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Cost-effectiveness threshold of first-trimester Down syndrome maternal serum screening for the use of cell-free DNA as a second-tier screening test

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1 **Titre : Evaluation de la valeur seuil la plus cout-efficace des marqueurs sériques du 1er**
2 **trimestre pour l'emploi du test d'ADN circulant dans le dépistage de la trisomie 21 : une**
3 **analyse médico-économique.**

4 Titre court : Analyse cout-efficacité de la stratégie de dépistage de la trisomie 21

5

6 **Title: Cost-effectiveness threshold of first-trimester Down syndrome maternal serum**
7 **screening for the use of cell-free DNA as a second-tier screening test**

8 Short-title: Cost-effectiveness study of Down syndrome screening strategy

9

10 **Institute where the work was conducted:** CHU of Clermont-Ferrand. France

11

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9 **Mots-clefs:** test ADN libre circulant, Trisomie 21, dépistage prénatal, analyse économique,
10 ratio cout-efficacité,

11 **Keywords:** Non-invasive prenatal testing, Down syndrome, prenatal screening, economic
12 analysis, cost-effectiveness ratio.

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1 **Résumé**

2 Introduction : Notre objectif était d'identifier la valeur seuil la plus cout-efficace des
3 marqueurs sériques du 1^{er} trimestre pour l'intégration du test ADN libre circulant en
4 deuxième ligne dans le cadre du dépistage prénatal de la trisomie 21 en France.

5 Matériel et méthodes : Une analyse cout-efficacité a été menée sur 108 121 grossesses
6 uniques en utilisant un modèle de simulation. Les valeurs seuils testées des marqueurs
7 sériques du 1^{er} trimestre étaient comprises entre 1/51 et 1/1000 par pas de 1/50. La valeur
8 seuil la plus coût-efficace a été déterminée par le calcul du ratio coût-efficacité (RCE, coûts=
9 coûts directs médicaux après le dosage des marqueurs du 1^{er} trimestre, efficacité=nombre de
10 cas de trisomie 21 dépisté).

11 Résultat : Dans notre échantillon, 161 cas de trisomie 21 ont été identifiés. Pour une valeur
12 seuil $\geq 1/50$, 47,2% des cas ont été diagnostiqués. Dans le modèle de simulation, pour un seuil
13 $\geq 1/250$, 73,9% des cas de trisomie 21 étaient identifiés, pour un seuil $\geq 1/500$, le pourcentage
14 de détection s'élevait à 78,8% et pour un seuil $\geq 1/1000$, 2 cas supplémentaires ont été
15 identifiés. Le montant des coûts était stable pour un seuil $\geq 1/250$ (978 634€), puis augmentait
16 rapidement pour un seuil $\geq 1/500$ (1 966 576€) et devenait exponentiel pour un seuil $\geq 1/1000$
17 (3 980 216€). Le RCE pour le seuil $\geq 1/500$ était de 38 560.

18 Conclusion : La valeur seuil la plus coût-efficace pour l'implémentation du test ADN libre
19 circulant en deuxième ligne semble être $\geq 1/500$.

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1 **Abstract**

2 Introduction: We aimed to identify the most relevant cost-effectiveness threshold of first-
3 trimester Down syndrome (DS) maternal serum screening (T21T1) for the use of cell-free
4 DNA (cfDNA) as a second-tier test in the French context.

5 Method: A cost-effectiveness analysis was performed on 108 121 singleton pregnancies
6 using a simulation model. The threshold of T21T1 screening was ranged from 1/51 to 1/1000
7 in steps of 1/50. The most relevant threshold was based on cost-effectiveness ratio (CER;
8 costs = direct medical costs after T21T1 screening/ effectiveness = number of DS cases
9 identified).

10 Results: In the sample, 161 cases of DS were identified. At the threshold of $\geq 1/50$, 47.2% of
11 total DS cases were diagnosed. In the simulation model, for a threshold $\geq 1/250$, 73.9% of
12 total DS cases were diagnosed, for $\geq 1/500$, 78.8% and for $\geq 1/1000$, only two additional
13 cases were diagnosed. The slope of the cost increase was slight from threshold $\geq 1/250$ (978
14 634€), then steep up to 1/500 (1 966 576€) and increased exponentially to 1/1000 (3 980
15 216€). The CER was 38 560 for a threshold $\geq 1/500$.

16 Conclusion: The most cost-effective threshold for cfDNA as a second-tier test seems to be \geq
17 1/500. For higher thresholds, costs increase dramatically for only a few additional cases of DS
18 identified.

19

1 **Introduction**

2 Over the last 50 years, prenatal diagnosis procedures and screening have become safer
3 and the capabilities of diagnostic laboratories have expanded[1–6]. Recently, the use of cell-
4 free DNA (cfDNA) has dramatically increased. While cfDNA is considered as a screening
5 test and not a diagnostic test by the scientific community, patients and most physicians see
6 cfDNA as a substitute for foetal karyotyping[7–9].

7 Recently, new guidelines drawn up by the French National Authority for Health (HAS;
8 Haute Autorité de Santé) recommend cfDNA for Down syndrome (DS) screening[10]. These
9 guidelines, based on a cost-effectiveness analysis, recommend cfDNA as a second-tier
10 screening test in women with a risk between 1/51 and 1/1000 after first-trimester combined
11 maternal serum screening (T21T1). Moreover, in high-risk women ($T21T1 \geq 1/50$), invasive
12 testing is proposed but, after clear information, women still have the choice of cfDNA.
13 However, these guidelines were based on simulated data.

14 CfDNA is a reliable technique that should be included in DS screening, but it remains
15 contingent on maternal serum screening and the terms of application need to be carefully
16 defined. It is necessary to identify the most relevant threshold of the calculated risk of DS
17 based on maternal serum markers for the use of cfDNA. Few studies have tested different
18 thresholds of T21T1 to identify the most cost-effective one[11–14]. Even though these studies
19 reached similar conclusions, the number of thresholds tested was limited and there was no
20 step-by-step analysis. The principal objective of this study was to identify the most relevant
21 cost-effectiveness threshold of T21T1 screening for use of cfDNA as a second-tier test, by
22 carrying out an economic analysis, in the French context.

23

24 **Methods**

25 **French prenatal screening for Down syndrome**

1 In France, prenatal DS screening has been regulated by the Ministry of Health since
2 1997[15]. The French DS screening policy is organized at a national scale and since 2010 has
3 been based on three steps. The first consists of first-trimester nuchal translucency (NT) and
4 crown rump length (CRL) measurements (T1US), a cut-off ≥ 3.5 mm leading to chorionic
5 villus sampling (CVS) for karyotyping. The second step consists of first-trimester maternal
6 serum screening (or second-trimester when NT is not performed or when maternal blood
7 sampling is performed after 13⁺⁶ weeks of gestation). First-trimester DS maternal serum
8 screening (T21T1) is performed at 11-13⁺⁶ weeks and combined maternal age, maternal serum
9 markers (pregnancy-associated plasma protein A, PAPP-A, and free beta-human chorionic
10 gonadotropin, hCG β) and nuchal translucency (NT). Karyotyping is offered for a calculated
11 risk $\geq 1/50$. If women have a risk between 1/51 and 1/1000 after first-trimester combined
12 maternal serum screening (T21T1), cfDNA is recommended as a second-tier screening
13 test[10]. The third step consists of two ultrasound scan examinations at 20-22 weeks and 30-
14 32 weeks of gestation.

15

16 **Study population**

17 Our economic analysis was applied to data from 108 121 singleton pregnancies with
18 T21T1 (Autodelfia, dual kit and LifeCycle 4.1 software, PerkinElmer, Turku, Finland) during
19 the year 2015 in the Biomnis Eurofins Laboratory, one of 86 accredited laboratories. Maternal
20 serum markers and NT were expressed as multiple of the median (MoM) for gestational age
21 (expressed in weeks and days of amenorrhea) as estimated by CRL measurement performed at
22 the same time as NT. MoMs were adjusted for three confounding factors (maternal weight,
23 smoking status and ethnicity). In accordance with French law, written informed consent for
24 biochemical testing was obtained from each woman.

1 If chorionic villous sampling or amniocentesis was performed, a second written consent
2 was needed for foetal karyotyping. The database has been reported to the French Data
3 Protection Authority (CNIL: Commission Nationale de l'Informatique et des Libertés) as
4 CNIL no. 1839545 V1.

5 **Economic analysis**

6 *Identification of DS in the database*

7 Cases in which embryo reduction was performed and cases in which a vanishing twin
8 was detected at ultrasound scan were excluded. Because of the French policy using NT as
9 contingent screening, all cases with NT ≥ 3.5 mm were excluded from the analysis. DS cases
10 were identified prenatally when women had T21T1 screening $\geq 1/250$ (based on French
11 policy of DS screening strategy in 2015) or when anomalies were detected at ultrasound scan
12 or at birth when the patient did not opt for an invasive procedure or for termination of
13 pregnancy or when T21T1 was $< 1/250$ or without ultrasound anomalies. To sum up, among
14 108 121 singleton pregnancies 161 cases of DS were diagnosed, 124 by T21T1 screening, 16
15 by means of abnormal ultrasound scans and 21 at birth. All karyotyping results for the cohort
16 were collected by the accredited laboratory, which performed serum marker screening.

17 *Simulation model*

18 The simulation model was based on actual data regarding DS status (including overall
19 cases) and T21T1 results. Three variables were simulated based on assumptions from the
20 international literature or expertise. Those variables were the women's characteristics (body
21 weight and ethnicity), cfDNA (sensitivity, specificity and failure rate) and karyotyping
22 acceptance rate. Women whose T21T1 results indicated a risk $\geq 1/1000$ were considered to be
23 part of a high-risk group in the simulation model, so the acceptability of cfDNA testing and
24 karyotyping was presumed to be high. Table 1 presents the percentages with the 95%
25 confidence intervals of each variable included in the model.

1 *Cost-effectiveness analysis*

2 A cost-effectiveness analysis (CEA) was performed for different thresholds and
3 calculated risk as a discrete variable of T21T1 screening was used to identify the most
4 relevant threshold. Figure 1 depicted the decision tree model used in the analysis describing
5 the clinical pathway where cfDNA was used as a second-tier test if T21T1 screening was
6 positive starting from $\geq 1/50$ to $\geq 1/1000$ by step of $1/50$.

7 The perspective chosen was that of the third-party payer, ie, the French national health
8 insurance fund (Caisse Nationale d'Assurance Maladie). Expressed in euros, the costs
9 included were the direct medical costs after T21T1 screening: the cost of karyotyping, the
10 invasive technique and the procedure used (chorionic villus sampling or amniocentesis) and
11 of karyotype analysis (Table 1). Costs were calculated for the sample of 108 121 women. The
12 incremental cost per DS case diagnosed was also calculated. The medical and societal costs of
13 an undetected DS-affected child were not taken into account. The costs and effectiveness
14 criteria were based on data from a single year and have not been actualized[16,17].

15 The most relevant threshold of T21T1 screening for use of cfDNA as a second-tier test
16 was based on cost-effectiveness ratio (CER). The criterion of effectiveness considered was the
17 number of DS cases diagnosed. The CER was calculated as follows: CER = total cost for each
18 threshold/number of DS cases diagnosed at each threshold. Univariate sensitivity analysis was
19 used to test the robustness of the results by varying the cost of cfDNA.

20

21 **Statistical analysis**

22 A descriptive analysis of the data base was done for quantitative variables with standard
23 deviation and for qualitative variables with 95% confidence interval (95% CI). The cohort's
24 advance through the decision tree was based on DS prevalence in the actual database, cfDNA
25 (sensitivity and specificity) and screening test participation rates for karyotyping (Table 1)

1 [16–21]. The variation in the failure rate of the cfDNA test as a function of body weight was
2 taken into consideration as was ethnicity[18,22]. Foetal loss due to invasive screening was
3 also considered for each threshold[19]. The threshold of T21T1 screening ranged from 1/51 to
4 1/1000 in steps of 1/50. We used R 3.0.2. Software for this modelling.

5 **Results**

6 **Descriptive analysis of actual data**

7 A total of 108 121 women were included in the study. The mean maternal age was 29.7
8 [standard deviation 4.9] years. Median measurement of NT was 1.4 [95% CI: 0.8; 2.1]. Mean
9 gestational age at T21T1 was 12⁺⁶ WG (11⁺⁰-13⁺⁴). In the sample, DS was diagnosed in 161
10 cases, giving a 0.2% [95% CI: 0.1; 0.2] global prevalence.

11 At the threshold of $\geq 1/50$, among 76 cases of DS diagnosed, 71 were confirmed by
12 foetal karyotyping and 5 after birth when the parents refused prenatal karyotyping (Table 2).

13

14 **Results of the simulation model**

15 For thresholds at 1/51-1/250, 43 additional cases were diagnosed (119 cases, 73.9% of
16 total DS cases). Then, for thresholds at 1/251-1/500, 8 additional cases were diagnosed (127
17 cases, 78.9% of total DS cases). Finally, for thresholds at 1/501-1/1000, 2 additional cases
18 were diagnosed (129 cases, 80.1% of total DS cases). One foetal loss was observed for a
19 threshold of 1/251 (Table 2).

20 Considering that a cfDNA test costs 330 €, the slope of the cost increase was slight from
21 a threshold 1/51-1/250 (978 634 €), then steep up to a threshold 1/251-1/500 (1 966 576 €)
22 and increased exponentially from 1/501 to 1/1000 (3 980 215 €) (Figure 2). From a threshold
23 1/750 to 1/1000, no additional DS case was diagnosed, whereas the cost still increased (Figure
24 2). The CER was 38 560 for threshold 1/51-1/500, 56 471 at 1/51-1/750 and 75 098 at 1/51-
25 1/1000. The incremental cost per DS case diagnosed was 191 637 € for threshold 1/51-1/500,

1 406 014 € at 1/51-1/750 and 735 092 € at 1/51-1/1000. The results were robust irrespective of
2 the cost of cfDNA (Figure 2).

3 Consequently, the most cost-effective threshold seems to be 1/51-1/500 as 127 (79.9% of total
4 DS cases) DS cases were identified for a total cost of 1 966 576 €, a CER of 38 560 and an
5 incremental cost per DS diagnosed of 191 637 € for a cfDNA cost of 330 € (Table 3).

6

7 **Discussion**

8 In our study based on actual data, the most cost-effective threshold of cfDNA as a
9 second-tier test was 1/51-1/500. For higher thresholds, costs increase dramatically for the
10 diagnosis of only a few additional cases of DS.

11 This is the first economic study based on actual data in the general population to assess
12 by a step by step analysis the inclusion of cfDNA in the French strategy of DS screening,
13 following new national guidelines. The study was based on a large sample: 20.4% of women
14 who underwent T21T1 in 2015[23]. Because of exclusion of high NT, the prevalence of DS in
15 our sample is 0.2% whereas in France in 2012 the estimated prevalence was 0.3%[24].
16 However, even if the prevalence of DS in our sample is low, the percentage of DS cases
17 identified by screening remains stable, especially at the threshold from 1/51-1/750 to 1/51-
18 1/1000, where no more cases of DS were identified.

19 First-trimester screening and cfDNA (based on the 1/1000 threshold[10]) identified up
20 to 129 cases (corresponding to a threshold 1/51-1/750) and missed 11 cases, all of which were
21 diagnosed by prenatal karyotyping. Considering the most cost-effective threshold of 1/51-
22 1/500, only two more DS cases were missed, but they may be identified later by second-
23 trimester ultrasound scan as it has been demonstrated that more than 30% of foetuses with DS
24 can be detected among women classified as low risk after T21T1 screening[25]. Different
25 costs for the cfDNA test were considered in a univariate sensitivity analysis. One limitation of

1 our study is that non-medical indirect costs were not considered[26]. The modelling did not
2 consider the parents' decision based on the screening results. The major ethical and legal
3 principle governing screening and prenatal diagnosis in France is that the final decision to
4 continue or terminate the pregnancy belongs to the parents[27,28]. Other chromosomal
5 aberrations such as trisomy 13 or 18 and sex chromosome abnormalities can be detected by
6 cfDNA[29], however only results for DS were considered as it is the only chromosomal
7 anomaly implemented in the national screening programme.

8 In our study, only the cfDNA contingent strategy was considered since most studies
9 have concluded that universal cfDNA is nowadays too expensive and so irrelevant[13,30]. We
10 are also in accordance with current national French guidelines which recommend cfDNA as a
11 second-tier test[10]. Few studies have tested several thresholds to identify the most cost-
12 effective cfDNA contingent strategy[11,12,14]. Chitty et al., Morris et al. and Nyet et al.
13 demonstrated that the cfDNA contingent strategy remained cost-effective until a threshold of
14 $\geq 1/150$, $\geq 1/500$ and $\geq 1/600$, respectively[11,12,14]. This is in line with our results regarding
15 the dramatic cost increase at $<1/500$. The marginal cost of the cfDNA contingent strategy is
16 very sensitive to the cost of cfDNA. In our study, for high-risk women ($T21T1 \geq 1/50$)
17 karyotyping was systematically proposed. To our knowledge, no study has implemented this
18 strategy in its model.

19 Based on a large series of actual data, the most cost-effective threshold for cfDNA as a
20 second-tier test in first-trimester screening seems to be $1/51$ - $1/500$. In the literature, the
21 optimal threshold is between $\geq 1/150$ and $\geq 1/600$ according to current national guidelines of
22 each country, assuming an unchanging budget[11,12,14,31]. For higher thresholds, costs
23 increase dramatically for only a few additional cases of DS identified. In a recent meta-
24 analysis of economic evaluations of prenatal screening by cfDNA testing, the authors
25 demonstrated that despite heterogeneity between studies mainly because of several time-

1 horizon considerations and different outcomes, the contingent strategy provides the best value
2 for money[30]. On the other hand, the universal strategy appears cost-effective when cost of
3 cfDNA decreases. In our study, the cost of cfDNA is the one used by the French National
4 Table of Laboratory Codes and has not been yet actualized. As already underlined, cost-
5 effectiveness studies results depend mainly of the cost of cfDNA. Another difference is also
6 that many studies with simulated data include controversial future costs for children born with
7 disabilities. However, a lifetime perspective is not appropriate in evaluating the prenatal
8 screening strategy, as it appears unethical to estimate the value of life [32]. In the same way,
9 we did not evaluate the viability of each pregnancy, as our objective was to simulate the foetal
10 loss induced by invasive procedures. Nonetheless, the psychosocial consequences for families
11 of these test results can be considerable and should be evaluated in economic studies[33]. Our
12 choice to evaluate the hospital, rather than societal, point of view of the costs generated by
13 positive test results means that we could not assess the costs of their psychosocial
14 consequences and their effects on pregnancy outcomes[34]. Although these intangible costs
15 are difficult to quantify, they can be approached by questionnaires, which should be used to
16 show the full value of the DS screening strategy to health policy decision makers.

17 We have demonstrated in accordance with the literature that the contingent strategy is
18 cost-effective when cfDNA testing is performed at a threshold $\geq 1/500$. National guidelines
19 should take into account these results, especially in terms of opportunity costs for French
20 society. Sensitivity analyses may be performed to assess validity of the model when cost of
21 cfDNA will decrease as it will be used in routine screening in many countries. New thresholds
22 may be more accurate than those used. The new challenge is to ensure that health
23 professionals have adequate prenatal screening understanding in order to protect women's
24 autonomy when consenting to genetic testing.

25

1 **Conflict of interest**

2 The authors declare that they have no conflict of interest.

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29

1 **Table 1: Values estimated for the variables included in the decision model to determine**
 2 **the most relevant threshold by performing cfDNA as the second-tier test**

	Value	Variations	Costs	References
	(%)	(%) [95%CI]	(€)	
Participation rate				
Karyotype	95.0	[90.0; 100.0]		Experts PEPRADE assumption
Sensitivity & Specificity				
Failure of cfDNA test, all causes combined	2.9	[0.8; 4.6]		Cuckle (2013)
FF < 4% (white, 60 kg, CRL 65 mm)	0.7	[0.2; 77.4]		Ashoor (2013)
Sensitivity of cfDNA test, all studies combined	99.2	[98.5; 99.6]		Gil (2015)
Specificity of cfDNA test, all studies combined	99.9	[99.87; 99.95]		Gil (2015)
Foetal loss after amniocentesis	0.11	[0.00; 0.26]		Akolekar (2015)
Foetal loss after trophoblast biopsy	0.22	[0.00; 1.16]		Akolekar (2015)
Costs and variations of costs included in the economic analysis				
cfDNA test			330	TNCB 2018
Amniocentesis + karyotyping			491	CCAM 2018; TNCB 2018
Chorionic villus sampling + karyotyping			593	CCAM 2018; TNCB 2018

3 cfDNA test: cell-free DNA, FF: foetal fraction, CRL: crown-rump length, CCAM:

4 Classification Commune des Actes Médicaux (French classification of medical procedures),

5 TNCB: Table Nationale de Codage de Biologie (National Table of Laboratory Codes)

6

Table 2: Performance of a conditional Down syndrome screening strategy including cell-free DNA testing as a second-tier test for first-trimester screening

Threshold value	n^a	cfDNA test	TP cfDNA test	FP cfDNA test	FN cfDNA test	Karyotype	Foetal loss	Total Down syndrome diagnosed
≥ 1/50	420	-	-	-	-	76	-	76
1/51-1/100	878	842	72	1	0	153	0	93
1/51-1/150	1430	1365	84	2	0	198	0	104
1/51-1/200	1992	1894	92	3	0	246	0	112
1/51-1/250	2627	2494	98	3	0	290	1	119
1/51-1/300	3108	2953	100	3	0	320	1	122
1/51-1/350	3668	3482	101	3	0	359	1	122
1/51-1/400	4300	4075	103	4	0	406	1	123
1/51-1/450	4905	4649	107	5	0	446	1	126
1/51-1/500	5480	5219	109	5	0	453	1	127
1/51-1/550	6049	5741	110	7	0	511	1	127
1/51-1/600	6698	6361	112	8	0	547	1	128

1/51-1/650	7274	6914	112	8	0	574	1	128
1/51-1/700	7863	7474	113	9	0	605	1	128
1/51-1/750	8429	8006	114	9	0	646	1	129
1/51-1/800	9029	8574	114	9	0	682	1	129
1/51-1/850	9611	9134	114	9	0	712	1	129
1/51-1/900	10187	9682	114	9	0	744	1	129
1/51-1/950	10754	10225	114	9	0	774	1	129
1/51-1/1000	11299	10744	114	9	0	803	1	129

cfDNA test: cell-free DNA test, TP: true positive, FP: false-positive, FN: false negative

^an: number of women concerned based on actual data in the simulation model

Table 3: Costs of the Down syndrome screening strategy considering different costs for cell-free DNA, CER and incremental cost.

Threshold value	cfDNA	cfDNA	cfDNA	cfDNA	CER	Cost per incremental DS diagnosed
	cost 330 euros† (euros)	cost 50 euros ^a (euros)	cost 100 euros† (euros)	cost 200 euros ^a (euros)	cfDNA cost 330 euros ^a (euros)	cfDNA cost 330 euros ^a (euros)
1/51-1/100	359 900	124 140	166 240	250 440	21 171	
1/51-1/150	555 900	173 700	241 950	378 450	19 854	
1/51-1/200	756 585	226 265	320 965	510 365	21 016	
1/51-1/250	978 634	280 314	405 014	654 414	22 759	
1/51-1/300	1 141 171	314 331	461 981	757 281	24 808	
1/51-1/350	1 342 734	367 774	541 874	890 074	29 190	
1/51-1/400	1 564 459	423 459	627 209	1 034 709	33 286	
1/51-1/450	1 774 940	473 220	705 670	1 170 570	35 499	
1/51-1/500	1 966 576	505 256	766 206	1 288 106	38 560	191 637
1/51-1/550	2 171 089	563 609	850 659	1 424 759	42 570	396 149
1/51-1/600	2 395 506	614 426	932 476	1 568 576	46 067	310 283

1/51-1/650	2 592 166	656 246	1 001 946	1 693 346	49 849	408 613
1/51-1/700	2 793 200	700 480	1 074 180	1 821 580	53 715	509 130
1/51-1/750	2 992 982	751 302	1 151 602	1 952 202	56 471	406 014
1/51-1/800	3 197 876	797 156	1 225 856	2 083 256	60 337	474 312
1/51-1/850	3 398 009	840 489	1 297 189	2 210 589	64 113	541 023
1/51-1/900	3 595 882	884 922	1 369 022	2 337 222	67 847	606 981
1/51-1/950	3 793 281	930 281	1 441 531	2 464 031	71 571	672 781
1/51-1/1000	3 980 215	971 895	1 509 095	2 583 495	75 098	7352

cfDNA: cell-free DNA test, CER: cost-effectiveness ratio, DS: Down syndrome

^aThe simulation model used to calculate total cost at each threshold included the failure rate of the cfDNA test, which was performed a second time when the first failed.

Figure legends

Figure 1: Decision tree model of Down syndrome screening using cell-free DNA (cfDNA) testing as a second-tier if first-trimester combined screening is positive, ranging from $\geq 1/50$ to $\geq 1/1000$ by step of $1/50$.

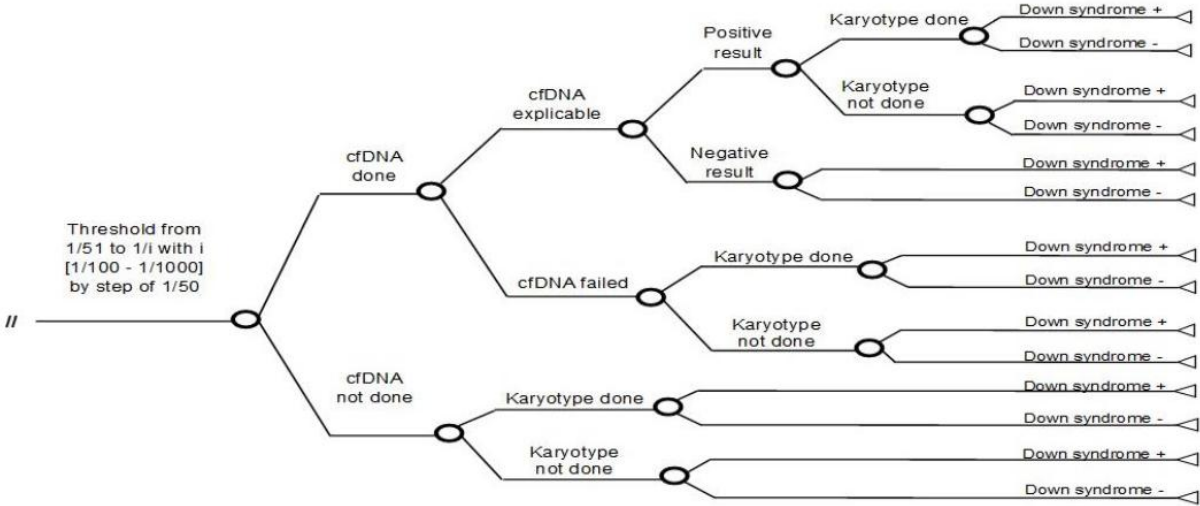


Figure 2: Cost of Down syndrome screening when performing cell-free DNA testing as a contingent strategy for a threshold of first-trimester combined screening 1/51-1/100 to 1/51-1/1000

