Cost of providing cell-free DNA screening for Down syndrome in Finland using different strategies

Cuckle, Howard

2022-03-28

Cuckle , H , Heinonen , S , Anttonen , A-K & Stefanovic , V 2022 , ' Cost of providing cell-free DNA screening for Down syndrome in Finland using different strategies ' , Journal of Perinatal Medicine , vol. 50 , no. 3 , pp. 233-243 . https://doi.org/10.1515/jpm-2021-0467

http://hdl.handle.net/10138/341943
https://doi.org/10.1515/jpm-2021-0467

Corner of Academy

Howard Cuckle, Seppo Heinonen, Anna-Kaisa Anttonen and Vedran Stefanovic*

Cost of providing cell-free DNA screening for Down syndrome in Finland using different strategies

https://doi.org/10.1515/jpm-2021-0467
Received September 12, 2021; accepted November 11, 2021; published online December 3, 2021

Abstract

Objectives: A financial analysis is carried out to assess costs and benefits of providing cell-free DNA screening in Finland, using different strategies.

Methods: Three cell-free DNA screening strategies are considered: Primary, all women; Secondary, those with positive Combined test; and Contingent, the 10–30% with the highest Combined test risks. Three costs are estimated: additional cost for 10,000 pregnancies compared with the Combined test; 'marginal' cost of avoiding a Down syndrome birth which occurs in a pregnancy that would have been false-negative using the Combined test; and marginal cost of preventing the iatrogenic loss of a non-Down syndrome birth which occurs in a pregnancy that would have been false-positive.

Results: Primary cell-free DNA will require additional funds of €250,000. The marginal cost per Down syndrome birth avoided is considerably less than the lifetime medical and indirect cost; the marginal cost per unaffected iatrogenic fetal loss prevented is higher than one benefit measure but lower than another. If the ultrasound component of the Combined test is retained, as would be in Finland, the additional funds required rise to €992,000. Secondary cell-free DNA is cost-saving as is a Contingent strategy with 10% selected but whilst when 20–30% costs rise they are much less than for the Primary strategy and are cost-beneficial.

Conclusions: When considering the place of cell-free DNA screening it is important to make explicit the additional and marginal costs of different screening strategies and the associated benefits. Under most assumptions the balance is favorable for Contingent screening.

Keywords: benefit; cell-free DNA; common trisomies; conventional; cost; nuchal translucency; prenatal screening.

Introduction

A single maternal plasma marker of Down syndrome ('Trisomy 21'), cell-free (cf)DNA, has considerably better screening performance than all conventional multi-marker screening tests. It has a detection rate above 99% and a false-positive rate below 0.2% [1]. By comparison the widely used 'Combined' test, based on first trimester maternal serum pregnancy associated plasma protein (PAPP)-A, free-β human chorionic gonadotrophin and ultrasound nuchal translucency (NT) has a detection rate of at most 87% for a 5% false-positive rate and 74% for a 1% false-positive rate [2]. The aim of this paper is to provide a financial analysis that could be used in assessing whether or not to provide cfDNA screening, particularly in Finland, and if so which screening strategy to adopt.

Currently, in Finland all women are offered free of charge a Combined test for Down syndrome and Edwards syndrome ('Trisomy 18'), including measurement of NT and fetal anatomical assessment. In 2015 the Fetomaternal Medical Center (FMC) of the Department of Obstetrics and Gynecology at Helsinki University Hospital (HUS) began to selectively offer cfDNA screening as the first public hospital in Finland. Women with a singleton pregnancy and either a positive Combined test (Down syndrome risk 1 in 10–250, Edwards syndrome risk ≥1 in 150) or an NT measurement in the range 3.0–3.4 mm could choose between cfDNA for Down syndrome, Edwards syndrome, Patau syndrome ('Trisomy 13') and fetal gender or an invasive

***Corresponding author: Vedran Stefanovic**, MD, PhD, Professor, Vice-President of the IAPM Educational Committee, Department of Obstetrics and Gynecology, Fetomaternal Medical Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland, Phone: +358 50 427 1230, E-mail: vedran.stefanovic@hus.fi. https://orcid.org/0000-0001-5230-1698
Howard Cuckle, Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
Seppo Heinonen, Department of Obstetrics and Gynecology, Fetomaternal Medical Centre, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
Anna-Kaisa Anttonen, HUSLAB Laboratory of Genetics and Department of Clinical Genetics, HUS Diagnostic Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

procedure followed by a quantitative fluorescent polymerase chain reaction (QF-PCR) test, for common trisomies and sex chromosome aneuploidies. Similar protocols have now been adopted in four other university hospital districts. Otherwise cfDNA screening is available only in private sector clinics. Pregnancies with Down syndrome risk ≥1 in 10 or/and NT ≥3.5 mm are referred for further examinations at FMC and primarily invasive procedure with molecular karyotype determination is offered in such cases.

In this paper the cost of different cfDNA screening strategies is estimated and compared with the benefits in terms of Down syndrome births avoided and iatrogenic fetal losses prevented. The implications for Finnish policy are considered, although not exclusively.

Materials and methods

cfDNA strategies

Three strategies are compared:

- 'Primary' screening, entirely replacing the Combined test by routine cfDNA.
- 'Secondary' screening, whereby all women with Down syndrome risk based on the Combined test ≥1 in 250 are offered cfDNA.
- 'Contingent' screening, as with Secondary screening but using a lower cut-off risk whereby 10–30% of women are offered cfDNA.

Additional and marginal cost

Three different measures of cost are estimated for each strategy:

- Additional cost for 10,000 pregnancies compared with the current paradigm of the Combined test. This represents the 'new' money needed to maintain the new policy.
- 'Marginal' cost of avoiding a Down syndrome birth which occurs in a pregnancy that would have been false-negative using the Combined test.
- Marginal cost of preventing the iatrogenic loss of a non-Down syndrome birth which occurs in a pregnancy that would have been false-positive using the Combined test.

Factors contributing to cost

Table 1 lists all the factors and the values which have been assigned to them in the analysis. The detailed derivation of these values are as follows:

Prior risk of Down syndrome: In the absence of screening or prenatal diagnosis the prevalence of Down syndrome in Finland is dependent of the maternal-age distribution. A histogram of maternities according to single years of age was provided from screening tests carried out at HUS during the period 15 May 2019–15 May 2020. This was multiplied by a published maternal age-specific birth Down syndrome prevalence curve to predict the number of affected and unaffected births at each age [3]. These were summed to derive the overall Down syndrome birth prevalence as well as the distribution of ages in Down syndrome and unaffected births. Published estimates of the

Table 1: Information used in the cost computations.

Information	Value	Source
Prior risk of Down syndrome		
Histogram of maternal ages (single years)	Finland 2019–2020	HUS
Maternal age-specific birth prevalence curve	Meta-analysis	Ref. [3]
Down syndrome birth prevalence	0.236%	Predicted[a]
Distribution of ages in affected and unaffected births	–	Predicted[a]
Down syndrome loss rate after first trimester	54%	Ref. [4]
Unaffected loss rate after first trimester	1.23%	Ref. [5]
Combined test results		
Risk cut-off	1 in 250 (at birth)	Finnish policy
Model parameters	Serum at 10 & NT at 11 weeks	Refs. [6, 7]
Detection rate	86.4%	Model predicted[b]
False-positive rate	4.10%	Model predicted[b]
cfDNA test results		
Detection rate	99.3%	Ref. [1][c]
False-positive rate	0.11%	Ref. [1][c]
Contingent testing		
Selected for cfDNA	10%, 20% & 30%	Fixed
Down syndrome positive rate	92.2%, 95.9% & 97.6%	Model predicted[b]
Unaffected positive rate	9.68%, 19.7% & 29.7%	Model predicted[b]
Invasive prenatal diagnosis		
Procedure related fetal loss rate after CVS	0.20%	Ref. [5]
Prices		
Ultrasound NT (including dating scan)	€75	Provided
Combined test serum markers	€25	Provided
cfDNA: Primary	€155	Provided
cfDNA: Secondary or Contingent 10% and 20%	€245	Provided
cfDNA: Contingent 30%	€200	Provided
CVS and karyotype	€1,055	Provided
Uptake		
Combined test or Contingent test	93%	Provided
CVS when a screening test is positive	95%	Provided
ToP when Down syndrome is confirmed	80%	Helsinki area

[a]Applying the curve to the histogram; [b]multivariate log Gaussian modeling with published parameters and the distribution of prior risks; [c]retrospective studies only.

spontaneous fetal loss rate between late first trimester and birth for Down syndrome and unaffected pregnancies were derived from the literature [4, 5]. These were applied to the prevalence of Down syndrome at birth to derive the relative number of pregnancies in the late first trimester and the Down syndrome prevalence at that gestational age.

Combined test results: The detection and false-positive rate were predicted by Gaussian modelling. Each marker follows an approximately log Gaussian distribution over most of their range for both Down syndrome and unaffected pregnancies, and the marker profiles follow multi-variate log Gaussian distributions. The model parameters – marker means, standard deviations, correlations between them and truncation limits – were published values used to calculate Down syndrome risks in Finland [6, 7]. Screening policy in Finland requires the maternal serum markers to be determined at 9–11 weeks and the NT measured at a 11–13 week fetal anatomical scan [8]. In practice, most women are booked at about 10 weeks have the scan at about 11–12 weeks. Therefore the parameters for serum markers at 10 weeks and NT at 11 weeks were used in the analysis.

The likelihood ratio (LR) for a marker profile is calculated by the ratio of the 'heights' of the two overlapping distributions at the specific profile after log transformation. The prior risk of a Down syndrome birth is multiplied by the LR to determine the posterior risk which is compared with a fixed cut-off to classify results as 'positive' or 'negative'.

The predicted detection and false-positive rates were obtained by numerical integration [9]. The theoretical range of marker levels is divided into a number of equal sections, thus forming a 'grid' in multi-dimensional space. The Gaussian distributions are then used to calculate for each section: the proportion of Down syndrome and unaffected pregnancies in the section and the LR. These are then applied to the prior risk distributions.

The model parameters were obtained largely from retrospective studies and the predicted detection and false-positive rates are more reliable than those that might be obtained directly from clinical screening results in Finland. This is because clinical results are subject to 'viability' bias which arises because a proportion of those with true-positive results who have a termination of pregnancy (ToP) would have been destined to miscarry anyway whereas non-viable affected pregnancies with normal screening results will not be known to the investigators [1].

cfDNA test results: The most recent meta-analysis includes data from 47 studies but in this analysis only those from retrospective studies are used. These were in high-risk women with complete outcome information since plasma samples were mostly drawn prior to invasive prenatal diagnosis. There is no evidence that performance is correlated with maternal age or screening results so such studies can be assumed to be substantially unbiased. In contrast, prospective studies, on samples drawn in a conventional screening program, generally have incomplete follow-up.

Contingent cfDNA strategy: Three versions were considered, according to the proportion of pregnancies with the highest Combined test risk selected for cfDNA. The proportions were 10%, 20% and 30% equivalent to three cut-off risks. The proportion of Down syndrome and unaffected births with risk about the cut-off was predicted in exactly the same way as the detection and false-positive rates of the Combined test.

Invasive prenatal diagnosis: Only chorionic villus sampling (CVS) is considered in the analysis as women will have received Combined and cfDNA test results well before 15 weeks gestation. The fetal loss rate of attributable to CVS of 0.20% used in here is derived by meta-analysis of seven controlled studies [5].The total number of women undergoing CVS was 13,011 and the control series totaled 232,680.

Prices: The price of an ultrasound NT scan, Combined test serum markers, CVS and karyotype were obtained from HUSLAB and the FMC service charge list. The total price of a cfDNA test is comprised of reagents and equipment (PerkinElmer), the Streck tube and other costs (obtained from HUS). There are three prices based on the laboratory throughput and where the samples are tested. Thus with a policy of Primary cfDNA all samples would be tested in-house (about 10,000 per year) and would have the lowest price. In contrast Secondary cfDNA would have less than 5% of samples tested and would involve out-testing at a much higher price. Similarly for Contingent cfDNA, when only 10% or 20% are tested, there would also be out-testing. For Contingent cfDNA with 30% selected for testing, it is assumed to be in-house but the price would be higher than for Primary cfDNA as the throughput would be lower (about 4,500 per year).

Uptake: Three scenarios were compared for the uptake of screening, CVS after a positive screening result and ToP following diagnosis by CVS were:

- 100% for each ('best case').
- Screen 93%, CVS 95%, ToP 80% ('realistic'; taken from experience with the Combined test in the Helsinki area).
- Enhanced uptake for cfDNA policies, Screen 100%, CVS 100% ('worse case'; some differentially increased uptake would be expected because the chance of needing a CVS is considerably reduced and it is known that the risk of a procedure related loss is a major reason why many high risk women forgo invasive prenatal diagnosis) [10, 11].

Cost computations

The methods used to compute: proportion of Down syndrome births avoided; proportion of unaffected pregnancies undergoing CVS; cost per 10,000 pregnancies; cost per Down syndrome birth avoided; additional cost for 10,000 pregnancies compared with the Combined test; marginal cost per Down syndrome birth avoided; and marginal cost per fetal loss prevented are shown in the Supplementary Material.

Financial benefits

In 11 economic studies of cfDNA screening benefit was derived from the cost of continuing a Down syndrome pregnancy [12–23]. One only included costs until age 18 [22].and the remainder considered lifetime costs which ranged from $583,000 to $1,497,000. Two studies discounted the cost to account for the reduced value of today's currency in the future when the expenses will be incurred, yielding estimates of $677,000 and $857,000 [16, 21]. In the absence of specifically Finnish

data on these costs, the average of these two studies (converted at $1.00 = €0.85) was used as a guide amounting to €902,000.

The benefit of preventing an iatrogenic fetal loss can be derived from the lost productivity of an adult's working life. In a recently published study from the UK this was estimated to be £213,000 which, converted at £1.00 = €1.10, amounts to €234,000 [24]. Another comparator is the upper cost limit set by the UK National Institute of Health and Care Excellence (NICE) when judging the value of potential new interventions. The limit is £30,000 per Quality Adjusted Life Year (QALY) saved by the intervention – a higher limit of £100,000, for treatment of the elderly or in the case of rare conditions [25]. A newborn child has 25 QALYs so the limit amounts to €825,000 after discounting at 3% per annum. Neither the lost productivity nor the QALY comparator is entirely satisfactory though since in a proportion of cases an iatrogenic fetal loss will be replaced by a subsequent viable pregnancy.

Ethics

According to the Finnish Law (https://finlex.fi/fi/laki/ajantasa/1999/19990488), the cost-analyses in medicine that uses data which may not be personalized in any way are exempted from the Ethical approval and Research permit in local setting.

Results

Down syndrome births avoided and CVS performed in unaffected pregnancies (Table 2)

Primary cfDNA screening increases avoidance of Down syndrome births by 15% compared with the Combined test and by 30% assuming enhanced uptake. It also reduces CVS being performed on unaffected pregnancies by 33–37 fold. Secondary cfDNA screening results in a slight reduction in Down syndrome births avoided except for enhanced uptake where there is a 12% *increase*. The reduction in CVS performed is 800–910 fold. Contingent screening increases avoidance of Down syndrome births by 6–12% or 20–27% with enhanced uptake; reduction in CVS is 110–370 fold.

Mean cost per pregnancy and per Down syndrome birth avoided (Table 2)

For all assumptions about uptake, the mean cost per pregnancy is higher for Primary cfDNA screening compared with the Combined test and lower for Secondary cfDNA screening. For Contingent cfDNA screening selecting 10% or 20% mean cost is also lower but selecting 30% it is higher than for Primary screening. The mean cost per Down syndrome birth avoided is higher for Primary cfDNA than Secondary cfDNA and intermediate for Contingent cfDNA strategies with 10% or 20% selected.

Additional cost for 10,000 pregnancies (Table 3)

Replacing the Combined test by Primary cfDNA screening will require additional funds amounting to €129–253,000,

Table 2: Down syndrome detection, invasive prenatal diagnosis and costs (€) according to screening strategy and assumptions about uptake.

	Down syndrome births avoided	CVS in unaffected pregnancies	Mean cost/pregnancy	Mean cost/DS birth avoided
100% uptake				
Combined screening	86.4%	4.10%	146	72,000
Primary cfDNA screening	99.3%	0.11%	158	69,000
Secondary cfDNA screening	85.8%	0.0045%	112	56,000
Contingent cfDNA screening – 10%	91.6%	0.011%	127	60,000
Contingent cfDNA screening – 20%	95.2%	0.022%	152	69,000
Contingent cfDNA screening – 30%	96.9%	0.033%	163	72,000
93% Screen, 95% CVS, 80% ToP				
Combined screening	61.1%	3.62%	133	94,000
Primary cfDNA screening	70.2%	0.097%	147	90,000
Secondary cfDNA screening	60.6%	0.0040%	104	74,000
Contingent cfDNA screening – 10%	64.7%	0.0094%	118	79,000
Contingent cfDNA screening – 20%	67.3%	0.019%	141	90,000
Contingent cfDNA screening – 30%	68.5%	0.029%	152	95,000
100% Screen, 100% CVS, 80% ToP				
Primary cfDNA screening	79.4%	0.11%	158	86,000
Secondary cfDNA screening	68.6%	0.0045%	112	70,000
Contingent cfDNA screening – 10%	73.2%	0.011%	127	75,000
Contingent cfDNA screening – 20%	76.2%	0.022%	152	86,000
Contingent cfDNA screening – 30%	77.5%	0.033%	163	91,000

depending on uptake assumptions. If instead Secondary or Contingent cfDNA screening with 10% selected is adopted there will be a *reduction* in costs (€214–337,000 and €58–181,000 respectively) but for Contingent screening with 20% or 30% selected additional funds will be needed (€66–190,000 and €177–301,000 respectively).

Marginal costs (Table 3)

For each additional Down syndrome birth avoided when replacing the Combined test by Primary cfDNA screening the cost will be €43,000–€95,000 depending on uptake assumptions. Each iatrogenic fetal loss of an unaffected pregnancy prevented by the change will cost €164,000–€365,000.

Secondary cfDNA and Contingent cfDNA screening with 10% selected have no marginal costs as they are cost saving. Contingent cfDNA with 20% selected has a lower marginal cost per Down syndrome birth avoided (€32,000–€56,000) than Primary cfDNA screening and a lower marginal cost per iatrogenic loss prevented (€82,000–€268,000). Selecting 30% increases avoidance at a higher marginal cost (€72,000–€107,000) except under the assumption of enhanced uptake when it is lower than for Primary cfDNA (€79,000 compared with €95,000) but the marginal cost of fetal reduction is high (€221,000–€425,000).

Comparing marginal costs and benefits

For Primary and Contingent strategies under all uptake scenarios, the marginal cost per Down syndrome birth avoided (€32–107,000) is considerably less than the discounted lifetime medical and indirect cost incurred by a Down syndrome birth of €902,000. Under the most realistic scenario of enhanced uptake the marginal cost per loss prevented (€268–425,000), due to the very low cfDNA false-positive rate is higher than the lost productivity of an adults working life of €234,000, but at most about half of the upper cost limit per QALY set by NICE when judging the value of potential new interventions of €825,000.

Discussion

This paper provides estimates of the costs and benefits for the different cfDNA strategies for Down syndrome screening. The costs were based on a number of simplifications [16]:

Termination of pregnancy

The cost of ToP is higher than the cost of treatment following a spontaneous abortion; $874 and $552 in one economic evaluation of cfDNA screening, a difference of

Table 3: Additional and marginal costs (€) compared with Combined test according to cfDNA screening strategy and assumptions about uptake.

	Additional cost for 10,000 pregnancies	Marginal cost/DS birth avoided (cf Combined test)	Marginal cost/unaffected fetal loss prevented (cf Combined test)
100% uptake			
Primary cfDNA screening	129,000	43,000	164,000
Secondary cfDNA screening	Saving 337,000	a	b
Contingent cfDNA screening – 10%	Saving 181,000	c	b
Contingent cfDNA screening – 20%	66,000	32,000	82,000
Contingent cfDNA screening – 30%	177,000	72,000	221,000
93% Screen, 95% CVS & 80% ToP			
Primary cfDNA screening	139,000	58,000	200,000
Secondary cfDNA screening	Saving 294,000	a	b
Contingent cfDNA screening – 10%	Saving 149,000	c	b
Contingent cfDNA screening – 20%	81,000	56,000	115,000
Contingent cfDNA screening – 30%	185,000	107,000	261,000
Combined, 93% Screen, 95%; cfDNA, 100% Screen, 100% CVS; both, 80% ToP			
Primary cfDNA screening	253,000	95,000	365,000
Secondary cfDNA screening	Saving 214,000	c	b
Contingent cfDNA screening – 10%	Saving 58,000	c	b
Contingent cfDNA screening – 20%	190,000	54,000	268,000
Contingent cfDNA screening – 30%	301,000	79,000	425,000

[a]Less DS births avoided and lower cost; [b]fetal losses prevented at reduced cost; [c]more DS births avoided at lower cost.

$322 or about €270 [10].When a cfDNA testing strategy leads to the avoidance of additional Down syndrome births, there will be an extra expense due to the termination of affected pregnancies which would have otherwise miscarried. However, this does not materially alter the marginal costs; for example, even when the additional births are 10% it would only increase by €270 × 10%/0.54 or €50.

Screening for common aneuploidies other than Down syndrome

Both the Combined test and cfDNA screening can be used to detect Edwards and Patau syndromes. The birth prevalence of Edwards and Patau syndromes are considerably lower than Down syndrome and they have a very high infant mortality rate. One economic study of cfDNA screening included all three aneuploidies and Turner syndrome ('Monosomy X') but found that the results were dominated by Down syndrome. The authors showed that the financial benefit of the other aneuploidies was offset by the additional cost of screening, and did not alter the overall cost-benefit comparisons between the Combined test and Primary cfDNA screening.

Primary cfDNA: retaining the ultrasound scan

The first trimester scan visit has many functions: confirm fetal viability; more accurately estimate gestational age than menstrual dates; identify multiple gestations and determine chorionicity; and examine and locate the placenta. In Finland, it is also an early 'anomaly' scan used to identify fetal structural anomalies. Moreover, using a very high NT cut-off level can select women at high risk of uncommon aneuploidies. Two studies have quantified this potential [26, 27]. The California Prenatal Screening Program found that using an 3.5 mm NT cut-off would select a group including 2.6% with uncommon aneuploidies detectable by classical karyotyping [26]. A national study in the Netherlands used a lower 95th centile cut-off but identified a group including 5.4% with uncommon aneuploidies detectable by karyotyping, submicroscopic copy number variants detectable by micro-array or single gene disorders detectable by sequencing [27]. Under these circumstances some centers would want to retain the NT scan after introducing Primary cfDNA screening. Table 4 shows how this would substantially increase the additional and marginal costs. The required additional funds would rise to €992,000 for 10,000 pregnancies. The marginal cost would still be much less than the lifetime medical and indirect cost incurred by a Down syndrome birth but the marginal cost per unaffected iatrogenic fetal loss prevented will be extremely high. The additional funds might be justified when taking account of savings resulting from the detection of serious structural abnormalities but this would require an economic analysis specifically focused on them.

Primary cfDNA: retaining maternal serum PAPP-A

Some centers may want to retain maternal serum PAPP-A as part of a screening program for pre-eclampsia (PE) [28]. However, it can be argued that the cost of this marker needs to be financially justified in a separate cost-benefit analysis rather than factoring them into an analysis of Down syndrome screening. For example, there is a published cost-benefit study of PE screening in Lebanon using first trimester mean arterial pressure measurement and

Table 4: Primary cfDNA screening: additional and marginal costs (€) according to whether the NT scan is retained and assumptions about uptake.

NT scan	Additional cost for 10,000 pregnancies	Marginal cost/DS birth avoided (cf Combined test)	Marginal cost/unaffected fetal loss prevented (cf Combined test)
100% uptake			
Not retained	129,000	43,000	164,000
Retained	868,000	289,000	1,104,000
93% Screen, 95% CVS & 80% ToP			
Not retained	139,000	58,000	200,000
Retained	827,000	344,000	1,189,000
Combined, 93% Screen, 95%; cfDNA, 100% Screen, 100% CVS; both, 80% ToP			
Not retained	253,000	95,000	365,000
Retained	992,000	268,000	1,433,000

maternal serum placental growth factor determination [29]. The study showed that the financial savings were more than sufficient to pay for screening.

Secondary cfDNA: choice of invasive prenatal diagnosis

At FMC the current Secondary cfDNA strategy allows individual choice between cfDNA and invasive prenatal diagnosis and one-fifth choose invasive testing (Vedran Stefanovic, unpublished results). Such an uptake would reduce the estimated cost savings in Table 3 by 19–30%. In 2017 Denmark introduced a similar Secondary cfDNA strategy and 80% choose invasive testing [30] which may be explained by their use of a micro-array rather than QF-PCR thus detecting submicroscopic copy number variants and counseling lower procedure-related miscarriage rates (negligible for CVS and 0.3% for amniocentesis) than quoted in Finland (0.5–1% for both procedures). This will have reduced the savings further. About 2% of cfDNA tests do not yield a result and such 'no-calls' were not included in the meta-analysis used to assess performance in this paper [1]. Consequently, the practical performance will be poorer than in the meta-analysis depending on how no-calls are treated. Referring all of them for invasive prenatal diagnosis, as some medical bodies currently suggest [31] will increase the detection rate but also considerably increase the false-positive rate. Taking no further action will reduce detection and false-positive rates whilst repeat testing will resolve about two-thirds of those due to low fetal fraction [32, 33].This has not been taken into account in the current analysis but this can be readily done. For example, with Primary cfDNA and 100% uptake the marginal detection rate is €43,000 (Table 3). Invasive prenatal diagnosis, assuming a 2% no-call rate, will substantially increase this to €102,000; no further action reduces it to €38,000 and repeat testing, assuming all no-calls are due to low fetal fraction and two-thirds are resolved, increases it to €46,000. Other categories of results may also have been excluded from some studies entered into [34] the meta-analysis, for example cases of confined placental mosaicism. This will have reduced the false-positive rate compared to clinical practice but this is likely to be a small effect.

In the 12 years since the discovery that maternal plasma cfDNA can be used to detect Down syndrome there has not been widespread replacement of conventional screening by cfDNA. A recent survey of European countries, Australia and the USA shows very uneven utilization hilst some have a form of Secondary or Contingent cfDNA screening, few provide even this minimal provision by public health funds. Only two countries, Belgium and the Netherlands, offer Primary cfDNA screening and whilst in Belgium the cost is fully reimbursed by insurance, in the Netherlands the pregnant woman pays for some of the cost.

The uptake of conventional screening in the Netherlands has been low, with a rate of abot 30% in 2007–2013 [35].There are many reasons for this, but a major factor is likely to be an unfavourable attitude towards screening in the local midwife community. Other potential factors could be a relatively positive attitude towards raising a child with Down syndrome, a negative view of selective pregnancy termination and the costs of screening. Screening in the Netherlands was never free of charge in contrast to Finland where there is no charge. The charges in The Netherlands are approximately €170 for combined screening and €175 for cfDNA screening. With the introduction of cfDNA screening, the uptake has increased to 46% [35] which is still much lower rate than in Finland. Furthermore, it should be noted that women in the Netherlands are not routinely screened for structural fetal abnormalities because the first-trimester ultrasound is not part of the current Dutch prenatal screening program. Hence, the Dutch experience is that the introduction of Primary cfDNA screening did not lead to a major increase in uptake. Also, regional and maternal age variations were observed. Authors highlight the importance of tailoring counseling to the diverse needs of pregnant women and a centralized approach ensuring access, quality and continuous monitoring. High-quality counseling for aneuploidy screening is imperative to ensure that women are free to make decisions in line with their personal values [35].

In Belgium, the uptake of first trimester screening is about 80% [36]. The introduction and reimbursement of Secondary cfDNA has substantially reduced procedure-related miscarriages without increasing the short-term costs. Almost full reimbursement of Primary cfDNA (for three common trisomies) has been available since 2017. All eight Belgian genetic centers perform a cfDNA test based on whole-genome sequencing, allowing not only for the detection of the three common trisomies, but also of rare autosomal trisomies (RATs), maternal subchromosomal aberrations, and, in some cases, large, noncryptic fetal aberrations throughout the genome [36].

Finland has a higher screening uptake rate than the Netherlands and Belgium and standardized first trimester fetal scan criteria, particularly nuchal translucency measurement, Also, invasive fetal procedures in Finland are concentrated to five university hospitals, while in Belgium many small centers still perform invasive procedures that may influence the procedure-related miscarriage risk [37].

Norway currently restricts the Combined test to women aged over 38 and recent changes in the law allow cfDNA testing in this age group. However, a survey of pregnant women found that 78% thought such testing should be offered as a public health service to all [38].

In Finland, for large centers like FMC, the practical choices are limited and the associated costs are shown in Figure 1. cfDNA secondary screening implementation in 2015 had a dramatic impact in decreasing the rate of invasive procedures (Figure 2).The first trimester scan would be retained for general obstetric care, as an early anomaly scan and to select women for further testing on the basis of a very large NT. Hence the Primary cfDNA strategy would be relatively costly. A version of the Secondary cfDNA strategy is already in place and is cost saving. Replacing this by a Contingent cfDNA strategy selecting 10% for testing would improve performance slightly and would also be cost saving. Contingent cfDNA selecting 20% or 30% for testing would involve additional costs but would be cheaper than Primary cfDNA and would increase the number of Down syndrome births avoided.

While Contingent cfDNA screening would be the most cost-effective strategy with the current prices, one has to take into account that using a lower cut-off risk (≥1 in 1,000) compared to the present one (≥1 in 250) would increase the proportion of screen positive tests from 5% to 20–30%. As a consequence more women would experience anxiety and conflicting decisions that require increased resources for counseling.

Due to the high uptake of the first trimester screening in Finland, we speculate that it would be possible to find a cfDNA laboratory provider with a relatively low price due to the high volume of tests from Primary cfDNA screening. We are not aware if the public health funds would be able to cover the price. If the cost would be only partially reimbursed, the Finnish Law should be changed: currently the combined screening and second trimester screening are provided completely free of charge for all women. In the current Finnish organization where FMC operates under a hospital budget, not as a part of public health, short-term health savings result from either not screening at all or selecting the cheapest option. This in turn results in higher downstream long-term health care costs, including offspring lifetime costs and the burden to families which are not valued when the cost effectiveness threshold is to be decided at the hospital level for budgetary purposes. The costs should therefore be explored across such borders and across health care providers to maximize the value for the money. This paper brings transparency to the controversy surrounding the cost-effectiveness estimates in the Finnish setting and shows that Contingent cfDNA screening is an underused tool despite its cost-effectiveness. One of the

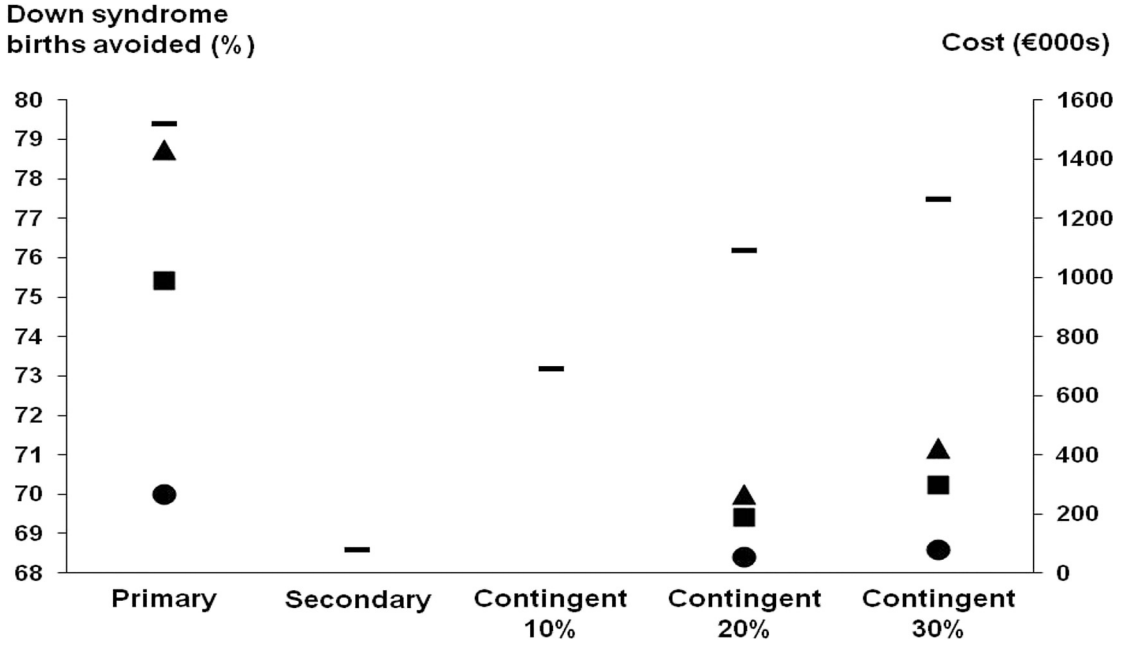

Figure 1: Different screening strategies: impact on Down syndrome births avoided and associated costs.
Down syndrome births avoided (⁻) and, compared with the Combined test, additional cost for 10,000 pregnancies (■), marginal cost per Down syndrome birth prevented (●) and per fetal loss avoided (▲), when there is a cost, according to cfDNA screening strategy. Combined test uptake, 93% Screen, 95% CVS; cfDNA, 100% Screen, 95% CVS; both, 80% ToP.

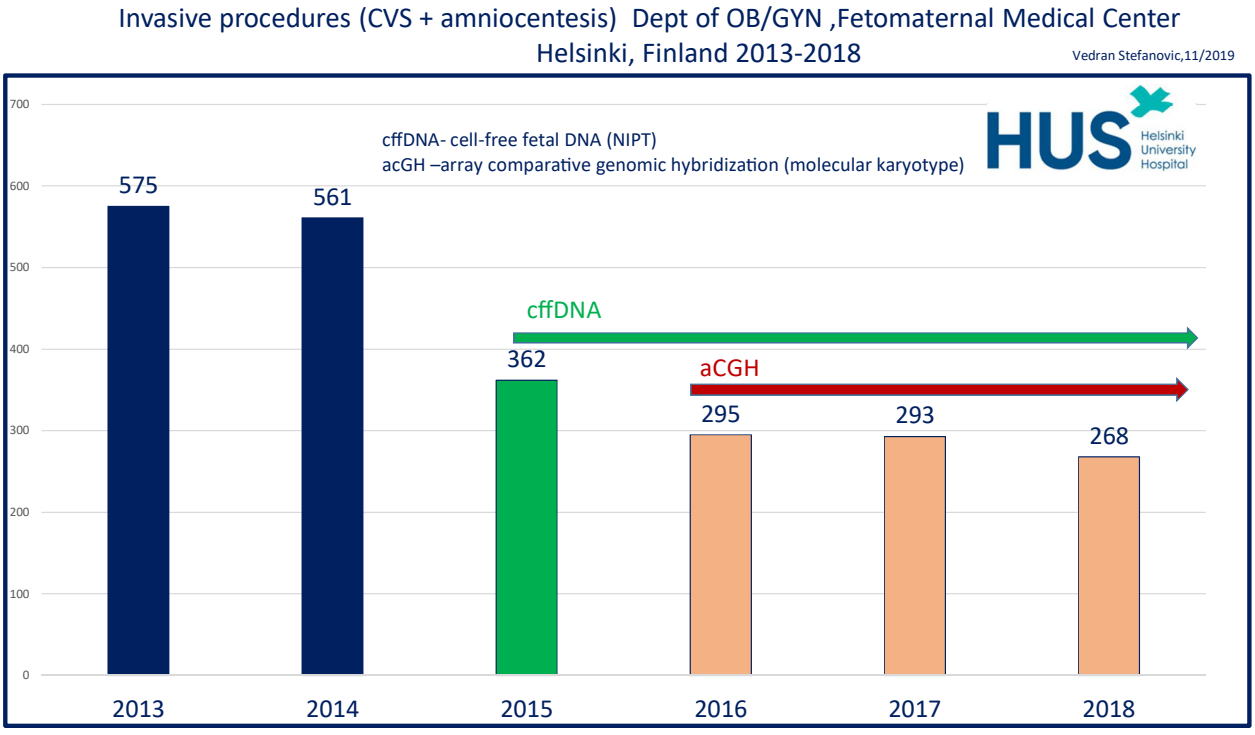

Figure 2: Invasive procedures (CVS + amniocentesis).
Dept. of OB/GYN, Fetomaternal Medical Center Helsinki, Finland 2013–2018 before and after introduction of cfDNA and micoarray (aCGH).

strengths of this study is that we included the screening uptake rates as well as the costs and uptake rates of invasive diagnostic which were the most uncertain variables in the most of the publications on the similar cost analyses [39].

Conclusions

This paper provides the information needed to select a cfDNA screening strategy at a national level, including additional and marginal costs and associated benefits. Primary screening has a good cost-benefit ratio but requires additional funds, which could be considerable if, like in Finland, the ultrasound component of the Combined test is retained. In contrast, Contingent screening has a favourable ratio in all circumstances.

Research funding: None declared.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: According to the Finnish Law (https://finlex.fi/fi/laki/ajantasa/1999/19990488), the cost-analyses in medicine that uses data which may not be personalized in any way are exempted from the Ethical approval and Research permit in local setting.

References

1. Gil MM, Accurti V, Santacruz B, Plana MN, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. Ultrasound Obstet Gynecol 2017;50: 302–14.
2. Cuckle HS. Multianalyte maternal serum screening for chromosomal abnormalities and neural tube defects. In: Milunsky A, Milunsky JM, editors. Genetic disorders and the fetus: diagnosis, prevention and treatment, 8th ed. Hoboken: Wiley-Blackwell; 2020.
3. Cuckle HS, Wald NJ, Thompson SG. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. Br J Obstet Gynaecol 1987; 94:387–402.
4. Snijders RJM, Holzgreve W, Cuckle H, Nicolaides KH. Maternal age-specific risks for trisomies at 9–14 weeks gestation. Prenat Diagn 1994;14:543–52.
5. Salomon LJ, Sotiriadis A, Wulff CB, Odibo A, Akolekar R. Risk of miscarriage following amniocentesis or chorionic villus

sampling: systematic review of literature and updated meta-analysis. Ultrasound Obstet Gynecol 2019;54:442–51.
6. Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM, et al. First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). Health Technol Assess 2003;7:1–88.
7. Wald N, Rodeck C, Rudnicka A, Hackshaw A. Nuchal translucency and gestational age. Prenat Diagn 2004;24:150–1.
8. Finnish Government Decree on Screening; 339; 2011. Available from: https://www.finlex.fi/en/laki/kaannokset/2011/en20110339?search%5Btype%5D=pika&search%5Bkieli%5D%5B0%5D=en&search%5Bpika%5D=Screening.
9. Royston P, Thompson SG. Model-based screening by risk with application to Down's syndrome. Stat Med 1992;11:257–68.
10. Kolbelka C, Mattman A, Langlois S. An evaluation of the decision-making process regarding amniocentesis following a screen-positive maternal serum screen result. Prenat Diagn 2009;29:514–9.
11. Tischler R, Hudgins L, Blumenfeld YJ, Greely HT, Ormond KE. Noninvasive prenatal diagnosis: pregnant women's interest and expected uptake. Prenat Diagn 2011;31:1292–9.
12. Cuckle H, Benn P, Pergament E. Maternal cfDNA screening for Down syndrome – a cost sensitivity analysis. Prenat Diagn 2013;33:636–42.
13. Song K, Musci TJ, Caughey AB. Clinical utility and cost of non-invasive prenatal testing with cfDNA analysis in high-risk women based on a US population. J Matern Fetal Neonatal Med 2013;26:1180–5.
14. Ohno M, Caughey A. The role of noninvasive prenatal testing as a diagnostic versus a screening tool – a cost-effectiveness analysis. Prenat Diagn 2013;33:630–5.
15. Beulen L, Grutters JP, Faas BH, Feenstra I, van Vugt JM, Bekker MN. The consequences of implementing non-invasive prenatal testing in Dutch national health care: a cost-effectiveness analysis. Eur J Obstet Gynecol Reprod Biol 2014;182:53–61.
16. Benn P, Curnow KJ, Chapman S, Michalopoulos SN, Hornberger J, Rabinowitz M. An economic analysis of cell-free DNA non-invasive prenatal testing in the US general pregnancy population. PLoS One 2015;10:e0132313.
17. Evans MI, Sonek JD, Hallahan TW, Krantz DA. Cell-free fetal DNA screening in the USA: a cost analysis of screening strategies. Ultrasound Obstet Gynecol 2015;45:74–83.
18. Walker BS, Jackson BR, LaGrave D, Ashwood ER, Schmidt RL. A cost-effectiveness analysis of cell free DNA as a replacement for serum screening for Down syndrome. Prenat Diagn 2015;35:440–6.
19. Walker BS, Nelson RE, Jackson BR, Grenache DG, Ashwood ER, Schmidt RL. A cost-effectiveness analysis of first trimester non-invasive prenatal screening for fetal trisomies in the United States. PLoS One 2015;10:e0131402.
20. Fairbrother G, Burigo J, Sharon T, Song K. Prenatal screening for fetal aneuploidies with cell-free DNA in the general pregnancy population: a cost-effectiveness analysis. J Matern Fetal Neonatal Med 2016;29:1160–4.
21. Ginsberg GM, Cuckle H. Cost-utility analysis of cfDNA screening for Down's syndrome in Israel. In: Studd J, Tan SL, Chevenak FA, editors. Current progress in obstetrics and gynecology. Mumbai: Kothari Medical; 2017, vol 4.
22. Zhang W, Mohammadi T, Sou J, Anis AH. Cost-effectiveness of prenatal screening and diagnostic strategies for Down syndrome: a microsimulation modeling analysis. PLoS One 2019;14:e0225281.
23. Wanapirak C, Buddhawongsa P, Himakalasa W, Sarnwong A, Tongsong T. Fetal Down syndrome screening models for developing countries; Part II: cost-benefit analysis. BMC Health Serv Res 2019;19:898.
24. Campbell HE, Kurinczuk JJ, Heazell A, Leal J, Rivero-Arias O. Healthcare and wider societal implications of stillbirth: a population-based cost-of-illness study. Br J Obstet Gynaecol 2018;125:108–17.
25. Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable? Expert Rev Pharmacoecon Outcomes Res 2017;17:239–42.
26. Berger VK, Norton ME, Sparks TN, Flessel M, Baer RJ, Currier RJ. The utility of nuchal translucency ultrasound in identifying rare chromosomal abnormalities not detectable by cell-free DNA screening. Prenat Diagn 2020;40:185–90.
27. Bardi F, Bosschieter P, Verheij J, Go A, Haak M, Bekker M, et al. Is there still a role for nuchal translucency measurement in the changing paradigm of first trimester screening? Prenat Diagn 2020;40:197–205.
28. Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther 2013;33:8–15.
29. Karaki H, Khazaal J, Chahine, Kharoubi M, Cuckle H. Cost-effectiveness of first trimester screening for preterm pre-eclampsia in Lebanon. J Fet Med 2020;7:119–23.
30. Lou S, Petersen OB, Jørgensen FS, Lund ICB, Kjaergaard S, Danish Cytogenetic Central Registry Study Group, et al. National screening guidelines and developments in prenatal diagnoses and live births of Down syndrome in 1973–2016 in Denmark. Acta Obstet Gynecol Scand 2018;97:195–203.
31. Rose NC, Kaimal AJ, Dugoff L, Norton ME. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics Committee on Genetics, Screening for fetal chromosomal abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol 2020;136:e48–69.
32. Cuckle H. cfDNA screening performance: accounting for and reducing test failures. Ultrasound Obstet Gynecol 2017;49:689–92.
33. Ericsson O, Ahola T, Dahl F, Karlsson F, Persson F, Karlberg O, et al. Clinical validation of a novel automated cell-free DNA screening assay for trisomies 21, 13, and 18 in maternal plasma. Prenat Diagn 2019;39:1011–5.
34. Gadsbøll K, Petersen OB, Gatinois V, Strange H, Jacobsson B, Wapner R, et al. Current use of noninvasive prenatal testing in Europe, Australia and the USA: a graphical presentation. Acta Obstet Gynecol Scand 2020;99:722–30.
35. van der Meij KRM, de Groot-van Mooren M, Carbo EWS, Pieters MJ, Rodenburg W, Sistermans EA, et al. Dutch NIPT Consortium. Uptake of fetal aneuploidy screening after the introduction of the non-invasive prenatal test: a national population-based register study. Acta Obstet Gynecol Scand 2021;100:1265–72.
36. Vervecken E, Blaumeiser B, Vanderheyden T, Hauspy J, Janssens K. Terminal deletion of chromosome 13 in a fetus with normal NIPT: the added value of invasive prenatal diagnosis in the NIPT era. Clin Case Rep 2020;8:1461–6.

37. Neyt M, Hulstaert F, Gyselaers W. Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis. BMJ Open 2014;4:e005922.
38. Sitras V, Ulriksen M, Benth JŠ, Haugen G. Gravide kvinners holdning til fosterdiagnostikk [Pregnant women's attitudes to prenatal screening in Norway]. Tidsskr Nor Laegeforen 2020;140. https://doi.org/10.4045/tidsskr.20.0098.
39. Nshimyumukiza L, Menon S, Hina H, Rousseau F, Reinharz D. Cell-free DNA noninvasive prenatal screening for aneuploidy versus conventional screening: a systematic review of economic evaluations. Clin Genet 2018;94:3–21.

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2021-0467).