,027.44	5,925.62	2,962.81
VLCADD	0.5	19	13,147	60,889.11	68,305.14	7416.02	3,708.01
CPT-II	0.3	12	8,217	40,745.59	39,323.49	-1,422.11	-426.63
CPT-I	0.1	5	3,287	71,615.02	108,993.50	37,378.47	3,737.85
GA-III	0.4	14	9,860	2,753.33	4,578.62	1,825.29	730.12
Amino acidemias							
NICCD	1.4	50	31,731	52,823.75	59,280.53	6,456.78	9,039.49
CIT-I	0.3	11	6,799	31,534.39	27,605.66	-3,928.74	-1,178.62
OTCD	0.1	5	3,022	79,830.72	105,773.90	25,943.20	2,594.32
CPS1	0	2	1,511	33,359.45	34,605.32	1,245.87	0
ARG	0.3	11	6,799	50,993.44	60,551.82	9,558.38	2,867.51
ASA	0	4	2,266	46,143.50	57,889.45	11,745.95	0
HCY	0	2	1,511	39,431.16	47,582.23	8,151.07	0

MET	0.9	33	21,154	44,425.73	57,965.59	13,539.86	12,185.87
MSUD	0.4	15	9,821	56,490.97	58,214.86	1,723.89	689.56
TYR	0	4	2,266	38,431.13	37,001.57	-1,429.55	0
PKU	5.3	190	121,635	21,901.71	28,474.33	6572.616	34,834.86
Total	24.5	869	585,681	1,218,771.26	1,426,624.81	207,853.56	146,291.35

\* Per 100,000 newborns.

Table 4 Lifetime costs per patient in screening and non-screening group

Costs	Screening group ¥RMB¥	Non-screening group ¥RMB¥
Cost of false-positive test results	23,905.00	-
Cost of true-positive test results	661.11	-
Cost of confirmatory tests	6,428.00	6,428.00
Cost of treatment	49,745.77	58,229.58
Total direct medical costs	80,739.88	64,657.58
Cost of transportations	7,622.68	10,220.98
Cost of special care	246,640.21	1,651,432.05
Total direct non-medical costs	239,017.53	1,641,211.07
Total direct costs	158,277.65	1,576,553.49
Cost of wage loss (family members)	160,420.19	232,917.86
Cost of wage loss (patients)	1,429,744.12	9,771,089.65
Total indirect costs	1,269,323.93	10,004,007.51
Total costs	1,427,601.59	11,580,560.99

Table 5 Potential Life Expectancy (in Years) and QALY

Condition	Life expectancy			Total undiscounted QALY		Total discounted QALY		Difference
	IMD	IMD	Source	IMD	IMD	IMD	IMD	
	Diagnosed	Diagnosed		Diagnosed	Diagnosed	Diagnosed	Diagnosed	
	Early	Late		Early	Late	Early	Late	
Organic acidemias								
MMA	13	8	[20]	12.35	2	8.92	1.62	7.31
PA	10	5	[21]	5.50	1.25	4.25	1.08	3.16
IVA	23	13	[22]	21.85	3.25	12.81	2.35	10.47
MCCD	71	54	[23]	67.45	13.50	18.41	4.64	13.76
BKD	75	20	-	71.25	5	18.51	3.12	15.40
HMG	71	54	[23]	67.45	13.50	18.41	4.64	13.76
HCS	75	20	-	71.25	5	18.51	3.12	15.40
Ga- $\beta$	20	13	[24]	19	3.25	11.84	2.35	9.49
IBD	75	65	-	71.25	16.25	18.51	4.79	13.72
2-MBD	71	54	-	67.45	13.50	18.41	4.64	13.76
Fatty acid oxidation disorders								
PCD	75	45	-	71.25	6.25	15.88	3.52	12.35
SCADD	75	65	-	71.25	16.25	18.51	4.79	13.72
MCADD	68	62	[25]	64.60	15.50	18.31	4.76	13.55
VLCADD	31	17	[26]	17.05	4.25	8.58	2.82	5.76
CPT $\beta$	25	14	[21]	23.75	3.50	13.39	2.47	10.91
CPT $\alpha$	57	43	[21]	31.35	10.75	10.32	4.39	5.93
GA- $\beta$	1	0.50	[21]	0.95	0.13	0.90	0.12	0.78
Amino acidemias								
NICCD	75	35	-	71.25	8.75	18.51	4.09	14.42
CIT-I	68	20	-	64.60	5	18.31	3.12	15.20
OTCD	32	19	-	30.40	4.75	15.01	3.02	11.99
CPS1	32	19	-	30.40	4.75	15.01	3.02	11.99
ARG	32	19	-	30.40	4.75	15.01	3.02	11.99
ASA	21	15	-	19.95	3.75	12.18	2.59	9.59
HCY	41	31	[27]	38.95	7.75	16.43	3.90	12.53
MET	75	65	-	71.25	16.25	18.51	4.79	13.72

MSUD	35	20	[28]	33.25	5	15.56	3.12	12.44
TYR	30	16	[29,30]	16.50	4	8.45	2.71	5.75
PKU	78	65	[21]	74.1	16.25	18.58	4.79	13.79
Total	1,355	876.50	-	1,236.05	214.13	406.03	93.39	312.64

Table 6 Results of cost-utility analysis for MS/MS screening

Costs and benefits	Screening group (per patient)	Non-screening group (per patient)
QALYs	16.57	3.81
Cost per QALY (CUR)	86,155.80	303,9517.32
QALYs gained by screening	12.76	-
Incremental cost	-10,152,959.41	-
Incremental cost per QALY(ICUR)	-795,686.47	-
Total costs /benefits	1,427,601.59	11,580,560.99
BCR	1:8.11	

## Figures

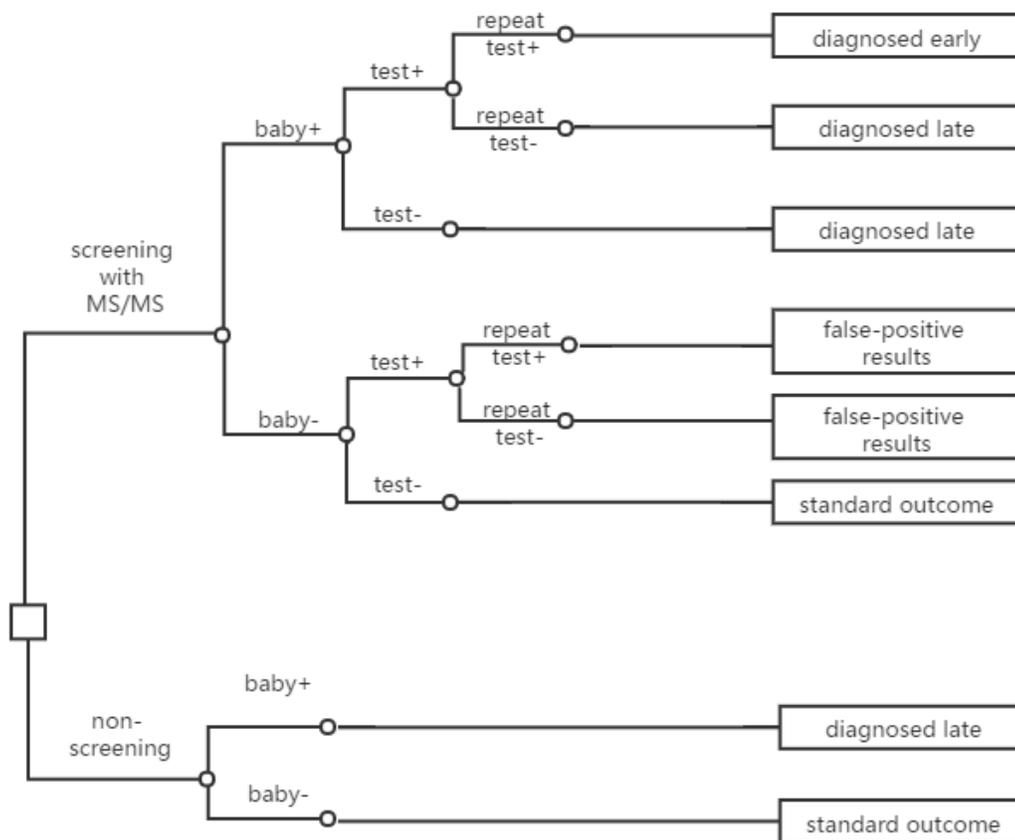
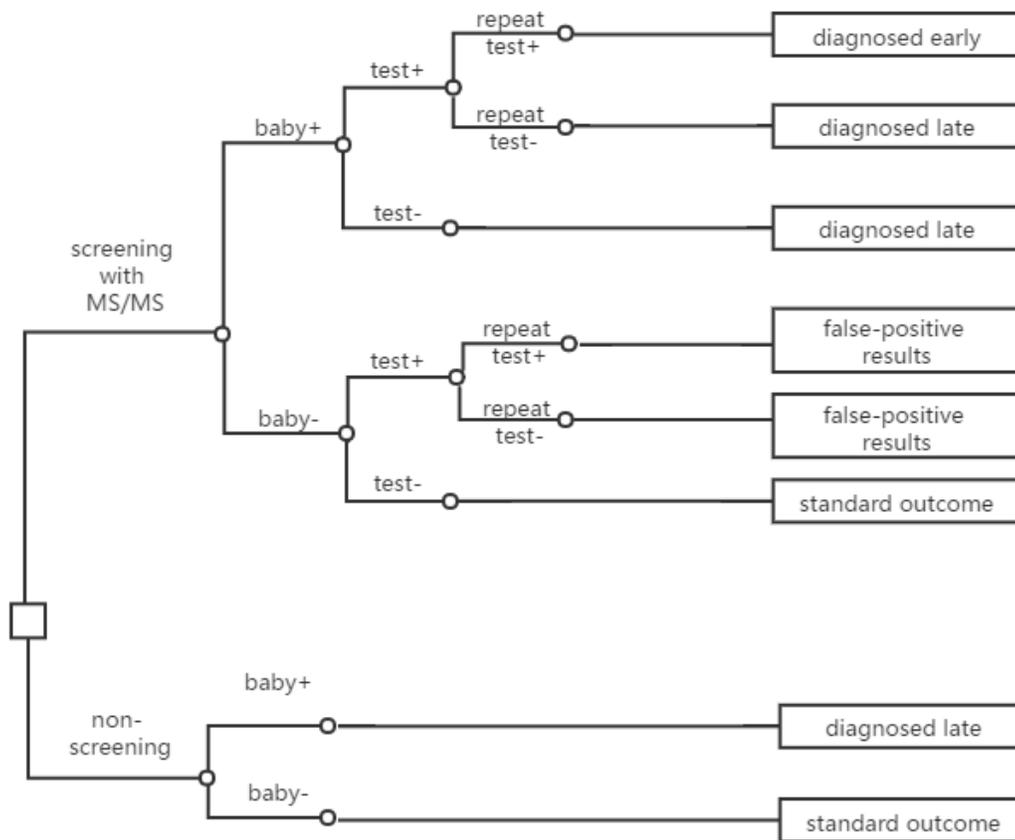


Figure 1

Schematic diagram of decision model



**Figure 1**

Schematic diagram of decision model