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Cost Effectiveness and Resource Allocation

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The cost-effectiveness analysis of newborn screening for inherited metabolic disorders in China using tandem mass spectrometry: a real-world evidence

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Abstract

Background Inherited metabolic disorders (IMDs) are a significant cause of morbidity and death among children. To determine the cost-effectiveness of newborn screening for IMDs using tandem mass spectrometry (MS/MS) compared to the non-screened group in China.

Methods We constructed a decision tree screening model based on the Chinese clinical path of tandem MS/MS screening for inherited metabolic disorders (IMDs) from the medical health system. This model simulated the mechanism of screening in the prevention and treatment of IMDs. The IMDs screening data was collected from Children's Hospital of Shanghai between 2010 and 2021. The Quality-adjusted life years (QALYs) and life expectancy were obtained from literature, while cost data was mainly sourced from hospital records and literature.

Results In the base-case analysis, the total lifetime cost per patient was higher for the MS/MS screened group at 1,000,452 Chinese Yuan (CNY) (USD 143,515), compared to 157,303 CNY (USD 22,565) for the non-screened group. The QALYs gained were 16.47 and 3.97 for the screened and non-screened groups, respectively. The incremental cost-effectiveness ratio (ICER) of the MS/MS screened group compared to the non-screened group was 67,417 CNY (USD 9,671) per QALY gained, which is under the threshold of 3 times per capita GDP of China in 2022 (242,928 CNY, USD 34,848). The benefit-cost ratio (BCR) was 4.23, which means that for every 1 CNY (USD 0.1434506) invested, a return of 4.23 CNY (USD 0.57) can be obtained. The probability of cost-effectiveness was 100% in the MS/MS screened group compared to the non-screened group, indicating that the results of the base case analysis were robust.

Conclusion Compared to the non-screened group, the MS/MS screened group incurs higher costs but also yields significantly greater QALY gains. Considering both the costs and benefits, the MS/MS screened group is an attractive cost-effective option at the current willingness-to-pay threshold for IMDs screening in China.

Key points

• Text Text Text.

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•Research Significance: The study assesses the cost-effectiveness of MS/MS screening for IMDs in Chinese newborns, crucial for resource allocation and policy decisions.
•Results Interpretation: MS/MS screening has higher costs but significantly better health outcomes, making it a cost-effective option below the GDP threshold.
•Innovativeness: The study introduces a rigorous cost-effectiveness analysis to evaluate different screening strategies for IMDs.
•Implications for Screening: The findings guide policymakers and healthcare providers towards a more effective and efficient newborn screening program for IMDs in China.

Keywords Tandem mass spectrometry, Inherited metabolic disorders, Screening, Cost-effectiveness analysis

Background

Inherited metabolic disorders (IMDs), also known as inborn errors of metabolism (IEM), which was a significant cause of morbidity and death among children [1]. The onset age of genetic metabolic diseases can be in different periods of newborns, infants, children, adolescence, or adulthood, with the highest incidence rate in neonatal period, and most of the initial symptoms are not obvious [2]. Although a single genetic metabolic disease is rare, the comprehensive incidence rate of genetic metabolic diseases can be as high as 1:800 ~ 1:4000 [3-7]. At present, there were few studies about the economic burden of genetic metabolic diseases in newborns, most of the existing studies focusing on the common phenylketonuria (PKU) and congenital hypothyroidism (CH). A study in Shanghai shows that the economic burden of the disease that can be avoided by screening a PKU child and a CH child by taking early treatment measures is 726,000 CNY and 713,000 CNY respectively. According to the national statistics in 1996, the total social and economic burden of PKU and CH in China was 874 million CNY and 2.915 billion CNY respectively [8].

Due to the wide range of genetic metabolic diseases, traditional screening technologies cannot comprehensively and effectively screen for multiple genetic metabolic diseases. In recent years, neonatal screening has utilized tandem mass spectrometry (MS/MS) and gene detection technologies to achieve "multiple detection". MS/MS can quickly detect the molecular biomarkers of more than 30 genetic metabolic diseases (including amino acid, organic acid, and fatty acid metabolic diseases) in a single sample at the same time [9]. Before the adoption of MS/MS, screening mainly focused on PKU, Glucose-6-phosphate dehydrogenase deficiency, CH, and Congenital adrenal hyperplasia, with other genetic metabolic disorders lacking effective screening methods. The implementation of MS/MS will enhance the prevention and control of IMDs in China.

Given the high disability rate and heavy economic burden associated with IMDs, some studies have confirmed the clinical value of MS/MS combined with gene detection technology in the screening and diagnosis of IMDs. Currently, several cost-effectiveness analysis study on genetic metabolic diseases in newborns has been published in China [10-14], but the main clinical screening data mainly come from different provinces. This study will use clinical screening data from Shanghai for further supplementary demonstration.

However, there is a lack of relevant economic evidence in China. Therefore, the primary objective of this study is to determine the cost-effectiveness of implementing MS/MS in screening for IMDs compared to no screening, which would facilitate evidence-based decision-making on the deployment of MS/MS in IMD screening.

Methods

Study design

Based on clinical screening data and literature, a cost-effectiveness analysis was conducted to analyze the MS/MS in the screening of IMDs compared to the non-screened group. The model simulates the lifelong progress of disease. The main outputs of the model are cost, quality-adjusted life years (QALYs), incremental cost-effectiveness ratio (ICER) and benefit–cost ratio (BCR). Based on the Chinese Pharmacoeconomic Evaluation Guide (2020) [15], the cost and health output are discounted at a discount rate of 5%.

Construction of screening model

From the medical and health system, a decision tree screening model based on literature [10] and screening path structure of IMDs in China was constructed to simulate the mechanism of screening in the prevention and treatment of neonatal genetic metabolic diseases (Fig. 1). The model was implemented by Microsoft® Excel 2019 software.

For newborns in the screening group, the MS/MS was used to detect genetic and metabolic diseases of newborns within 72 h after birth. Newborn with positive results would be required to return to the hospital for another MS/MS test within 30 days. Newborn with positive results in both tests would be subject to gene sequencing for final diagnosis.

Study population

Neonates in Shanghai China.

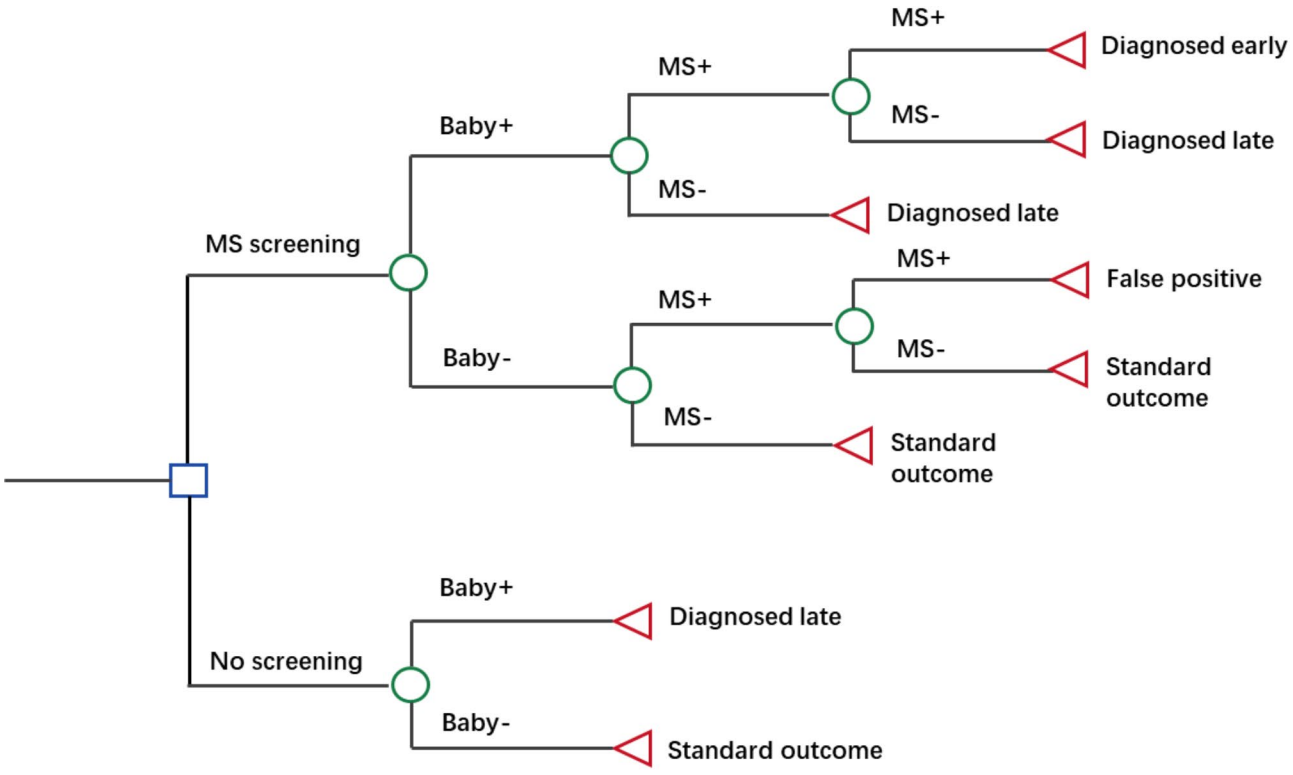

Fig. 1 Schematic diagram of decision model

Clinical screening data

The clinical screening data of this study was derived from the screening data of children in Shanghai from December 2010 to November 30, 2021. The total number of screening cases was 254,207(IRB approval number: 2019R071-F03). Since this study did not measure false negative, considering that the incidence rate of neonatal genetic metabolic diseases was relatively low, and most of the neonatal genetic metabolic diseases had been screened by tandem mass spectrometry, there were fewer patients missed diagnosis, assuming false negative was 0, see supplementary material 1 for details.

QALYs data and life years

The life expectancy and QALYs of early diagnosis and late diagnosis of various genetic metabolic diseases were derived from the literature [10] and maintains the same time horizon as stated in those studies. See supplementary material 1 for details.

Cost data

The cost of pharmacoeconomic evaluation includes three parts: direct cost (including direct medical cost and direct non-medical cost), indirect cost and intangible cost. In this study, direct medical cost was considered from the perspective of the healthcare system, and other costs were not calculated. The direct medical costs included in this study included screening costs, diagnosis costs, treatment costs, etc.

(1) Screening cost, diagnosis cost and hospitalization cost

The screening cost was derived from the screening data of Shanghai tandem mass spectrometry screening for neonatal genetic and metabolic diseases. All the newborns in the screening group would undergo a round of tandem mass spectrometry screening, and the second round of tandem mass spectrometry screening would be conducted for the newborns with positive screening results, and the double positive newborns would undergo gene sequencing.

The cost of diagnosis comes from Shanghai Children's Hospital, and the double positive newborns in the screening group would undergo gene sequencing. Although the newborns in the non-screening group will not be screened, as time goes on, the newborns suffering from genetic and metabolic diseases would get sick one after another, and the newborns after the disease still need to be confirmed by gene sequencing. It should be noted that false positive (double positive) newborns in the screening group will also be sequenced, the cost of diagnosis in the screening group was higher than that in the non-screening group.

As for the cost of hospitalization, early diagnosis could reduce the number of hospitalizations compared with late diagnosis. In addition, based on the research of Zhao

Table 1 Screening cost, diagnosis cost and hospitalization cost per time

Item	Value (CNY)
Screening tests	
First-round MS/MS	250
Second-round MS/MS	250
Confirmatory tests	
Gene sequence test	3,600
Genetic counselling	80
Pediatrician consult	25
Hospitalizations	
Early diagnosed	5,000
Late diagnosed	10,000

Table 2 Number and proportion of hospitalizations

Item	Early diagnosed	Late diagnosed	Proportion
	Number of hospitalizations per year	Number of hospitalizations per year	
VLCD	3	4	20%
CPT	3	4	80%
OTCD	3	4	60%
ARG	3	4	20%
MMA	2	3	50%
IVA	2	3	10%
PA	2	3	30%
GA	2	3	30%

et al. [10], the average annual hospitalization cost of each early diagnosed newborn patient in 2021 was 5,000 CNY, and late diagnosis was 5,000 CNY higher than early diagnosis, that was, 10,000 CNY.

As for medicine cost, it was difficult to estimate due to the variety and complexity of medicine use of neonatal genetic metabolic diseases. However, incremental analysis would be carried out in the base-case analysis, and the medicine cost of screening group and non-screening group could be basically offset, so medicine cost would not be considered in this study. This process method was also the same as the literature [10, 16]. See Table 1 for details of relevant expenses.

(2) Number and proportion of hospitalizations

Some neonatal genetic and metabolic diseases did not require hospitalization. The data of neonatal genetic and metabolic diseases requiring hospitalization were derived from Shanghai Children's Hospital in 2021. See Table 2 for details.

(3) Follow-up cost

The average annual follow-up cost for early diagnosis of IMDs was derived from screening data from Shanghai Children's Hospital from December 2010 to November 30, 2021. Early diagnosed patients were followed up four times a year before the age of 5, and once a year after the age of 5. And assume that patients with late diagnosis will be followed up twice a year more than patients with early diagnosis. See Table 3 for details.

Incremental analysis

The key metric in incremental analysis is the incremental cost-effectiveness ratio (ICER), which is calculated using the following formula [15]:

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C1-C2}{E1-E2}$$

In this equation, C1 and C2 represent the costs of the test group and control group, respectively, while E1 and E2 represent the effects of the test group and control group, respectively. Based on the latest data from the National Bureau of Statistics, China's per capita GDP in 2022 is projected to be 85,698 CNY [17]. Therefore, three times the per capita GDP would be 257,094 CNY.

Benefit-cost ratio analysis

When using QALYs as the effectiveness measure, the WHO recommends setting the threshold value at three times the local per capita GDP. In this scenario, the calculation formula for benefit-cost ratio (BCR) is as follows: BCR = C / (E * λ), where C represents the total cost of the intervention group, E represents the total QALYs gained by the intervention group, and λ represents the threshold value [15].

One-way sensitivity analysis

One-way sensitivity analysis refers to the degree of influence that a single variable has on the outcome when its value changes, while if all other variables remain constant. This method is relatively simple and provides clear results, but its drawback is that it may overlook the correlations between variables in the model, leading to an underestimation of overall uncertainty [15].

The one-way sensitivity analysis in this study involves clinical data, cost data, QALYs, and other variables. While the upper and lower limits of relevant parameters were primarily sourced from literature, alternative methods were used when these limits cannot be determined. A common approach was to assume that these limits vary by 10% above and below the average value. The sensitivity analysis results could be visually presented in a tornado diagram, which facilitates the identification of the variables with the greatest impact on the outcomes, particularly when multiple variables require analysis.

Probabilistic sensitivity analysis

With the advancement of statistics and computer science, probabilistic sensitivity analysis (PSA) has become the primary method of uncertainty analysis in Pharmacoeconomics [15]. The most common method used in PSA is Monte Carlo simulation. In current Pharmacoeconomics research, PSA is widely used to explore

Table 3 Follow-up cost and frequency

Item	Unit price	Whether to carry out this test (1 is yes, and 0 is no)											
		MMA	PA	IVA	BKD	MCCD	HMG	HCS	Ga-I	PCD	SCADD	SCHADD	MCADD
Frequency (Times)													
MS/MS	250	1	1	1	1	1	1	1	1	1	1	1	1
Blood gas	117	1	1	1	1	1	1	1	1	1	0	1	1
Blood ammonia	40	1	1	1	1	1	1	0	1	1	0	1	1
Blood homocysteine	120	1	1	0	0	0	0	0	0	0	0	0	0
liver function	190	1	1	0	1	1	1	0	1	1	0	1	1
Phenylalanine	18	0	0	0	0	0	0	0	0	0	0	0	0
Alpha fetoprotein	32	0	0	0	0	0	0	0	0	0	0	0	0
Urine gas chromatography	258	1	1	1	1	1	1	1	1	1	1	1	1
Routine blood test	20	1	1	0	1	0	0	1	1	0	0	0	0
Blood biochemistry	181	1	1	1	1	1	1	0	1	1	0	1	1
Trace element	39	0	0	1	0	0	0	0	0	0	0	0	0
Echocardiography	225	0	0	0	0	0	0	0	0	1	0	0	0
Electrocardiogram	20	0	0	0	0	0	0	0	0	1	0	0	0
Magnetic resonance	620	1	1	1	0	0	1	0	1	0	0	0	0
Electroencephalogram	45	1	1	0	0	0	0	0	0	0	0	1	0
Urinalysis	10	0	0	0	1	0	1	1	1	0	0	0	0
Myocardial zymogram	210	0	0	0	0	0	0	0	0	0	0	0	0
Blood fat	45	0	0	0	0	0	0	0	0	0	0	0	0
Annual cost of early diagnosis (CNY): 1 to 5 years old	N/A	7,364	1,841	1,505	1,066	1,036	1,666	655	1,686	1,281	508	1,081	1,036
Annual cost of early diagnosis (CNY): After 5 years old	N/A	1,841	1,841	1,505	1,066	1,036	1,666	655	1,686	1,281	508	1,081	1,036
Annual cost of late diagnosis (CNY): 1 to 5 years old	N/A	11,046	11,046	9,030	6,396	6,216	9,996	3,930	10,116	7,686	3,048	6,486	6,216
Annual cost of late diagnosis (CNY): After 5 years old	N/A	5523	5523	4515	3198	3108	4998	1965	5058	3843	1524	3243	3108
Item	**Unit price**	**Whether to carry out this test (1 is yes, and 0 is no)**											
		VLCADD	LCHAD	Gall	NICCD	CIT-I	OTC	CPS1	ARG	MET	MSUD	TYR	PKU
Frequency (Times)													
MS/MS	250	1	1	1	1	1	1	1	1	1	1	1	1
Blood gas	117	1	1	1	0	0	1	1	1	0	1	0	0
Blood ammonia	40	1	1	0	1	1	1	1	1	0	1	0	0
Blood homocysteine	120	0	0	0	0	0	0	0	0	1	0	0	0
liver function	190	1	1	1	1	1	1	1	1	1	0	1	0
Phenylalanine	18	0	0	0	0	0	0	0	0	0	0	0	1
Alpha fetoprotein	32	0	0	0	1	0	0	0	0	0	0	1	0
Urine gas chromatography	258	1	1	1	1	1	1	1	1	0	1	1	1
Routine blood test	20	0	0	0	0	0	0	0	0	0	0	1	0
Blood biochemistry	181	1	1	1	1	0	0	0	0	0	1	1	0
Trace element	39	0	0	0	0	0	0	0	0	0	0	0	0
Echocardiography	225	0	0	0	0	0	0	0	0	0	0	0	0

Table 3 (continued)

Item	Unit price	Whether to carry out this test (1 is yes, and 0 is no)											
		VLCADD	LCHAD	Gall	NICCD	CIT-I	OTC	CPS1	ARG	MET	MSUD	TYR	PKU
Electrocardiogram	20	0	0	0	0	0	0	0	0	0	0	0	0
Magnetic resonance	620	0	0	1	0	0	0	0	1	1	1	1	0
Electroencephalogram	45	0	0	0	0	0	0	0	0	0	0	0	0
Urinalysis	10	1	1	0	0	0	0	0	0	0	1	1	0
Myocardial zymogram	210	0	0	1	0	0	0	0	0	0	0	0	0
Blood fat	45	0	0	0	1	0	0	0	0	0	0	0	0
Annual cost of early diagnosis (CNY): 1 to 5 years old	N/A	4,184	4,144	4,184	7,304	3,984	2,952	3,420	3,420	5,900	4,720	5,904	2,104
Annual cost of early diagnosis (CNY): After 5 years old	N/A	1,046	1,036	1,046	1,826	996	738	855	855	1,475	1,180	1,476	526
Annual cost of late diagnosis (CNY): 1 to 5 years old	N/A	6,276	6,276	10,956	5,976	4,428	5,130	5,130	8,850	7,080	8,856	9,366	3,156
Annual cost of late diagnosis (CNY): After 5 years old	N/A	3138	3138	5478	2988	2214	2565	2565	4425	3540	4428	4683	1578

parameter uncertainty in models. PSA analyzes changes in all parameters within the model and simulates their values based on their parameter distribution to explore the possible distribution of results. The results of PSA can typically be presented through ICER scatter charts and cost-effectiveness acceptability curves. The cost-effectiveness acceptability curve illustrates the probability of each scheme being cost-effective in each pharmacoeconomic evaluation, given a specific willingness-to-pay value. The sum of the probabilities of all comparison schemes is 100%.

In this evaluation, PSA was used to analyze most of the parameters in the model. Typically, the cost was assumed to follow a gamma distribution, while the clinical parameters and QALYs were assumed to follow a Lognormal distribution.

Results

Base-case analysis results

In the base-case analysis, for each newborn patient, the lifetime cost of the MS/MS screening group was 1,000,452 CNY, with a lifetime available QALYs of 16.47. The lifetime cost of the non-screening group was 157,303 CNY, with a lifetime available QALYs of 3.97. When compared to the non-screening group, the lifetime cost of the screening group was843,148 CNY higher, with 12.51 additional QALYs, resulting in an ICER of 67,417 CNY/QALY. Under current threshold conditions (where China's per capita GDP in 2022 is 85,698 CNY [17]), the screening group is cost-effective, as indicated in Table 4.

Benefit-cost ratio results

According to the base-case analysis results, the cost of implementing MS/MS screening was 1,000,452 CNY, while the expected lifetime gain in QALYs was 16.47. To determine whether the investment was worthwhile, a threshold of three times China's per capita GDP in 2022 was used [15]. Based on this threshold, the input-output ratio was calculated to be 1:4.23. This means that for every 1 CNY invested in MS/MS screening, a return of 4.23 CNY can be expected in terms of QALYs and economic benefits. Therefore, it can be concluded that the increased investment is fully worth it, as the expected return on investment exceeds the threshold.

One-way sensitivity analysis results

In addition to the base-case analysis, this study performed a one-way sensitivity analysis on key variables in the model, such as clinical data, cost data, and QALYs. Each parameter was varied by 10% from its base value to evaluate the impact of these variations on the results.

The results of the sensitivity analysis revealed that the single most influential factor was the cost of the first round of MS/MS screening. This was followed by the

Table 4 Base-case analysis results

Item	Screening group	non-screening group	Increment (screening vs. non screening)
Total cost (CNY)	1,000,452	157,303	843,148
Screening costs	924,134	0	924,134
Diagnosis costs	45,861	3,705	42,156
Treatment costs	30,456	153,598	-123,142
QALYs	16.47	3.97	12.51
ICER(CNY/QALY)	67,417		

number of QALYs gained through early diagnosis of phenylketonuria (PKU) and the number of true positive cases detected by the screening. Figure 2 provides further details on these findings.

Probabilistic sensitivity analysis results

To further assess the robustness of the results, a PSA was conducted using the nonparametric bootstrap method with 5,000 Monte Carlo simulations. This allowed for the calculation of the probability of cost-effectiveness of the MS/MS screening group compared to the non-screening group under different willingness-to-pay values. From the cost-effectiveness acceptability analysis, it can be observed that as the threshold increases, the probability of the screening group being cost-effective continuously rises. Once the threshold reaches 100,000 CNY/QALY, the probability of the screening group being cost-effective remains at 100%. The results showed that under the threshold of 1.5 times and 3 times the national GDP per capita in 2022, the probability of the screening group been cost-effective was 100%. This indicates that the findings from the base-case analysis were robust, and that the implementation of the screening program is highly likely to be cost-effective. See Figs. 3 and 4 for the corresponding cost-effectiveness acceptability curves.

Scenario analysis results

Scenario analysis was also conducted. When assuming false positives was 3% or 10% respectively, the screening group was cost effective compared to the non-screening group. When assuming the cost discount rates was 1% and 3% respectively, the screening group also was cost-effective. This also proved that the result of the basic analysis was robust, as indicated in Table 5.

Discussion

The base case analysis, conducted from the perspective of the medical and health system, demonstrated that although the screening group incurred higher costs than the non-screening group, the patients in the former had higher QALYs. The ICER was also found to be less than the threshold, indicating that the screening program was cost-effective. Moreover, the sensitivity analysis conducted on key variables showed that the results of the base case analysis were stable, further supporting the robustness of the findings. Overall, the study suggested that implementing the tandem mass spectrometry screening program would be beneficial from both a clinical and economic perspective.

Currently, there are several studies on the cost-effectiveness of neonatal genetic metabolic disease screening programs in China, the estimated BCR varied widely [10~14]. A study conducted by Zhao et al. in Zhejiang province showed that the screening group was more cost effective than the non-screening group, and the BCR was1:8.11 [10]. As for this BCR was higher than our study, the reason for the difference is that we did not consider direct medical costs and indirect costs in our study.

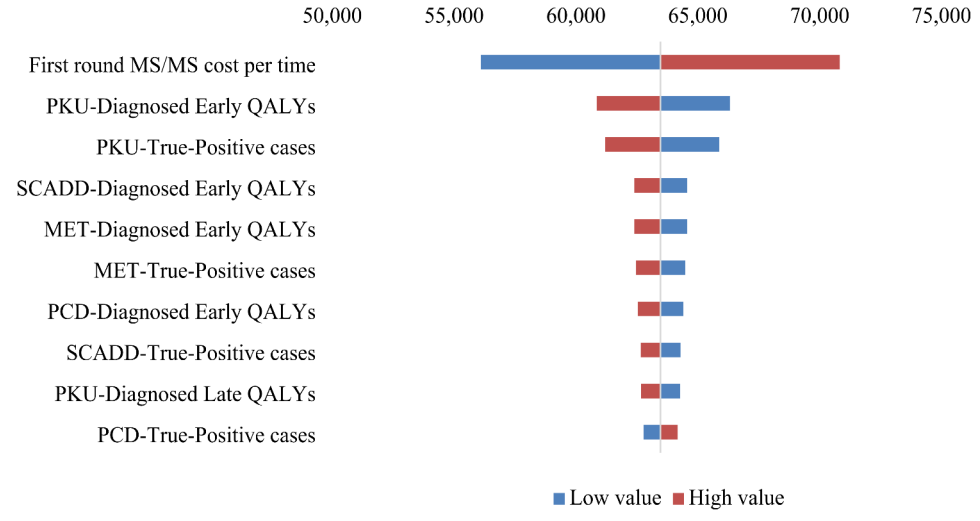

Fig. 2 Tornado diagram (screening group vs. no screening, ICER)

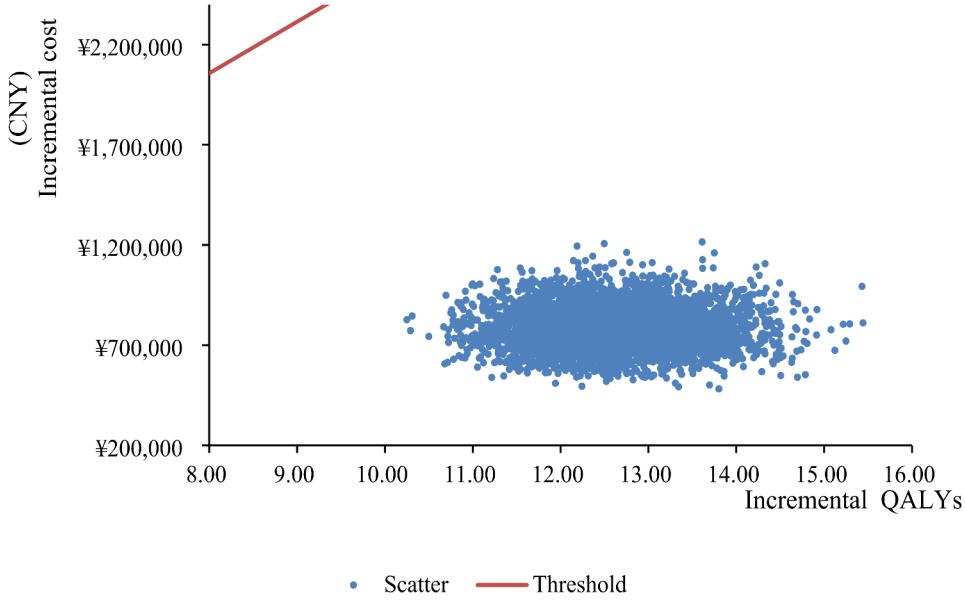

Fig. 3 Scatter plot (screening group vs. no screening)

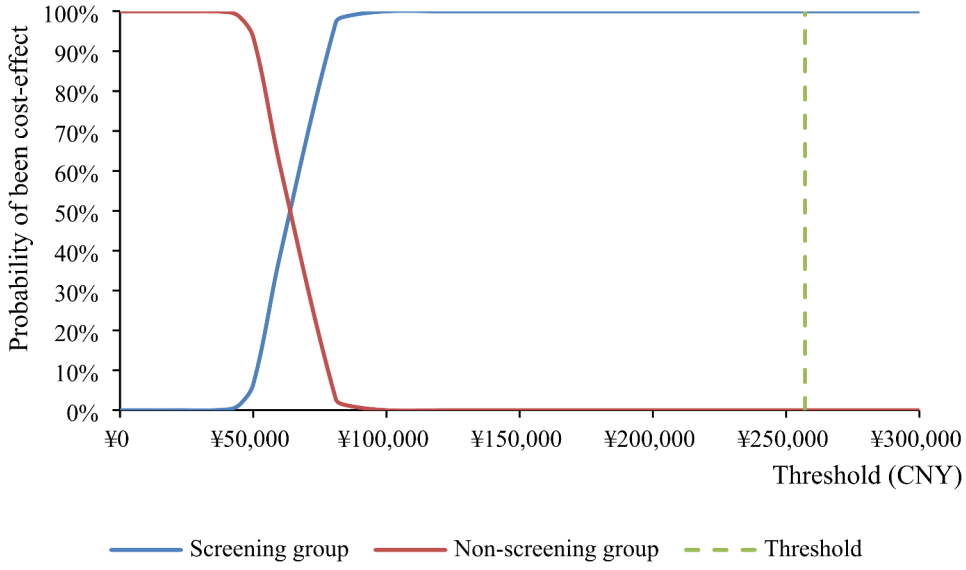

Fig. 4 Cost effectiveness acceptability curve

On the other hand, research on the cost-effectiveness of MS/MS screening for neonatal genetic metabolic diseases has been widely conducted abroad. For instance, a study by Bessey et al. in the UK demonstrated that such screening was both more effective and cost-effective than no screening [18]. And a review of medium-chain acyl CoA dehydrogenase deficiency in the Canadian population found that the screening program was cost-effective if the threshold was set at 20,000 Canadian dollars per QALY [19]. Similarly, a study in the United States showed that screening for congenital metabolic genetic diseases using tandem mass spectrometry was beneficial compared to other large-scale screening programs [20]. Additionally, studies in France [21] and Australia [22] have also obtained similar results, with screening groups been cost-effective compared to non-screening groups.

This study has some limitations stemming from the lack of available data. Firstly, the clinical data collection was restricted due to time and resource constraints, which led to the exclusion of false negative data. As such, the assumption of a false negative rate of 0 used in the study may differ from actual clinical practice. Secondly, there were numerous types of neonatal genetic metabolic diseases, and some utility values were not available in the study, requiring reliance on literature values for QALY calculations. Thirdly, the study estimated the

Table 5 Scenario analysis results

Item	Screening group	non-screening group	ICER(CNY/QALY) (screening vs. non screening)
Scenario 1(Assume false negative was 3%)			
Total cost (CNY)	1,001,853	157,303	71,084
QALYs	15.85	3.97	
Scenario 2(Assume false negative was 10%)			
Total cost (CNY)	1,003,254	157,303	75,157
QALYs	15.22	3.97	
Scenario 3(Assume cost discount rate was 3%)			
Total cost (CNY)	1008068.117	202573.5775	64,407
QALYs	16.47	3.97	
Scenario 4(Assume cost discount rate was 1%)			
Total cost (CNY)	1,023,691	285,458	59,029
QALYs	16.47	3.97	

hospitalization cost of late diagnosis to be double that of early diagnosis, based on the data available, which may not accurately reflect actual clinical practice. Lastly, we did not consider medicine cost in the study, though majority medicine cost of screening group and non-screening group could be basically offset in the incremental analysis, there was still a little difference in the two groups.

Conclusion

Major national strategic plans such as the "Healthy China 2030" Plan Outline and the "Decision of the Central Committee of the Communist Party of China and the State Council on Optimizing Fertility Policies to Promote Long-term and Balanced Population Development" all took the prevention and reduction of birth defects as important goals. Although our work has inherent limitations due to modeling and limited available information, our study emphasizes that MS/MS screening of neonatal genetic metabolic diseases can be considered cost-effective within the reported range of willingness-to-pay thresholds in China. Considering these findings, the implementation of this screening method in clinical practice is encouraged.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12962-025-00608-w.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author contributions
Dunming contributed to the study design, data collection, model construction and manuscript writing. Jiaqi contributed to the literature review and data collection. Shimeng Liu contributed to the manuscript review. Yi Yang contributed to manuscript review and data process. Prof. Chen contributed to the conception, design, execution, and manuscript review.

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Data availability
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
The study was approved by the Shanghai Children's Hospital, Shanghai Jiao Tong University (IRB approval number: 2019R071-F03).

Consent to publish
All authors consent to the publication of this manuscript in Cost Effectiveness and Resource Allocation, acknowledging that the content has not been previously published and is not under consideration for publication elsewhere.

Competing interests
The authors declare no competing interests.

Consent to participates
We obtained informed consent from all participants prior to their involvement in the study, ensuring their voluntary participation and understanding of the research aims and procedures.

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