

# BMJ Open Introducing the non-invasive prenatal testing for detection of Down syndrome in China: a cost-effectiveness analysis

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## ABSTRACT

**Objective** This study aimed to compare the health economic value of a non-invasive prenatal testing (NIPT) strategy against a second-trimester triple screening (STS) strategy for the detection of Down syndrome based on real-world data from China.

**Design** A decision-analytical model was developed to compare the cost-effectiveness of five strategies from a societal perspective. Cost and probability input data were obtained from the real-world surveys and published sources.

**Setting** China.

**Participants** Women with a singleton pregnancy.

**Interventions** The five strategies for screening were: (A) maternal age with STS (no NIPT); (B) STS plus NIPT screening; (C) age-STS plus NIPT screening (the currently referral strategy in China); (D) maternal age with NIPT screening and (E) universal NIPT screening.

**Main outcome measures** Incremental cost-effectiveness ratios (ICERs) per additional Down syndrome case terminated, univariate and probabilistic sensitivity analysis and cost-effectiveness acceptability curves were obtained.

**Results** Strategy A detected the least number of Down syndrome cases. Compared with the cheapest Strategy B, Strategy D had the lowest ICER (incremental cost, US\$98 944.85 per additional Down syndrome case detected). Strategy D had the highest probability of being cost-effective at the willingness-to-pay level between US\$110 000.00 and US\$535 000.00 per additional Down syndrome case averted. Strategy E would not be cost-effective unless the unit cost of the NIPT could be decreased to US\$60.50.

**Conclusion** Introducing NIPT screening strategies was beneficial over the use of STS strategy alone. Evaluating maternal age in combination with the NIPT screening strategy performs better than China's currently referral strategy in terms of cost-effectiveness and safety. Lowering the price of NIPT and optimising payment methods are effective measures to promote universal NIPT strategies in China.

## INTRODUCTION

Down syndrome, which is caused by trisomy 21, is the most frequently occurring autosomal aneuploidy and is associated with delayed physical growth, neurocognitive retardation and other medical issues.<sup>1</sup> Antenatal screening for Down syndrome, prior

## Strengths and limitations of this study

- From a societal perspective, this study compared the costs and health outcomes of five different screening strategies for Down syndrome, which cover the introduction of non-invasive prenatal testing strategies and second-trimester triple screening (STS) strategy in China.
- Using context-specific real-world information on probability and cost parameters from a survey in Fuyang City allowed an accurate evaluation in a policy-specific context.
- The findings may provide evidence for other developing countries where STS is more common than first-trimester combined screening in clinical practice.
- Considering the differences in the clinical practice and cost of Down's screening across countries, evidence of effectiveness must be cautiously interpreted when applied to other settings.

to a definitive diagnosis, is a routine practice in many countries. Traditional screening methods are based on combinations of advanced maternal age and maternal serum biomarkers, with or without ultrasonographic 'nuchal translucency (NT)' during the first and/or second trimester.<sup>2</sup> Novel non-invasive prenatal testing (NIPT) is a promising technology that uses cell-free fetal DNA that originates from the placenta and is present in the maternal blood between weeks 11 and 22 of pregnancy. NIPT can ensure more significant prenatal detection of Down syndrome (detection rate (DR) of approximately 99%) and a lower false-positive rate (FPR; 0.0%–0.2%) than conventional screening tests, such as first-trimester combined screening (FTCS; NT with maternal serum biomarkers; DR of 92%; FPR of 7%) and second-trimester triple screening (STS) (DR of 79%, FPR of 4%).<sup>3–5</sup> These advantages contribute to the mitigation of the risk associated with invasive diagnostic testing.<sup>6</sup> Increasingly, guidelines in a number of countries support the use of NIPT for prenatal screening in pregnant women.<sup>7–9</sup>

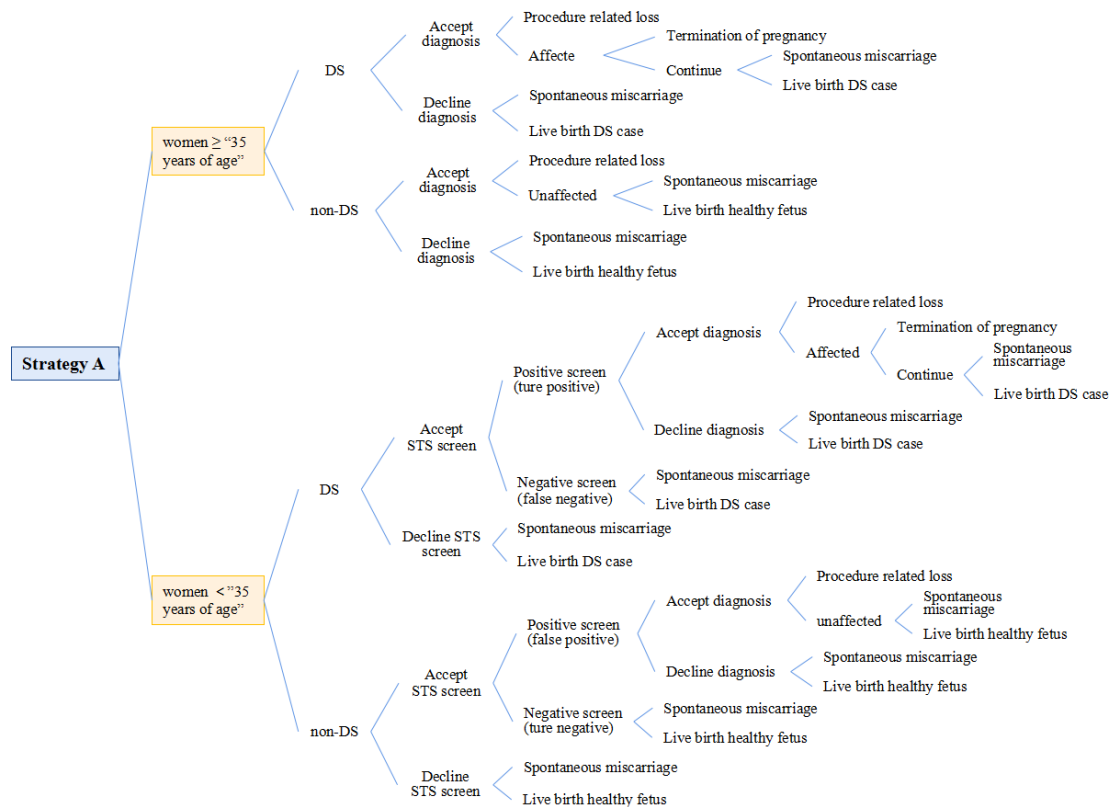
**Table 1** Five prenatal screening strategies in the model

Strategies	Name of the strategy	Components of prenatal screening strategies for Down syndrome
Strategy A	Maternal age with STS (age-STS) screening	<ol style="list-style-type: none"> <li>1. For women <math>\geq 35</math> years of age, the invasive diagnostic tests (amniocentesis (AC) or percutaneous umbilical cord puncture for the prenatal diagnosis) were directly offered.</li> <li>2. For women <math>&lt; 35</math> years of age, STS (nuchal translucency (NT), maternal serum markers such as unconjugated estriol (uE3), free <math>\beta</math>-human chorionic gonadotrophin (<math>\beta</math>-HCG) and alpha-fetoprotein (<math>\alpha</math>-FP) in the second trimester) was offered; and women who were determined to have intermediate-risk or high-risk group by STS (a cut-off between 1/1000–1/270 and <math>\geq 1/270</math>, respectively) would undergo the invasive diagnostic tests (figure 1).</li> </ol>
Strategy B	STS plus NIPT screening	All pregnant women in 14–22 gestational weeks were offered the STS test. Women with screening results indicating an intermediate-risk or high-risk of a fetus with Down syndrome were considered for further NIPT screening; only women testing NIPT-positive would undergo the invasive diagnostic tests (online supplemental appendix figure a).
Strategy C	Age-STS plus NIPT screening	<ol style="list-style-type: none"> <li>1. All women <math>\geq 35</math> years of age were directly offered the invasive diagnostic tests.</li> <li>2. Women <math>&lt; 35</math> years of age were offered the STS test, and intermediate-risk or high-risk pregnancies were considered for further NIPT screening; only women testing NIPT-positive would undergo the invasive diagnostic tests (online supplemental appendix figure b).</li> </ol>
Strategy D	Maternal age with NIPT screening	<ol style="list-style-type: none"> <li>1. For women <math>\geq 35</math> years of age, NIPT was directly offered. Women who were identified to be at high-risk would undergo the invasive diagnostic tests.</li> <li>2. All women <math>&lt; 35</math> years of age were offered STS, and intermediate-risk or high-risk pregnancies were considered for further screening by NIPT; and only women who tested NIPT-positive would undergo invasive diagnostic tests (online supplemental appendix figure c).</li> </ol>
Strategy E	Universal NIPT strategy	All women were offered NIPT, and women who tested NIPT-positive would undergo the invasive diagnostic tests (online supplemental appendix figure d).

NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

Compared with FTCS, STS is the most widely performed screening method in mainland China because of the availability and convenience of this test.<sup>5</sup> In clinical practice, most pregnant women can easily miss undergoing primary screening in the first trimester. Moreover, the NT test, which requires experts with demonstrated expertise in fetal ultrasound, is not widely available in the settings with scarce health resources and a large population. Therefore, screening in the second trimester is commoner than that in the first trimester. In recent years, NIPT with higher safety and accuracy has become available in China. The National Health Commission (formerly China's National Health and Family Planning Committee) has, since 2016, specified guidelines for the use of high-throughput, NIPT for autosomal aneuploidy.<sup>10 11</sup> Currently, in China, for pregnant women in the second trimester, NIPT is offered as an optional test for those women who (1) are younger than 35 years, and (2) have STS results indicative of intermediate or high risk; however, an invasive test is offered for pregnant women aged 35 years or older directly.<sup>12</sup>

There is a trend to include NIPT under public medical insurance coverage; however, currently NIPT is not covered by insurance or is only partially reimbursed in most countries.<sup>13 14</sup> Moreover, the cost of NIPT varies widely, which creates a potential financial burden for pregnant women in low-income and middle-income countries.<sup>15</sup> These factors may further limit the widespread use of NIPT.<sup>16</sup> In China, the price of NIPT in the private sectors varies from US\$202.49 to US\$332.46, as the cost is only partially covered by health insurance in most provinces, pregnant women may have to bear the cost for this service. However, STS costs less than US\$45.33, is covered by health insurance or local government policies in most provinces, and pregnant women are more likely to choose STS over NIPT, despite the higher DR of NIPT for Down syndrome screening.<sup>4 5 17</sup> Therefore, the clinical application of NIPT has been partly restricted. In order to maximise the advantages of NIPT and improve its clinical application, in April 2017, the government initiated a free NIPT service programme in Fuyang City, located in



**Figure 1** An algorithm of the flow of pregnant women for screening strategies. Strategy A, testing flow of pregnant women when combining maternal age with the STS (age–STS) screening strategy. DS, Down syndrome; STS, second-trimester triple screening.

eastern China, whereby through negotiation with private sector, the local government purchased NIPT services for US\$112 per case and provided free fetal chromosome aneuploidy (trisomy 21, 18 and 13) screening for all pregnant women. The potential cost and performance of implementing Fuyang’s free NIPT service programme for first-line screening of Down syndrome remains to be evaluated. Therefore, healthcare authorities have been concerned whether this screening strategy can be widely implemented as compared with the referral strategy.

The cost-effectiveness among the available prenatal screening strategies for Down syndrome is unapparent, given the diversity across different health service systems and analytical perspectives. Walker *et al*<sup>18</sup> indicated that the use of NIPT for first-line testing is beneficial in terms of the number of Down syndrome cases detected and the number of miscarriages, despite the considerably higher cost than the first-trimester and second-trimester screening tests.<sup>18</sup> A recent systematic review stated that universal NIPT is more effective and costlier than the usual screening, and that the cost-effectiveness of contingent NIPT is uncertain, given that NIPT ranges from being dominant to a dominated strategy.<sup>19</sup> Furthermore, the cost-effectiveness results are significantly affected by analytical perspectives, test accuracy, uptake rate of the tests and the unit cost of NIPT in the sensitivity analysis.<sup>19–20</sup> Most studies adopted FTCS as a comparator,

despite its good performance, is not widely implemented in some developing countries because of resource constraints. Moreover, previous studies only considered direct medical costs during the screening procedure. Thus, the previously reported results do not provide enough evidence for developing countries.

This study aimed to address these gaps in clinical practice and the existing cost-effectiveness studies with the following objectives: (1) to compare the costs and performance outcomes of prenatal screening with STS and NIPT within a singleton pregnancy population from a societal perspective; (2) to identify whether China’s referral strategy is optimal and (3) to determine whether universal NIPT screening can be promoted based on government-funded projects.

## METHODS

### Decision analytic model

The decision-analytical model was constructed using decision analysis software (TreeAge Pro 2019). The costs and health outcomes were assessed using five prenatal screening strategies for Down syndrome from a societal perspective.

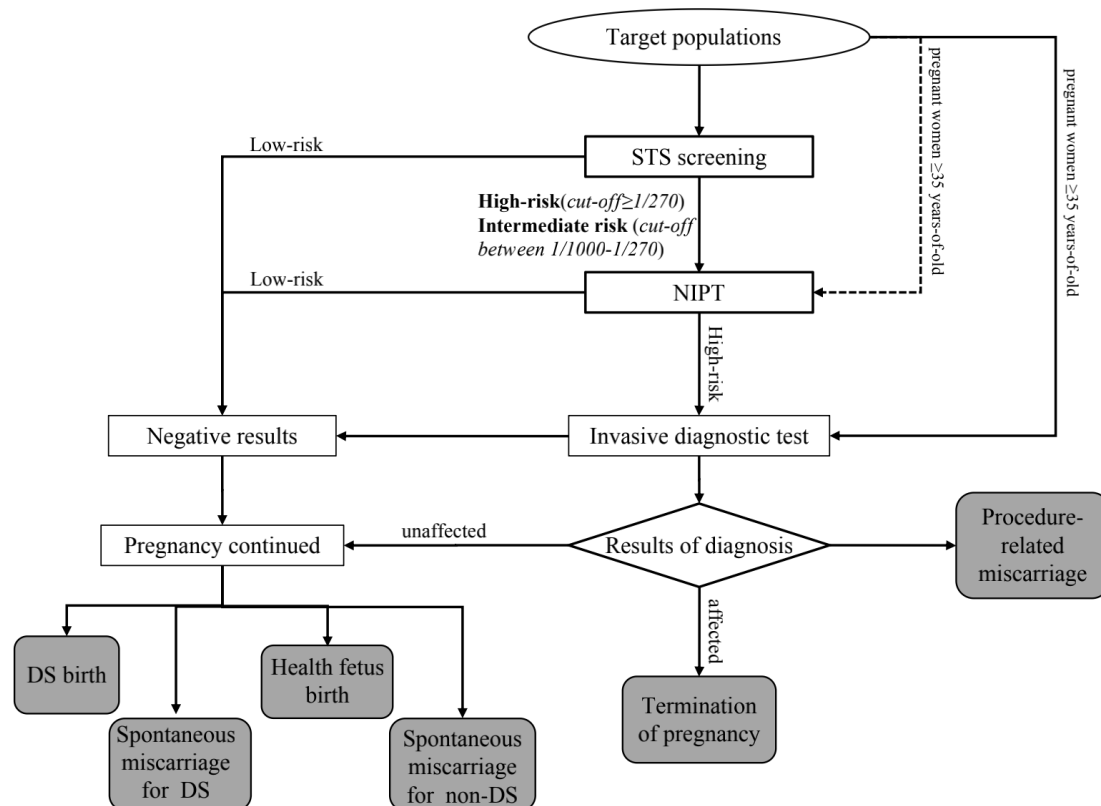
The five strategies compared in the analysis were: (1) Strategy A: maternal age with STS (age–STS) screening (only STS); (2) Strategy B: STS plus NIPT screening (NIPT as a second-line test); (3) Strategy C: age–STS plus

NIPT screening which is recommended by the China National Health Committee; (4) Strategy D: maternal age with NIPT screening and (5) Strategy E: the universal NIPT strategy, which is fully funded by the local government and is currently implemented in Fuyang City. The pregnant women pathways for all strategies and the model structure for Strategy A are described in [table 1](#) and [figure 1](#), and the details of the model structure are reported in online supplemental appendix 1 in the supplementary materials. In all strategies, ultrasonographic NT measurements were excluded from the model because they would not be widely available in China. Our study focused only on fetal trisomy 21, although NIPT has higher sensitivity and specificity in screening for trisomy 18 and 13 than the traditional screening tests.<sup>21</sup> Trisomy 21 is the most common birth defect that is being screened for and supported by clinical standards. Furthermore, the fetal survival rates in trisomy 13 and 18 are very low (frequently, they would result in spontaneous abortion), therefore, the benefits of NIPT are relatively limited as compared with those for trisomy 21.

Six health outcomes were calculated: (1) Down syndrome cases that were detected and terminated with the informed consent of the pregnant women; (2) live-birth Down syndrome cases; (3) spontaneous miscarriage of a Down syndrome fetus; (4) live birth of a healthy fetus; (5) spontaneous miscarriage of a non-Down syndrome fetus; (6) procedure-related losses (PRLs) caused by invasive diagnostic test ([figure 2](#)).

## Data sources

[Table 2](#) lists the relative parameters included in the model. The population-based data and the uptake rate of prenatal screening and diagnosis tests for Down syndrome were calculated based on official records from April 2017 to October 2018 that were provided by Fuyang City People's Hospital (FCPH), Fuyang Health Commission and Fuyang Maternal and Child Healthcare Hospital. In 2018, the total number of pregnant women was approximately 100 000, of which 6.85% were associated with advanced maternal age ( $\geq 35$  years of age). The calculation showed that 80% of women with a singleton pregnancy (including women  $\geq 35$  years of age) underwent NIPT. According to previous studies, the sensitivity and specificity of NIPT for trisomy 21 were 99.50% (95% CI 98.7% to 99.8%) and 100% (95% CI 99.9% to 100%), respectively.<sup>4</sup> For STS, the prenatal screening uptake rate was assumed to be 75%, and the sensitivity and specificity were 79% (95% CI 72% to 85%) and 96% (95% CI 94% to 97%), respectively.<sup>5</sup> Moreover, 60% of the pregnant women with a high probability of aneuploidy on STS were assumed to opt directly for invasive diagnostic tests. Meanwhile, it is assumed that none of the women with a high probability of aneuploidy after NIPT declined invasive diagnostic testing. Overall, 95% of women underwent elective abortion due to a diagnosis of trisomy 21 that was confirmed by invasive diagnostic tests. With regard to the adverse effects associated with invasive diagnostic tests, the proportion of PRLs was 0.30%.<sup>6</sup>



**Figure 2** Six health outcomes included in the prenatal screening pathway for Down syndrome fetuses. DS, Down syndrome; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

**Table 2** Relative variables in the decision-analytical model

Parameters	Base value	Range	Distribution	Sources*
Epidemiology, %				
Incidence of T21	0.075	0.0099–0.1470	–	25–27
Incidence of T21 in women ≥35 years old	0.29	0.282–1.160	–	25–27
Incidence of T21 in women <35 years old	0.059	0.031–0.088	–	25–27
Percentage of women ≥35 years old	6.846	2.969–6.994	–	A
Clinical practice, %				
STS performance				
Sensitivity, T21	79	72–85	Beta ( $\alpha=119.68$ , $\beta=32.78$ )	5
Specificity, T21	96	94–97	Beta ( $\alpha=699.78$ , $\beta=32.97$ )	5
Uptake rate	75	10–100	Beta ( $\alpha=2.42$ , $\beta=1.60$ )	28,A
Diagnostic uptake rate in high-risk pregnant women	60	18–100	Beta ( $\alpha=1.27$ , $\beta=1.97$ )	29,A
NIPT performance				
Sensitivity, T21	99.5	98.70–99.8	Beta ( $\alpha=937.31$ , $\beta=7.08$ )	4
Specificity, T21	100	99.9–100.0	Beta ( $\alpha=7674.52$ , $\beta=3.84$ )	4
Uptake rate in women ≥35 years old	80	47.80–100.00	Beta ( $\alpha=3.32$ , $\beta=0.83$ )	30,A
Diagnostic uptake in NIPT-positive pregnant women	100	–	–	B
Uptake in Strategy E	80	10–100	Beta ( $\alpha=5.42$ , $\beta=1.39$ )	31,A
Uptake in STS-positive pregnant women	95	10–100	Beta ( $\alpha=2.57$ , $\beta=2.04$ )	30 32,A
Diagnostic uptake in women ≥35 years old	80	3.42–100	Beta ( $\alpha=27.78$ , $\beta=3.32$ )	30
Rate of procedure-related losses associated with invasive testing	0.30	0.11–0.49	–	6,A
Termination rate of pregnancy for T21	95	0.92–1.00	–	33,A
Rate of spontaneous miscarriage for Down syndrome	25	21–31	–	34
Rate of spontaneous miscarriage for non-Down syndrome	3.50	0.16–12.20	–	35,A

\*Data sources: A means data from local official statistics; B means model assumption based on expert opinion. NIPT, non-invasive prenatal testing; STS, second-trimester triple screening; T21, trisomy 21.

In the model, both direct medical costs and direct non-medical and indirect costs were considered from a societal perspective (table 3). The direct medical costs of health service items were replaced by the local list prices of the FCPH. Among them, the NIPT service was purchased by the local government at US\$112.58 per case. The direct non-medical costs and indirect costs were obtained from a questionnaire survey of 1400 maternal women in FCPH from March to June 2019, which included lost earnings for pregnant women and caregivers due to missing work, transportation costs and accommodation costs during the process of prenatal screening, diagnosis and childbirth. The EpiData database was used to manage the questionnaire survey data, and the mean cost was calculated using MS Excel. The cost parameters are presented in table 3. The model adopted a short-term (1 year) time horizon, therefore, long-term effects related to infants with Down syndrome were not considered, and the costs were not

discounted. All costs were calculated in Chinese Yuan but converted and presented in US\$ (using the 2018 yearly average currency exchange rate: 6.6174 CNY=1 US\$).

### Economic analysis

A cohort of 100 000 pregnant women was simulated in the model, corresponding to the current estimated annual number of pregnant women in Fuyang City. The effectiveness and total cost of each screening strategy were calculated. Effectiveness was measured in terms of the number of Down syndrome cases that ended in the termination of pregnancy with the informed consent of the pregnant woman. The cost-effectiveness (CE) ratio was defined as the cost per case of Down syndrome that was averted. Meanwhile, to determine which strategy was optimal, the incremental cost-effectiveness ratios (ICERs) were calculated between each strategy and the cheapest strategy. The ICER refers to the difference in the costs

**Table 3** Relative variables in the decision-analytic model

Parameters	Base value	Range	Distribution	Sources**
Costs, US\$				
Direct medical costs				
Registration fee	1.74	1.21–2.27	–	A
Cost of STS	36.27	21.16–45.34	Gamma ( $\alpha=16.35$ , $\lambda=0.50$ )	A
Cost of NIPT	112.58	45.34–362.28	Gamma ( $\alpha=6.79$ , $\lambda=0.03$ )	A
Cost of genetic counselling	1.74	1.21–2.27	–	A
Cost of invasive diagnosis	876.48	717.80–876.48	Gamma ( $\alpha=206.66$ , $\lambda=0.24$ )	A
Cost of pregnancy termination	423.13	377.79–453.35	–	A
Cost of procedure-related losses	528.91	453.35–604.47	–	A
Cost of spontaneous abortion	166.23	54.40–204.01	–	A
Cost of natural labour	1133.38	755.58–1511.17	–	A
Direct non-medical costs (transportation and accommodation costs of pregnant women and caregivers)				
During screening, STS	1.51	0–3.02	–	A
During screening, NIPT	1.51	0–15.11	–	A
During diagnosis	4.53	0–24.18	–	A
During childbirth	3.02	0–7.56	–	A
Indirect costs (lost earnings for pregnant women and caregivers)				
During screening, STS	41.01	40.00–63.84	–	A
During screening, NIPT	44.03	18.89–53.59	–	A
During diagnosis	41.50	40.00–137.35	–	A
During childbirth†	138.98	99.90–218.69	–	A

\*Data sources: A means data from local official statistics.

†Calculation of the indirect costs of lost earning during childbirth only includes caregivers, because lost earning for pregnant women in China is covered by maternity insurance.

NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

between the two strategies divided by the difference in the number of Down syndrome cases detected by the two strategies ( $ICER=\Delta C/\Delta E$ ). This ratio indicates the incremental cost of using one screening strategy compared with the other per additional case of Down syndrome that is averted.

### Sensitivity analyses

Univariate sensitivity analyses and probabilistic sensitivity analyses (PSA) were conducted. One-way sensitivity analyses were conducted to determine the impact of relevant parametric values on the cost-effectiveness ratios. The parameters were determined according to the available literature evidence and expert opinions. The impacts of the following changes on the outcomes were assessed: first, NIPT when used as a part of the prenatal screening, its uptake rate could increase as a result of exemption of out-of-pocket expenses; second, the cost per NIPT could range from US\$45.34 to US\$362.28. PSA were conducted to determine the overall uncertainty by repeating the Monte Carlo simulation 1000 times. For each repetition, new parametric values were obtained from the parameter distributions shown in tables 2 and 3. Gamma distributions were fitted to costs, whereas probability parameters were

drawn from the beta distributions. The cost-effectiveness acceptability curves (CEACs) are presented graphically.

### Patient and public involvement

The pregnant women were not invited to comment on the study design and were not consulted to interpret the results. The pregnant women were not invited to contribute to the writing or editing of this paper.

## RESULTS

### Economic analysis

The results for each of the Down syndrome screening strategies are listed in table 4. Strategy A resulted in the detection of 33.55 Down syndrome cases, with a greater number of live-birth Down syndrome cases (30.87), and the greatest number of PRL cases of 21.52. The number of Down syndrome cases detected for Strategy B was 39.78, and the number of PRL cases was only 0.13. Moreover, Strategy B was the cheapest strategy, with a total cost of US\$7 671 818.41. Strategies C and D resulted in 44.20 and 44.12 Down syndrome cases detected, respectively. Nevertheless, Strategy C resulted in more PRL cases than Strategy D (16.52 vs 0.14). Strategy E resulted in

**Table 4** Cost-effectiveness analysis results

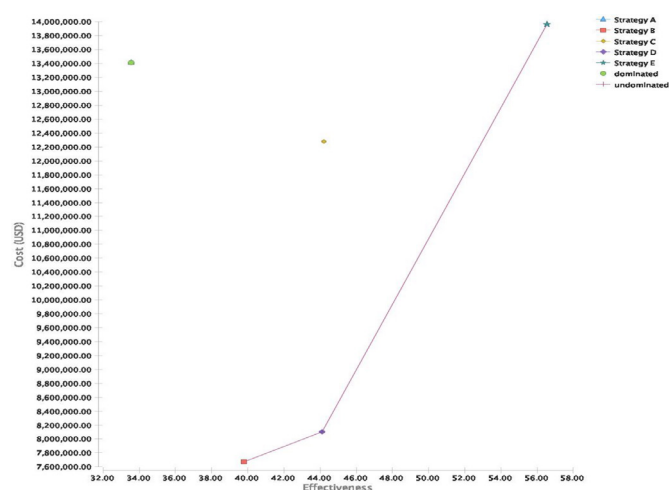
Screening and diagnostic strategy	Strategy A	Strategy B	Strategy C	Strategy D	Strategy E
Effectiveness (number of Down syndrome cases terminated)	33.55	39.78	44.20	44.12	56.54
Number of live-birth Down syndrome cases	30.87	26.32	22.86	22.91	13.71
Number of spontaneous miscarriages for Down syndrome cases	10.29	8.77	7.62	7.64	4.57
Number of spontaneous miscarriages for non-Down syndrome cases	3496.63	3497.38	3453.12	3497.38	3497.38
Number of procedure-related pregnancy losses	21.52	0.13	16.52	0.14	0.18
Number of live births of healthy fetuses	96 407.14	96 427.63	96 455.68	96 427.80	96 427.63
Total	100 000.00	100 000.00	100 000.00	100 000.00	100 000.00
Cost, US\$	13 413 465.50	7 671 818.41	12 278 635.67	8 101 239.07	13 964 988.03
C/E	399 813.70	192 833.84	277 810.17	183 606.98	246 971.86
Incremental cost, US\$	5 741 647.09	–	4 606 817.26	429 420.66	6 293 169.62
Incremental effectiveness	–6.24	–	4.41	4.34	16.76
ICER	–920 135.75	–	1 044 629.76	98 944.85	375 487.45

Strategy A, maternal age with STS (age-STs) screening, Strategy B, STS plus NIPT screening, Strategy C, age-STs plus NIPT screening, Strategy D, maternal age with NIPT screening and Strategy E, universal NIPT screening.

ICER, incremental cost-effectiveness ratio; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

the detection of the highest number of Down syndrome cases (56.54) and the fewest number of live-birth Down syndrome cases (13.71). The total cost of Strategy E was US\$13 964 988.03. [table 4](#) shows the incremental costs and outcomes using Strategy B as the comparator. Strategy D has the lowest ICER, with an incremental cost of US\$98 944.85 per additional Down syndrome case detected.

[Figure 3](#) shows that Strategies A and C were absolute-dominated and extended-dominated strategy, respectively,

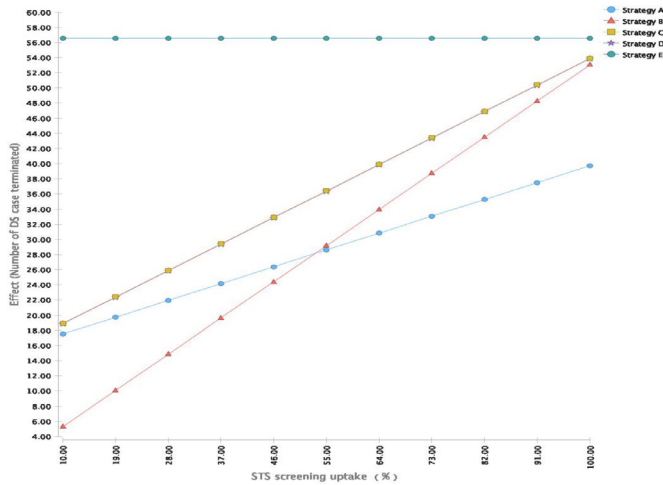


**Figure 3** Cost-effectiveness analysis results. Strategy A: maternal age with STS (age-STs) screening, Strategy B: STS plus NIPT screening, Strategy C: age-STs plus NIPT screening, Strategy D: maternal age with NIPT screening and Strategy E: universal NIPT screening. NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

which might be rejected as alternative strategies. In contrast, Strategies B, D and E could possibly be ideal in different contexts.

### Univariate sensitivity analyses

Univariate sensitivity analysis was performed on the key variables using the ranges shown in [tables 2 and 3](#). In the one-way sensitivity analysis, when the screening uptake rate with STS in pregnant women exceeded 53.00%, the number of Down syndrome cases detected in Strategy B surpassed those in Strategy A, and the number of Down syndrome detected in Strategies D and C was always better than the number of cases detected in Strategy B ([figure 4](#)). When the screening uptake rate with NIPT in advanced maternal age pregnancies exceeded 80.00%, the number of Down syndrome cases detected in Strategy D would surpass those of Strategy C ([figure 5](#)). When the NIPT uptake rate in STS-positive pregnant women exceeded 60.00%, the number of Down syndrome cases detected in Strategies C and D would surpass those of Strategy A. When this value exceeded 80%, the effectiveness of Strategy B would exceed that of Strategy A. The effectiveness of Strategies C and D was always better than that of Strategy B ([figure 6](#)). When NIPT was adopted as a first-line screening strategy for all pregnant women, the effectiveness of Strategy E would overtake Strategies C and D if the uptake rate of NIPT exceeded 62.53% ([figure 7](#)). When the price of NIPT was between US\$60.60 and US\$193.70, Strategy D had the lowest CE ratio. Moreover, when the cost of NIPT decreased to US\$60.50 or less, Strategy E showed the lowest CE ratio and surpassed

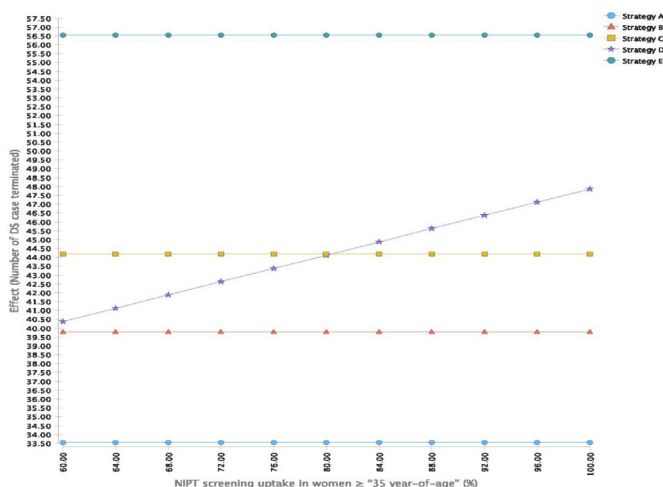


**Figure 4** One-way sensitivity analysis: the impact of STS screening uptake (%) (Strategy A: maternal age with STS (age-STs) screening, Strategy B: STS plus NIPT screening, Strategy C: age-STs plus NIPT screening, Strategy D: maternal age with NIPT screening and Strategy E: universal NIPT screening). DS, Down syndrome; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

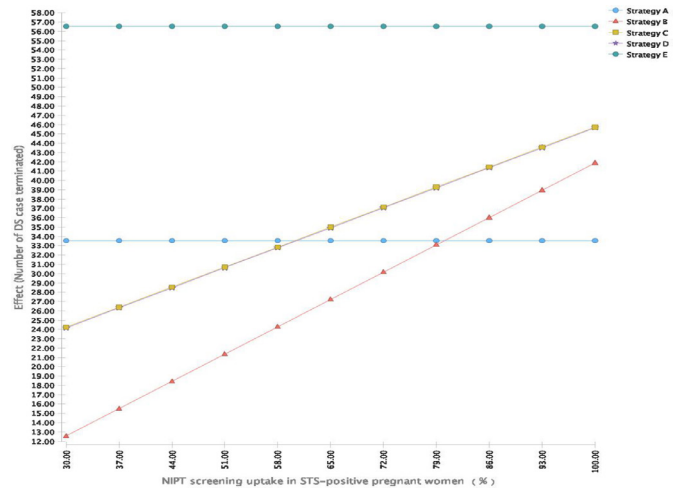
Strategy D (figure 8). This means that, on that occasion, Strategy E could be the best choice for pregnant women to screen fetuses with Down syndrome.

**Probabilistic sensitivity analyses**

The cost-effectiveness planes for the 1000 Monte Carlo simulation (figures 9 and 10) show the results from PSA for the optimal strategy in the model analysis (Strategy D) and the strategy implemented in Fuyang City (Strategy E) vs the current strategy that is followed in China (Strategy C). Figure 9 shows a few spots (34.3%) in the fourth



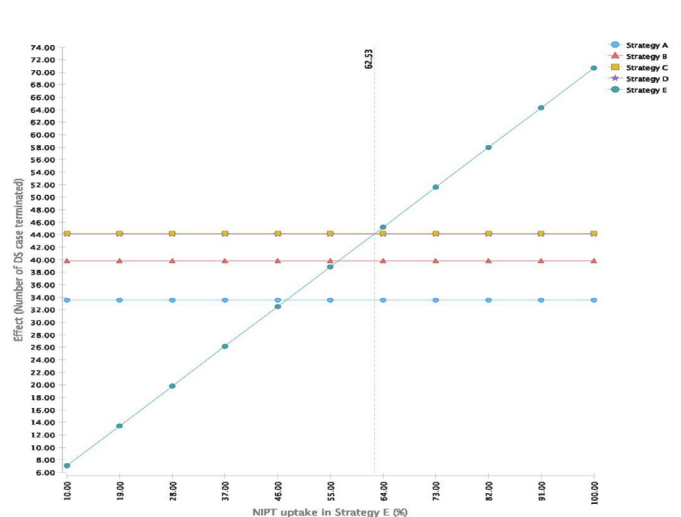
**Figure 5** One-way sensitivity analysis: the impact of the NIPT screening uptake in women ≥35 years of age (%) (Strategy A: maternal age with STS (age-STs) screening, Strategy B: STS plus NIPT screening, Strategy C: age-STs plus NIPT screening, Strategy D: maternal age with NIPT screening, Strategy E: universal NIPT screening). DS, Down syndrome; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.



**Figure 6** One-way sensitivity analysis: the impact of NIPT uptake in STS-positive pregnant women (%) (Strategy A: maternal age with STS (age-STs) screening, Strategy B: STS plus NIPT screening, Strategy C: age-STs plus NIPT screening, Strategy D: maternal age with NIPT screening and Strategy E: universal NIPT screening). DS, Down syndrome; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

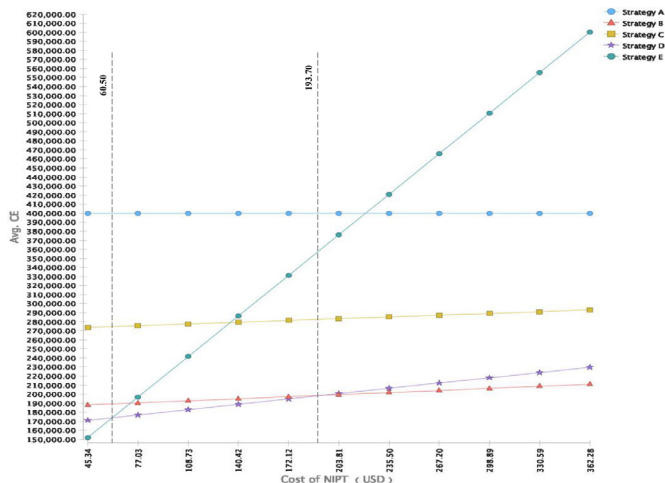
quadrant, where Strategy D was more effective and less costly than Strategy C, and most spots (65.7%) fell in the third quadrant, where Strategy D was less costly than Strategy C. Figure 10 shows that most spots (91.1%) fell in the first quadrant, where Strategy E was more effective and costly than Strategy C.

The CEACs compare the probabilities of being cost-effective for each strategy under different willingness to pay (WTP) per additional case of Down syndrome averted. Figure 11 shows that the most likely cost-effective strategy initially started with Strategy B and switched to Strategy



**Figure 7** One-way sensitivity analysis: the impact of NIPT uptake in Strategy E (%) (Strategy A: maternal age with STS (age-STs) screening, Strategy B: STS plus NIPT screening, Strategy C: age-STs plus NIPT screening, Strategy D: maternal age with NIPT screening and Strategy E: universal NIPT screening). DS, Down syndrome; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.





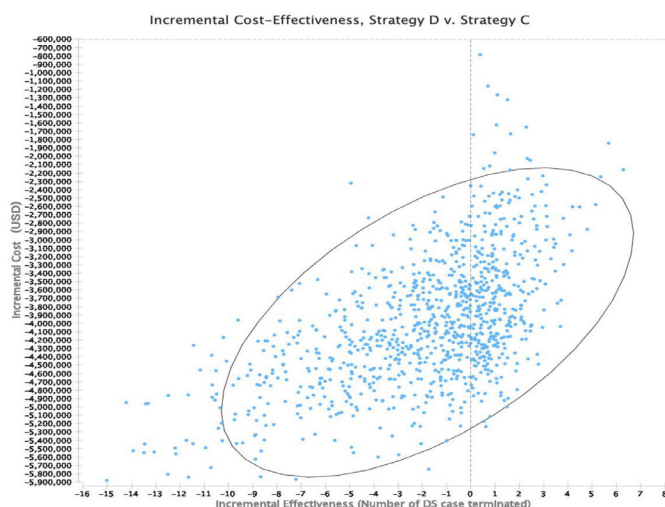
**Figure 8** One-way sensitivity analysis: the impact of the cost of NIPT (Strategy A: maternal age with STS [age-STS] screening, Strategy B: STS plus NIPT screening, Strategy C: age-STS plus NIPT screening, Strategy D: maternal age with NIPT screening, and Strategy E: universal NIPT screening). CE, cost effectiveness; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

D at thresholds of WTP starting at US\$110 000.00. For thresholds of WTP per additional case of Down syndrome averted that exceeded US\$535 000.00, Strategy E had the highest probability of being cost-effective.

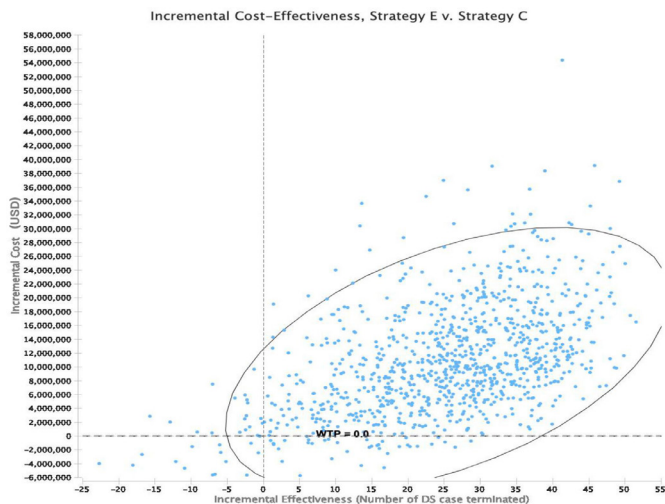
## DISCUSSION

### Introducing NIPT in prenatal screening for Down syndrome is more beneficial than conventional maternal serum screening strategy

This cost-effectiveness analysis from a societal perspective compared five different screening strategies that covered Down syndrome screening strategies in different

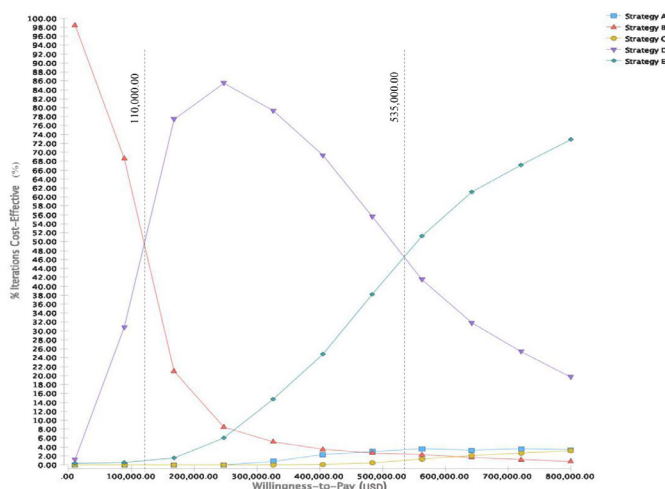


**Figure 9** Incremental cost-effectiveness scatter plot (Strategy D vs Strategy C) (Strategy D: maternal age with NIPT screening, Strategy C: age-STS plus NIPT screening). DS, Down syndrome; NIPT, non-invasive prenatal screening; STS, second-trimester triple screening.



**Figure 10** Incremental cost-effectiveness scatter plot (Strategy E vs Strategy C) (Strategy C: age-STS plus NIPT screening, Strategy E: universal NIPT screening). DS, Down syndrome; NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

regions of China. Meanwhile, using context-specific real-world information on probability and cost parameters from the survey in Fuyang City allows an accurate evaluation in a policy-specific context. Our results demonstrate that, at the current NIPT screening uptake rate and the price of NIPT paid through a government-funded programme, introducing NIPT in prenatal screening strategies for Down syndrome was beneficial over the STS strategy. NIPT with a high DR and a low FPR in prenatal screening for Down syndrome identifies more Down syndrome cases, provides more efficient referral for invasive testing, avoids unnecessary PRL, decreases live-birth Down syndrome cases and saves costs per Down syndrome



**Figure 11** Cost-effectiveness acceptability curve: Five screening strategies (Strategy A: maternal age with STS (age-STS) screening, Strategy B: STS plus NIPT screening, Strategy C: age-STS plus NIPT screening, Strategy D: maternal age with NIPT screening and Strategy E: universal NIPT screening). NIPT, non-invasive prenatal testing; STS, second-trimester triple screening.

case that is detected. In our study, Strategy D was the most optimal choice, instead of Strategy C (the currently referred screening strategy in China). Furthermore, universal NIPT screening (Strategy E) is the most effective option and shows several clinical benefits, although it is also the most expensive strategy compared with other alternative strategies. This result is consistent with some previous cost-effectiveness analysis studies in other countries, including the USA, Australia and some European countries.<sup>19 22 23</sup>

**Compared with the current screening strategy (Strategy C), maternal age with NIPT screening strategy (Strategy D) may be a better prenatal screening strategy for Down syndrome in China**

The current referred screening strategy (Strategy C) directly provided invasive diagnostic tests to pregnant women with advanced maternal age ( $\geq 35$  years), whereas Strategy D offered NIPT first, followed by invasive diagnostic tests for NIPT-positive pregnant women with advanced maternal age. Thus, Strategy D can reduce unnecessary PRLs caused by invasive diagnostic tests. As mentioned in the results of base case analysis, Strategies D and C detected almost the same number of Down syndrome cases (44.12 and 44.20, respectively). However, Strategy D was associated with significantly less miscarriages following invasive procedures (0.14 vs 16.52). Thus, these two strategies had similar effects, but Strategy D was safer for pregnant women. In clinical practice, the safety of the screening strategy is one of the most important factors.<sup>24</sup> Furthermore, Strategy D has a lower CE ratio than Strategy C, which is the most recommended prenatal screening strategy for Down syndrome in China. However, given the safety and cost-saving concerns, Strategy D may be a better choice, especially for pregnant women with advanced maternal age who have a higher risk of Down syndrome fetuses. Furthermore, the CEACs indicate that, at a threshold below US\$535 000.00, Strategy D was always more likely to be cost-effective when compared with Strategy C. This positive evidence might facilitate better resource allocation, considering the extremely limited WTP threshold information in China.

**Reducing the price of NIPT, universal NIPT screening (Strategy E) could become a priority choice**

In the context that NIPT was approved and funded by the government and freely offered to each eligible pregnant woman, Strategy E was not the optimal choice compared with the other strategies at the existing price. The sensitivity analysis indicated that the results were sensitive to the screening uptake rate and cost per NIPT. If the screening adherence of NIPT can be improved to 62.53%, Strategy E would be able to detect the maximum number of Down syndrome cases. The context-specific real-world survey in Fuyang City showed that NIPT screening uptake substantially increased to 80%. Furthermore, the sensitivity analysis showed that when the cost was less than US\$60.50, the CE ratio of Strategy E was the lowest compared with the other strategies. Fuyang City implemented Strategy E, and the cost of NIPT was

US\$112.58 for each pregnant woman, which is relatively low because of the local government's price negotiation. However, local governments might face fiscal pressure if they fully fund the programme in the long term, unless the unit cost of NIPT can be further reduced. Further regulation of the cost of NIPT might be achieved by the national health authority through negotiations with the private sector. Moreover, exploiting better payment methods, such as cost sharing by the government and the patient, might ensure the sustainability of the project.

Some limitations of the study must be considered when interpreting of results. First, the analysis was conducted based on a province in China, whereas the screening in actual clinical practice and costs can be quite different from those in other countries. Therefore, the results must be interpreted cautiously in the context of other settings. However, these findings may provide evidence for other developing countries with similar prenatal screening and diagnostic policies. Second, our study focused only on fetal trisomy 21. Including trisomy 18 and 13 in the model may confer greater clinical benefits of NIPT due to the better detection and less reliance on unnecessary invasive procedures for these aneuploidies. However, such an inclusion will greatly increase the complexity of the model and affect the reliability of the model due to scarce clinical data for aneuploidies. Third, we assumed that the uptake of invasive diagnostic testing after a positive NIPT result was 100%, but it may be lower in clinical practice. For social or religious reasons or out of the fear of miscarriage, some pregnant women do not accept any invasive procedure even when genetic counsellors recommend further testing. Even though assumptions have been made, the decision-analytical modelling can still be used to guide better allocation of resources.

## CONCLUSION

In summary, our economic analysis from a societal perspective of China's pregnant population suggests that the introduction of NIPT as a screening strategy for Down syndrome would be more cost-effective than the use of STS. Given the safety and cost-saving benefits, factoring in the maternal age with the NIPT screening strategy may be a better choice than the currently referred screening strategy in China and should be recommended to pregnant women, especially those who are older than 35 years. The universal NIPT strategy can identify a higher number of Down syndrome cases, reduce unnecessary invasive procedures and incur the highest cost. The NIPT screening strategy is still non-optimal at the current price in the government-funded projects; however, our results indicate that lowering the price of NIPT is an effective measure to promote the acceptance of a universal NIPT strategy.

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