Accuracy of first trimester combined test in screening for trisomies 21, 18 and 13

Marta Santorum,[1] David Wright,[2] Argyro Syngelaki,[1] Natalia Karagioti,[1] Kypros H Nicolaides[1]

Key words: Trisomy 21, Trisomy 18, Trisomy 13, Screening for chromosomal abnormalities, First trimester combined test.

1. Harris Birthright Research Centre for Fetal Medicine, King's College, London, UK
2. Institute of Health Research, University of Exeter, Exeter, UK.

Acknowledgement: This study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116).

Correspondence
Professor KH Nicolaides
Harris Birthright Research Centre for Fetal Medicine
King's College Hospital
Denmark Hill
London SE5 9RS
Tel: 00 44 2032998256
Fax: 00 44 2032993898
Mail: kypros@fetalmedicine.com

ABSTRACT

Objective: To examine the diagnostic accuracy of a previously developed model for the first-trimester combined test in screening for trisomies 21, 18 and 13.

Methods: This was a prospective validation study of screening for trisomies 21, 18 and 13 by a combination of maternal age, fetal nuchal translucency, fetal heart rate and serum free ß-hCG and PAPP-A at 11^{+0} -13^{+6} weeks' gestation in 108,982 singleton pregnancies undergoing routine care in three maternity hospitals. A previously published algorithm was used for the calculation of patient-specific risk of trisomy 21, trisomy 18 and trisomy 13 in each patient. The detection rates (DR) and false positive rates (FPR) at estimated risk cut-offs from 1 in 2 to 1 in 1000 were determined. The proportions of trisomies were compared to their expected values in different risk groups.

Results: In the study population there were 108,112 (99.2%) cases with normal fetal karyotype or the birth of a phenotypically normal neonate and 870 (0.8%) cases with abnormal karyotype including trisomy 21 (n=432), trisomy 18 (n=166), trisomy 13 (n=56), mosomy X (n=63), triploidy (n=35) or other aneuploidy (n=118). The screen positive rates, standardized according to the maternal age distribution of England and Wales in 2011, of fetuses with abnormal and normal karyotype were compatible with those predicted from the previous model; at risk cut-off of 1 in 100, the FPR was about 4% and the DRs for trisomies 21, 18 and 13 were 90, 97 and 92%, respectively. There was evidence that the algorithm over-estimated risks. This could to some degree reflect under ascertainment in pregnancies ending in miscarriage or stillbirth.

Conclusion: In a prospective validation study the first-trimester combined test detected 90, 97 and 92% of trisomies 21, 18 and 13, respectively, as well as >90% of cases of monosomy X, >85% of triploidies and >30% of other chromosomal abnormalities, at FPR of 4%.

INTRODUCTION

Scientific and clinical background

Effective screening for fetal trisomies 21, 18 and 13 can be provided at 11-13 weeks' gestation by a combination of maternal age, fetal nuchal translucency thickness (NT), fetal heart rate (FHR) and maternal serum-free ß-hCG and pregnancy associated plasma protein-A (PAPP-A). In a previous study we used data from prospective screening in 56,954 singleton pregnancies between July 1999 and February 2006 to develop an algorithm for the calculation of patient-specific risk of trisomy 21, trisomy 18 and trisomy 13 [1]. First, the maternal age-related risk for each trisomy at term was calculated and adjusted according to the gestational age at the time of screening [2-4]. Second, the measured NT was transformed into likelihood ratio for each trisomy using the mixture model of NT distributions; in both, trisomic and unaffected pregnancies fetal NT follows two distributions, one in which NT increases with fetal crown-rump length (CRL-dependent) and another which is CRL-independent [5]. Third, the measured free ß-hCG and PAPP-A were converted into a multiples of the median (MoM) for gestational age adjusted for maternal weight, ethnicity, smoking status, method of conception, parity and machine for the assays [6,7]. Fourth, the measured FHR were adjusted for gestational age and delta values were calculated as deviations from the expected normal mean [1]. Fifth, trivariate Gaussian distributions were fitted to the joint distribution of delta FHR, log MoM free ß-hCG and log MoM PAPP-A in normal, trisomy 21, trisomy 18 and trisomy 13 pregnancies. Sixth, the likelihood ratios for NT, FHR and for the biochemical markers were multiplied with the age-related odds at the time of screening in each case. Seventh, detection rates (DR) and false positive rates (FPR) were calculated by taking the proportions with risks above a given risk threshold after adjustment for maternal age according to the distribution of pregnancies in England and Wales in 2000–2002 [8]. It was estimated that such combined screening would be associated with DR of 91%, 97% and 94% for trisomies 21, 18 and 13, respectively, at overall FPR of 3.1% [1].

Study objectives and hypothesis

The objective of this study is to report the accuracy of the first-trimester combined test in screening for trisomies 21, 18 and 13 [1] in 108,982 prospectively examined singleton pregnancies. The hypothesis is that the performance of screening would be similar to that estimated from the original model [1].

The Standards for Reporting Diagnostic accuracy studies (STARD) [9] were adhered to.

METHODS

Study design and participants

This was a prospective screening study for trisomies 21, 18 and 13 by a combination of maternal age, fetal NT, FHR and serum free ß-hCG and PAPP-A at 11^{+0} -13^{+6} weeks' gestation in women booking for routine pregnancy care at King's College Hospital, London (March 2006 to May 2015), University College London Hospital, London (April 2009 to July 2013) and Medway Maritime Hospital, Gillingham (April 2010 to May 2015). The eligibility criteria were singleton pregnancies with live fetus demonstrated on the 11-13 weeks scan.

Test methods

The index test, or test whose accuracy has been evaluated, is the previously reported algorithm for the first trimester combined test which includes maternal age, fetal NT, FHR and serum free ß-hCG and PAPP-A (DELFIA Xpress system, PerkinElmer Life and

Analytical Sciences, Waltham, USA) [1]. The index test was carried out prospectively in consecutive singleton pregnancies at 11^{+0} -13^{+6} weeks' gestation; gestational age was determined from the measurement of fetal CRL [10].

The reference standard, or best available method for establishing the presence of the target condition, was prenatal fetal karyotype by chorionic villous sampling or amniocentesis, postnatal karyotype from neonatal blood; absence of the target condition was established by either prenatal karyotyping or clinical examination of a phenotypically normal neonate.

Analysis

The previously described algorithm was used for the calculation of patient-specific risk of trisomy 21, trisomy 18 and trisomy 13 in each patient [1]. Two pre-specified analyses were then carried out. First, the observed screen positive rate and the standardized rates according to the maternal age distribution of England and Wales in 2011 [11], at risk cut-offs from 1 in 2 to 1 in 1000, of fetuses with abnormal and normal karyotype in screening by a combination of maternal age, fetal NT, serum free ß-hCG and PAPP-A with and without FHR. Second, the observed number and percentage of fetuses in each fetal karyotype group according to estimated risk derived from screening by a combination of maternal age, fetal NT, serum free ß-hCG and PAPP-A with and without FHR.

The statistical software package R was used for data analyses [12].

RESULTS

Participants

During the study period, we examined 115,838 singleton pregnancies. We excluded 6,856 (5.9%) cases because they had missing outcome data (n=5,150) or the fetal karyotype was not known and the pregnancies resulted in termination, miscarriage or stillbirth (n=1,706).

In the study population of 108,982 cases there were 108,112 (99.2%) cases with normal fetal karyotype or the birth of a phenotypically normal neonate and 870 (0.8%) cases with abnormal karyotype including trisomy 21 (n=432), trisomy 18 (n=166), trisomy 13 (n=56), mosomy X (n=63), triploidy (n=35) or other aneuploidy [n=118; sex chromosome aneuploidies (n=15), deletions or duplications (n=68), mosaic sex aneuploidies (n=11), mosaic deletions or duplications (n=6), and mosaic trisomies 2, 4, 8, 9, 13, 16, 21 or 22 (n=18)]. Baseline demographic and clinical characteristics of participants are shown in Table 1.

Test results

The screen positive rate, with 95% confidence interval, of fetuses with abnormal and normal karyotype in screening by the previously reported algorithm [1] are shown in Table 2. At a risk cut-off of 1 in 100 for trisomy 21 or 1 in 100 for trisomies 18 or 13, at the gestational age of screening, the observed FPR was 4.6% and the DR was 92, 96 and 93% for trisomies 21, 18 and 13, respectively; at the same risk cut-off, 98% of cases of Turner syndrome, 97% of triploidies and 55% of other chromosomal abnormalities were also detected. Inclusion of FHR in combined screening improved the DR of trisomy 13, especially at risk cut-offs of >1 in 50, but had no material effect on the DR of other chromosomal abnormalities. The risk cut-off of 1 in 100 for trisomy 21 at the gestational age of screening corresponds to a risk of 1 in 150 at term which is the cut-off recommended by the UK National Screening Committee to define the high-risk group that should be offered invasive testing or further screening by cfDNA testing.

The standardized rates according to the maternal age distribution of England and Wales in 2011 are shown in Table 3. At risk cut-off of 1 in 100, the FPR was about 4%, the DR of trisomy 21 was 90%, the DR of trisomy 18 was 97% and the DR of trisomy 13 was 92%; the respective values for risk cut-off of 1 in 10 were 0.6, 73, 91 and 85% and the values for risk cut-off if 1 in 1000 were 20, 98, 99 and 96%. These rates are compatible with those predicted from the previous algorithm [1]. The DR and screen positive rates for each trisomy are shown in Figure 1. Inclusion of FHR improves the performance of screening for trisomy 13, but not trisomies 21 and 18. Improvement of the DR for trisomy 21 from 96% to 98, 99 and 99.5% would necessitate an increase in screen positive rate from about 13% (risk cut-off 1 in 500) to 20% (risk cut-off 1 in 1,000), 40% (risk cut-off 1 in 3,500) and 54% (risk cut-off 1 in 6,500), respectively.

The observed number and percentage, with 95% confidence interval, of fetuses in each fetal karyotype group according to estimated risk for trisomy 21 and trisomies 18 or 13 derived from first-trimester combined screening are shown in Table 4 and illustrated in Figure 2. There was a tendency for the estimated risks to be overestimated but the 95% confidence interval for each observed prevalence of trisomies was within the estimated risks.

The observed and standardized rates in screening according to the UK National Screening Committee, where the risk cut-offs refer to risks at term rather than at the time of first-trimester screening, are given in supplementary Tables 1 and 2.

DISCUSSION

Main findings

The findings of this large prospective validation study demonstrate that the performance of first-trimester screening for trisomies 21, 18 and 13 by the combined test is similar to that estimated from the original model [1]. At a risk cut-off of 1 in 100 at the time of first-trimester screening the DR of each of the three trisomies was $\geq$90% at FPR of 4%. At this risk cut-off, nearly all cases of monosomy X and triploidy and more than half of all other chromosomal abnormalities can also be detected. Inclusion of FHR in the combined test, which takes only a few seconds to measure at no cost, improves the DR of trisomy 13.

There was a tendency for overestimation of risks for trisomies 21, 18 and 13 by the combined test, but the 95% confidence interval for each observed prevalence of trisomies was within the estimated risks. One possible explanation for such overestimate of risks is under ascertainment of these trisomies; in the 1,706 pregnancies excluded from the study because of termination, miscarriage or stillbirth without fetal karyotyping the rate of chromosomal abnormalities is likely to be overrepresented [13].

Study limitations

The main limitation of our screening study relates to ascertainment of pregnancy outcome. In the case of trisomies 21, 18 and 13 the lack of karyotyping in some terminations, miscarriages and stillbirths may have underestimated the performance of screening because these abnormalities are associated with a higher rate of intrauterine lethality than euploid fetuses, especially in the screen positive group. Unlike the situation with trisomies 21, 18 and 13, most neonates with sex chromosome aneuploidies and those in the heterogeneous group classified as other chromosomal abnormalities are often phenotypically normal [14]. Consequently, studies that do not involve karyotyping of the whole population will inevitably underestimate the true prevalence of these abnormalities and overestimate the potential

sensitivity of a prenatal screening test. For example, we previously reported that the erroneous conclusion could be reached that screening for trisomies 21, 18 and 13 by the combined test and carrying out an invasive test for those with a risk of ≥1:100 could identify 67% of fetuses with 47,XXY, 47,XYY or 47,XXX, but the true sensitivity may be as low as 8% [14].

Implications for practice

The combined test provides effective screening for trisomies 21, 18 and 13 and helps identify a high proportion of other chromosomal abnormalities, at FPR of 4%. In the last five years a major improvement in screening for trisomies has been achieved through analysis of cell-free (cf) DNA in maternal blood. A meta-analysis of clinical validation and implementation studies has reported that with cfDNA testing the DR for trisomies 21, 18 and 13 were 99%, 96% and 91%, respectively, at overall FPR of 0.35%.[15] Universal screening by cfDNA testing as an alternative to the combined test, would improve the DR of trisomy 21 and reduce the rate of invasive testing. However, such policy would be expensive and ignore the other benefits of the combined test, including early detection of many major fetal defects, diagnosis of multiple pregnancies and their chorionicity, detection of chromosomal defects beyond trisomies 21, 18 and 13 and early prediction of pregnancy complications, such as preeclampsia, with the potential of prevention through prophylactic pharmacological interventions.

The alternative to universal screening by the cfDNA test is a strategy of cfDNA testing contingent on the results of first-line screening by the combined test. This approach retains the major advantages of cfDNA testing in increasing DR and decreasing FPR, but at considerably lower cost than offering cfDNA testing to the whole population. As demonstrated in this study, at a combined test risk cut-off of 1 in 500 about 13% of the population would be selected and these would contain 96% of cases of trisomy 21. If the cut-off was increased to 1 in 1000 about 20% of the population would be selected and these would contain 98% of cases of trisomy 21. Further improvement in DR of trisomy 21 to 99% would necessitate the offer of cfDNA testing to 40% of the population.

A preferred third strategy is to offer invasive testing to pregnancies with a very high combined test risk of ≥1 in 10 and reserve cfDNA testing for an intermediate risk group with risk of 1 in 11 to 1 in 500 or 1 in 1000. The very high risk group of <1% of the population would contain about 80% of trisomies 21, 18 and 13 as well as >90% of cases of monosomy X, >85% of triploidies and >30% of other chromosomal abnormalities.

References

1. Kagan KO, Wright D, Valencia C, Maiz N, Nicolaides KH. Screening for trisomies 21, 18 and 13 by maternal age, fetal nuchal translucency, fetal heart rate, free {beta}-hCG and pregnancy-associated plasma protein-A. Hum Reprod 2008; **23**: 1968-1975.

2. Snijders RJM, Holzgreve W, Cuckle H, Nicolaides KH. Maternal age-specific risks for trisomies at 9–14 weeks' gestation. Prenat Diagn 1994; **14**: 543–552.

3. Snijders RJM, Sebire NJ, Cuckle H, Nicolaides KH. Maternal age and gestational age-specific risks for chromosomal defects. Fetal Diagn Ther 1995; **10**: 356–367.

4. Snijders RJM, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age and gestation-specific risk for trisomy 21. Ultrasound Obstet Gynecol 1999; **13**: 167–170.

5. Wright D, Kagan KO, Molina FS, Gazzoni A, Nicolaides KH. A mixture model of nuchal translucency thickness in screening for chromosomal defects. Ultrasound Obstet Gynecol 2008; **31**: 376-383.

6. Kagan KO, Wright D, Spencer K, Molina FS, Nicolaides KH. First-trimester screening for trisomy 21 by free beta human chorionic gonadotropin and pregnancy-associated plasma protein-A: impact of maternal and pregnancy characteristics. Ultrasound Obstet Gynecol 2008; **31**: 493–502.

7. Wright D, Spencer K, Kagan K, Tørring N, Petersen OB, Christou A, Kallikas J, Nicolaides KH. First-trimester combined screening for trisomy 21 at 7-14 weeks' gestation. Ultrasound Obstet Gynecol 2010; **36**: 404-411.

8. Office for National Statistics. Birth Statistics (2000–2002) Review of the Registrar General on Births and Patterns of Family Building in England and Wales. Series FM1, Nos 29–31. London: Stationary Office.

9. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, LijmerJG Moher D, Rennie D, de Vet HCW, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, For the STARD Group. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015; **351**: h5527.

10. Robinson HP, Fleming JE. A critical evaluation of sonar crown rump length measurements. Br J Obstet Gynaecol 1975; **182**: 702-710.

11. http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-241261

12. R Development Core Team. R. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2011;ISBN 3-900051-07-0, URL http://www.R-project.org/.

13. Akolekar R, Bower S, Flack N, Bilardo CM, Nicolaides KH. Prediction of miscarriage and stillbirth at 11-13 weeks and the contribution of chorionic villus sampling. Prenat Diagn 2011; **31**: 38-45.

14. Syngelaki A, Pergament E, Homfray T, Akolekar R, Nicolaides KH. Replacing the combined test by cell-free DNA testing in screening for trisomies 21, 18 and 13: impact on the diagnosis of other chromosomal abnormalities. Fetal Diagn Ther 2014; **35**: 174-84.

15. Gil MM, Quezada MS, Revello R, Akolekar R, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for fetal aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol* 2015; **45** : 249-266.

Figure legends

Figure 1. Relationship of detection rate (DR) and screen positive rate (SPR) in first trimester combined testing of a population with the maternal age distribution of pregnancies in England and Wales in 2011. The red circles illustrate the DR and SPR at cut-offs for the total risk of trisomies 21, 18 and 13 of 1 in 10, 1 in 100 and 1 in 1,000. The numbers in brackets on the Y-axis are the number of cases of trisomies in a population of 100,000 pregnancies at the time of screening. At a risk cut-off of 1 in 1,000 the SPR is about 20% and the DRs are 98%, 99% and 96% for trisomies 21, 18 and 13, respectively.

Figure 2. Prevalence of trisomies 21, 18 or 13, with 95% confidence intervals, plotted at the estimated mean risk within each group. There is a tendency for an overestimate of risks. The red boxes show the upper and lower limits of each risk group.

Table 1: Characteristics of study population. Footnote: Maternal characteristics in median (interquartile range) or n (%); * p<0.05

Maternal characteristics	**Abnormal karyotype**						**Normal (n=108,112)**
	T21 (n=432)	**T18 (n=166)**	**T13 (n=56)**	**Triploidy (n=35)**	**Turner (n=63)**	**Other (n=118)**	
Maternal Age in years	37.9 (34.7, 40.5)*	37.8 (33.0, 41.4)*	34.5 (29.9, 38.0)*	33.5 (30.2, 35.5)*	30.1 (26.2, 34.7)	33.9 (29.9, 37.9)*	31.5 (27.2, 35.2)
Maternal weight in Kg	65.8 (60.0, 74.85)	67.5 (60.4, 76.9)	69.8 (60.8, 79.9)	63.0 (57.6, 67.0)	65.5 (57.1, 75.6)	67.1 (60.0, 75.3)	66.0 (59.0, 76.0)
Maternal height in cm	165 (160, 170)	165 (161, 170)	165. (163, 172)*	167 (161, 170)	165 (160, 171)	165 (161, 170)	164 (160, 169)
Body mass index in Kg/m^2	24.3 (22.0, 27.2)	25.0 (22.2, 28.1)	25.3 (22.1, 27.8)	23.5 (21.7, 25.0)*	23.6 (21.3, 27.1)	23.7 (22.0, 27.7)	24.3 (21.8, 28.0)
Gestational age in weeks	12.8 (12.4, 13.2)*	12.1 (11.8, 12.5)*	12.3 (12.0, 12.7)*	12.0 (11.7, 12.5)*	12.5 (12.1, 12.9)*	12.6 (12.1, 13.0)*	12.7 (12.3, 13.1)
Racial origin	*						
Caucasian	348 (80.6)	117 (70.5)	46 (82.1)	26 (74.3)	51 (81.0)	85 (72.0)	78,552 (72.7)
Afro Caribbean	51 (11.8)	33 (19.9)	7 (12.5)	5 (14.3)	7 (11.1)	22 (18.6)	17,954 (16.6)
South Asian	13 (3.0)	8 (4.8)	2 (3.6)	2 (5.7)	4 (6.4)	6 (5.1)	5,744 (5.3)
East Asian	15 (3.5)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)	2,933 (2.7)
Mixed	5 (1.2)	5 (3.0)	1 (1.8)	2 (5.7)	1 (1.6)	2 (1.7)	2,929 (2.7)
Medical history							
Chronic hypertension	7 (1.6)	5 (3.0)	2 (3.6)	0 (0.0)	0 (0.0)	3 (2.5)	1,370 (1.3)
Diabetes mellitus	3 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	2 (3.2)	2 (1.7)	871 (0.8)
SLE / APS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	247 (0.2)
Smoker	33 (7.6)	11 (6.6)	2 (3.6)	1 (2.9)	6 (9.5)	11 (9.3)	9,287 (8.6)
Conception	*	*		*	*	*	
Spontaneous	396 (91.7)	147 (88.6)	53 (94.6)	33 (94.3)	56 (88.9)	110 (93.2)	104,242 (96.4)
In vitro fertilization	18 (4.2)	8 (4.8)	1 (1.8)	0 (0.0)	1 (1.6)	2 (1.7)	2,665 (2.5)
Ovulation drugs	18 (4.2)	11 (6.6)	2 (3.6)	2 (5.7)	6 (9.5)	6 (5.1)	1,205 (1.1)
Previous Trisomy 21	7 (1.6)*	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	361 (0.3)
Previous Trisomy 18	3 (0.7)*	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	133 (0.1)
Previous Trisomy 13	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	75 (0.1)
Pregnancy interval in years	3.4 (2.1, 6.2)*	3.6 (2.2, 7.7)*	2.9 (2.4, 4.4)	2.5 (2.0, 3.6)	3.4 (2.5, 5.4)	3.4 (2.2, 5.3)	2.9 (1.9, 4.8)

Table 2. Observed screen positive rate, with 95% confidence interval, of fetuses with abnormal and normal karyotype in screening by a combination of maternal age, fetal nuchal translucency thickness, serum free ß-hCG and PAPP-A and fetal heart rate (FHR) and at 11-13 weeks' gestation. In the lower part of the table are the rates derived from screening without FHR.

Risk cut-off	Abnormal karyotype														Normal karyotype (n=108,112)		All pregnancies (n=108,982)	
	Trisomy 21 (n=432)		Trisomy 18 (n=166)		Trisomy 13 (n=56)		Trisomy 21, 18, 13 (n=654)		45XO (n= 63)		Triploidy (n=35)		Other (n=118)					
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
With FHR																		
1 in 2	232	53.7 (48.9, 58.5)	137	82.5 (75.9, 88.0)	41	73.2 (59.7, 84.2)	410	62.7 (58.9, 66.4)	41	65.1 (52.0, 76.7)	28	80 (63.1, 91.6)	17	14.4 (8.6, 22.1)	185	0.2 (0.1, 0.2)	681	0.6 (0.6, 0.7)
1 in 5	289	66.9 (62.2, 71.3)	146	88.0 (82.0, 92.5)	45	80.4 (67.6, 89.8)	480	73.4 (69.8, 76.7)	55	87.3 (76.5, 94.4)	30	85.7 (69.7, 95.2)	32	27.1 (19.3, 36.1)	463	0.4 (0.4, 0.5)	1,060	1.0 (0.9, 1.0)
1 in 10	327	75.7 (71.4, 79.7)	151	91.0 (85.5, 94.9)	48	85.7 (73.8, 93.6)	526	80.4 (77.2, 83.4)	59	93.7 (84.5, 98.2)	30	85.7 (69.7, 95.2)	38	32.2 (23.9, 41.4)	833	0.8 (0.7, 0.8)	1,486	1.4 (1.3, 1.4)
1 in 25	356	82.4 (78.5, 85.9)	155	93.4 (88.5, 96.6)	51	91.1 (80.4, 97.0)	562	85.9 (83.0, 88.5)	61	96.8 (89.0, 99.6)	33	94.3 (80.8, 99.3)	51	43.2 (34.1, 52.7)	1,732	1.6 (1.5, 1.7)	2,439	2.2 (2.2, 2.3)
1 in 50	377	87.3 (83.8, 90.3)	157	94.6 (90.0, 97.5)	51	91.1 (80.4, 97.0)	585	89.4 (86.8, 91.7)	62	98.4 (91.5, 100)	33	94.3 (80.8, 99.3)	62	52.5 (43.1, 61.8)	2,957	2.7 (2.6, 2.8)	3,699	3.4 (3.3, 3.5)
1 in 100	**398**	**92.1 (89.2, 94.5)**	**160**	**96.4 (92.3, 98.7)**	**52**	**92.9 (82.7, 98.0)**	**610**	**93.3 (91.1, 95.1)**	**62**	**98.4 (91.5, 100)**	**34**	**97.1 (85.1, 99.9)**	**65**	**55.1 (45.7, 64.3)**	**4,989**	**4.6 (4.5, 4.7)**	**5,760**	**5.3 (5.2, 5.4)**
1 in 150	405	93.8 (91.0, 95.8)	161	97.0 (93.1, 99.0)	53	94.6 (85.1, 98.9)	619	94.6 (92.6, 96.2)	62	98.4 (91.5, 100)	34	97.1 (85.1, 99.9)	66	55.9 (46.5, 65.1)	6,790	6.3 (6.1, 6.4)	7,571	6.9 (6.8, 7.1)
1 in 200	408	94.4 (91.8, 96.4)	163	98.2 (94.8, 99.6)	53	94.6 (85.1, 98.9)	624	95.4 (93.5, 96.9)	62	98.4 (91.5, 100)	34	97.1 (85.1, 99.9)	69	58.5 (49.0, 67.5)	8,407	7.8 (7.6, 7.9)	9,196	8.4 (8.3, 8.6)
1 in 300	416	96.3 (94.1, 97.9)	164	98.8 (95.7, 99.9)	53	94.6 (85.1, 98.9)	633	96.8 (95.1, 98.0)	62	98.4 (91.5, 100)	34	97.1 (85.1, 99.9)	74	62.7 (53.3, 71.4)	11,261	10.4 (10.2, 10.6)	12,064	11.1 (10.9, 11.3)
1 in 500	420	97.2 (95.2, 98.6)	164	98.8 (95.7, 99.9)	54	96.4 (87.7, 99.6)	638	97.6 (96.1, 98.6)	63	100 (94.3, 100)	34	97.1 (85.1, 99.9)	79	66.9 (57.7, 75.3)	15,914	14.7 (14.5, 14.9)	16,728	15.3 (15.1, 15.6)
1 in 1,000	425	98.4 (96.7, 99.3)	165	99.4 (96.7, 100)	54	96.4 (87.7, 99.6)	644	98.5 (97.2, 99.3)	63	100 (94.3, 100)	35	100 (90.0, 100)	89	75.4 (66.6, 82.9)	25,618	23.7 (23.4, 24.0)	26,449	24.3 (24.0, 24.5)
No FHR																		
1 in 2	230	53.2 (48.4, 58.0)	136	81.9 (75.2, 87.5)	30	53.6 (39.7, 67.0)	396	60.6 (56.7, 64.3)	39	61.9 (48.8, 73.9)	25	71.4 (53.7, 85.4)	15	12.7 (7.3, 20.1)	162	0.1 (0.1, 0.2)	637	0.6 (0.5, 0.6)
1 in 5	289	66.9 (62.2, 71.3)	147	88.6 (82.7, 93.0)	38	67.9 (54.0, 79.7)	474	72.5 (68.9, 75.9)	54	85.7 (74.6, 93.3)	29	82.9 (66.4, 93.4)	30	25.4 (17.9, 34.3)	423	0.4 (0.4, 0.4)	1,010	0.9 (0.9, 1)
1 in 10	327	75.7 (71.4, 79.7)	153	92.2 (87.0, 95.8)	41	73.2 (59.7, 84.2)	521	79.7 (76.4, 82.7)	56	88.9 (78.4, 95.4)	30	85.7 (69.7, 95.2)	38	32.2 (23.9, 41.4)	788	0.7 (0.7, 0.8)	1,433	1.3 (1.2, 1.4)
1 in 25	355	82.2 (78.2, 85.7)	154	92.8 (87.7, 96.2)	46	82.1 (69.6, 91.1)	555	84.9 (81.9, 87.5)	61	96.8 (89.0, 99.6)	32	91.4 (76.9, 98.2)	55	46.6 (37.4, 56.0)	1,700	1.6 (1.5, 1.6)	2,403	2.2 (2.1, 2.3)
1 in 50	377	87.3 (83.8, 90.3)	157	94.6 (90.0, 97.5)	49	87.5 (75.9, 94.8)	583	89.1 (86.5, 91.4)	62	98.4 (91.5, 100)	33	94.3 (80.8, 99.3)	61	51.7 (42.3, 61.0)	2,931	2.7 (2.6, 2.8)	3,670	3.4 (3.3, 3.5)
1 in 100	**394**	**91.2 (88.1, 93.7)**	**160**	**96.4 (92.3, 98.7)**	**51**	**91.1 (80.4, 97.0)**	**605**	**92.5 (90.2, 94.4)**	**62**	**98.4 (91.5, 100)**	**34**	**97.1 (85.1, 99.9)**	**63**	**53.4 (44.0, 62.6)**	**5,075**	**4.7 (4.6, 4.8)**	**5,839**	**5.4 (5.2, 5.5)**
1 in 150	403	93.3 (90.5, 95.5)	162	97.6 (93.9, 99.3)	51	91.1 (80.4, 97.0)	616	94.2 (92.1, 95.9)	62	98.4 (91.5, 100)	34	97.1 (85.1, 99.9)	69	58.5 (49.0, 67.5)	6,912	6.4 (6.2, 6.5)	7,693	7.1 (6.9, 7.2)
1 in 200	406	94.0 (91.3, 96.0)	163	98.2 (94.8, 99.6)	51	91.1 (80.4, 97.0)	620	94.8 (92.8, 96.4)	62	98.4 (91.5, 100)	34	97.1 (85.1, 99.9)	71	60.2 (50.7, 69.1)	8,581	7.9 (7.8, 8.1)	9,368	8.6 (8.4, 8.8)
1 in 300	411	95.1 (92.7, 97.0)	164	98.8 (95.7, 99.9)	52	92.9 (82.7, 98.0)	627	95.9 (94.0, 97.3)	63	100 (94.3, 100)	34	97.1 (85.1, 99.9)	75	63.6 (54.2, 72.2)	11,539	10.7 (10.5, 10.9)	12,338	11.3 (11.1, 11.5)
1 in 500	419	97.0 (94.9, 98.4)	164	98.8 (95.7, 99.9)	54	96.4 (87.7, 99.6)	637	97.4 (95.9, 98.5)	63	100 (94.3, 100)	34	97.1 (85.1, 99.9)	80	67.8 (58.6, 76.1)	16,381	15.2 (14.9, 15.4)	17,195	15.8 (15.6, 16.0)
1 in 1,000	427	98.8 (97.3, 99.6)	165	99.4 (96.7, 100)	55	98.2 (90.4, 100)	647	98.9 (97.8, 99.6)	63	100 (94.3, 100)	35	100 (90.0, 100)	89	75.4 (66.6, 82.9)	26,388	24.4 (24.2, 24.7)	27,222	25.0 (24.7, 25.2)

Table 3. Standardized screen positive rate, with 95% confidence interval, of fetuses with abnormal and normal karyotype in screening by a combination of maternal age, fetal nuchal translucency thickness, serum free ß-hCG and PAPP-A and fetal heart rate (FHR) and at 11-13 weeks' gestation. In the lower part of the table are the rates derived from screening without FHR. The rates were standardized according to the maternal age distribution in England and Wales in 2011. The risk cut-off for trisomy 21 for defining the high-risk group is 1 in 100 at the time of screening at 11-13 weeks' gestation, which is equivalent to the cut-off of 1 in 150 at birth recommended by the UK National Screening Committee.

Risk cut-off	Trisomy				Normal karyotype/ phenotype
	21	18	13	21, 18 or 13	
With FHR					
1 in 2	51 (47, 55)	81 (74, 87)	76 (65, 86)	61 (58, 64)	0.11 (0.1, 0.12)
1 in 5	66 (62, 69)	88 (82, 94)	82 (72, 92)	73 (70, 76)	0.34 (0.31, 0.36)
1 in 10	73 (69, 77)	91 (86, 96)	85 (76, 94)	79 (76, 81)	0.63 (0.6, 0.67)
1 in 25	81 (77, 84)	94 (89, 98)	88 (80, 97)	85 (82, 87)	1.35 (1.3, 1.39)
1 in 50	86 (83, 89)	96 (91, 99.9)	91 (83, 99)	89 (87, 91)	2.32 (2.26, 2.39)
1 in 100	**90 (87, 92)**	**97 (93, 99.9)**	**92 (85, 99.9)**	**92 (90, 94)**	**3.97 (3.89, 4.06)**
1 in 150	92 (89, 94)	97 (94, 99.9)	93 (86, 99.9)	93 (92, 95)	5.38 (5.29, 5.47)
1 in 200	93 (91, 95)	98 (94, 99.9)	94 (87, 99.9)	94 (93, 96)	6.64 (6.54, 6.75)
1 in 300	95 (93, 96)	98 (95, 99.9)	94 (88,99.9)	95 (94, 97)	8.90 (8.78, 9.01)
1 in 500	96 (95, 98)	99 (96,99.9)	95 (89, 99.9)	97 (96, 98)	12.67 (12.53, 12.81)
1 in 1,000	98 (97, 99)	99 (97, 99.9)	96 (92, 99.9)	98 (97, 99)	19.97 (19.8, 20.15)
No FHR					
1 in 2	51 (47, 54)	80 (73, 87)	57 (47, 68)	59 (56, 61)	0.14 (0.12, 0.15)
1 in 5	65 (61, 69)	88 (82, 93)	69 (59, 79)	71 (69, 74)	0.38 (0.35, 0.4)
1 in 10	73 (69, 77)	91 (86, 96)	75 (66, 85)	78 (75, 80)	0.67 (0.64, 0.71)
1 in 25	81 (78, 84)	94 (89, 98)	81 (73, 90)	84 (82, 86)	1.37 (1.33, 1.42)
1 in 50	86 (83, 89)	95 (91, 99)	85 (77, 94)	88 (86, 90)	2.32 (2.25, 2.38)
1 in 100	**90 (87, 92)**	**97 (93, 99.9)**	**89 (82, 97)**	**91 (90, 93)**	**3.90 (3.82, 3.99)**
1 in 150	92 (89, 94)	97 (93, 99.9)	92 (85, 99)	93 (92, 95)	5.25 (5.16, 5.35)
1 in 200	93 (91, 95)	98 (94, 99.9)	93 (86, 99.9)	94 (93, 96)	6.46 (6.36, 6.56)
1 in 300	95 (93, 96)	98 (95, 99.9)	94 (88, 99.9)	95 (94, 97)	8.62 (8.5, 8.73)
1 in 500	96 (95, 98)	99 (96, 99.9)	96 (90, 99.9)	97 (96, 98)	12.25 (12.11, 12.39)
1 in 1,000	98 (96, 99)	99 (97, 99.9)	97 (92, 99.9)	98 (97, 99)	19.26 (19.08, 19.43)

Table 4. Observed number and percentage, with 95% confidence interval, of fetuses in each fetal karyotype group according to estimated risk derived from screening by a combination of maternal age, fetal nuchal translucency thickness, serum free ß-hCG and PAPP-A and fetal heart rate (FHR) and at 11-13 weeks' gestation. In the lower part of the table are the rates derived from screening without FHR.

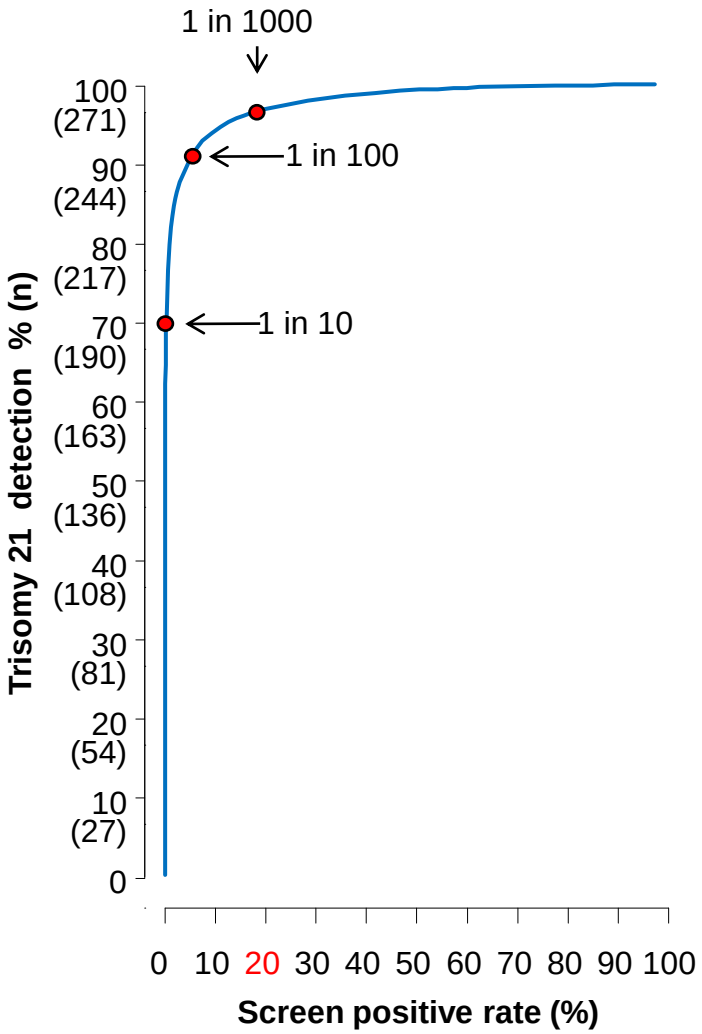
Risk category	Abnormal karyotype														Normal karyotype/ phenotype (n=108,112)		All pregnancies (n=108,982)
	Trisomy 21 (n=432)		Trisomy 18 (n=166)		Trisomy 13 (n=56)		Trisomy 21, 18, 13 (n=654)		45XO (n= 63)		Triploidy (n=35)		Other (n=118)				
With FHR																	
>50%	232	34.1 (30.5, 37.6)	137	20.1 (17.2, 23.1)	41	6 (4.4, 8)	410	60.2 (56.4, 63.5)	41	6 (4.4, 8.0)	28	4.1 (2.7, 5.8)	17	2.5 (1.5, 4.1)	185	27.2 (23.9, 31.0)	681
20% - 50%	57	15 (11.6, 18.4)	9	2.4 (1.1, 4.3)	4	1.1 (0.3, 2.6)	70	18.5 (14.7, 22.0)	14	3.7 (2.0, 5.9)	2	0.5 (0.1, 1.8)	15	4 (2.2, 5.9)	278	73.4 (68.6, 78.7)	379
10% - 20%	38	8.9 (6.4, 11.8)	5	1.2 (0.4, 2.7)	3	0.7 (0.1, 2.0)	46	10.8 (8.0, 13.9)	4	0.9 (0.3, 2.4)	0	0.0 (0.0, 0.9)	6	1.4 (0.5, 3.0)	370	86.9 (83.3, 90.1)	426
4% -10%	29	3 (2.0, 4.4)	4	0.4 (0.1, 1.1)	3	0.3 (0.1, 0.9)	36	3.8 (2.7, 5.2)	2	0.2 (0.0, 0.7)	3	0.3 (0.1, 0.9)	13	1.4 (0.7, 2.3)	899	94.3 (92.7, 95.7)	953
2% - 4%	21	1.7 (1.0, 2.4)	2	0.2 (0.0, 0.6)	0	0.0 (0.0, 0.3)	23	1.8 (1.2, 2.6)	1	0.1 (0.0, 0.4)	0	0.0 (0.0, 0.3)	11	0.9 (0.4, 1.5)	1,225	97.2 (96.2, 98.1)	1,260
1% - 2%	21	1.0 (0.6, 1.5)	3	0.1 (0.0, 0.4)	1	0 (0.0, 0.3)	25	1.2 (0.8, 1.8)	0	0.0 (0.0, 0.2)	1	0.0 (0.0, 0.3)	3	0.1 (0.0, 0.4)	2,032	98.6 (98.0, 99.1)	2,061
0.67% - 1%	7	0.4 (0.2, 0.8)	1	0.1 (0.0, 0.3)	1	0.1 (0.0, 0.3)	9	0.5 (0.2, 0.9)	0	0.0 (0.0, 0.2)	0	0.0 (0.0, 0.2)	1	0.1 (0.0, 0.3)	1,801	99.4 (99.0, 99.7)	1,811
0.5% - 0.67%	3	0.2 (0.0, 0.5)	2	0.1 (0.0, 0.4)	0	0.0 (0.0, 0.2)	5	0.3 (0.1, 0.7)	0	0.0 (0.0, 0.2)	0	0.0 (0.0, 0.2)	3	0.2 (0.0, 0.5)	1,617	99.5 (99.0, 99.8)	1,625
0.33% - 0.5%	8	0.3 (0.1, 0.5)	1	0.0 (0.0, 0.2)	0	0.0 (0.0, 0.1)	9	0.3 (0.1, 0.6)	0	0.0 (0.0, 0.1)	0	0.0 (0.0, 0.1)	5	0.2 (0.1, 0.4)	2,854	99.5 (99.2, 99.7)	2,868
0.2% - 0.33%	4	0.1 (0.0, 0.2)	0	0.0 (0.0, 0.1)	1	0.0 (0.0, 0.1)	5	0.1 (0.0, 0.2)	1	0.0 (0.0, 0.1)	0	0.0 (0.0, 0.1)	5	0.1 (0.0, 0.2)	4,653	99.8 (99.6, 99.9)	4,664
0.1% - 0.2%	5	0.1 (0.02, 0.12)	1	0.0 (0.0, 0.06)	0	0.0 (0.0, 0.04)	6	0.1 (0.02, 0.13)	0	0.0 (0.0, 0.04)	1	0.0 (0.0, 0.06)	10	0.1 (0.05, 0.19)	9,704	99.8 (99.7, 99.9)	9,721
<0.1%	7	0.01 (0.0, 0.02)	1	0.0 (0.0, 0.01)	2	0.0 (0.0, 0.01)	10	0.01 (0.01, 0.02)	0	0.0 (0.0, 0.0)	0	0.0 (0.0, 0.0)	29	0.04 (0.02, 0.05)	82,494	100 (99.9, 100)	82,533
No FHR																	
>50%	230	36.1 (32.4, 2)	136	21.4 (18.2, 40)	30	4.7 (3.2, 24.7)	396	62.2 (58.3, 6.7)	39	6.1 (4.4, 65.9)	25	3.9 (2.6, 8.3)	15	2.4 (1.3, 5.7)	162	25.4 (22.1, 22.8)	637
20% - 50%	59	15.8 (12.3, 5)	11	2.9 (1.5, 19.9)	8	2.1 (0.9, 5.2)	78	20.9 (16.9, 4.2)	15	4 (2.3, 25.4)	4	1.1 (0.3, 6.5)	15	4 (2.3, 2.7)	261	70 (65, 63.5)	373
10% - 20%	38	9 (6.4, 10)	6	1.4 (0.5, 12.1)	3	0.7 (0.1, 3.1)	47	11.1 (8.3, 2.1)	2	0.5 (0.1, 14.5)	1	0.2 (0, 1.7)	8	1.9 (0.8, 1.3)	365	86.3 (82.6, 78.8)	423
4% -10%	28	2.9 (1.9, 25)	1	0.1 (0, 4.1)	5	0.5 (0.2, 0.6)	34	3.5 (2.4, 1.2)	5	0.5 (0.2, 4.9)	2	0.2 (0, 1.2)	17	1.8 (1, 0.7)	912	94 (92.3, 85.2)	970
2% - 4%	22	1.7 (1.1, 50)	3	0.2 (0, 2.6)	3	0.2 (0, 0.7)	28	2.2 (1.5, 0.7)	1	0.1 (0, 3.2)	1	0.1 (0, 0.4)	6	0.5 (0.2, 0.4)	1,231	97.2 (96.1, 87.3)	1,267
1% - 2%	17	0.8 (0.5, 100)	3	0.1 (0, 1.3)	2	0.1 (0, 0.4)	22	1 (0.6, 0.3)	0	0 (0, 1.5)	1	0 (0, 0.2)	2	0.1 (0, 0.3)	2,144	98.8 (98.3, 89)	2,169
0.67% - 1%	9	0.5 (0.2, 150)	2	0.1 (0, 0.9)	0	0 (0, 0.4)	11	0.6 (0.3, 0.2)	0	0 (0, 1.1)	0	0 (0, 0.2)	6	0.3 (0.1, 0.2)	1,837	99.1 (98.5, 90.8)	1,854
0.5% - 0.67%	3	0.2 (0, 200)	1	0.1 (0, 0.5)	0	0 (0, 0.3)	4	0.2 (0.1, 0.2)	0	0 (0, 0.6)	0	0 (0, 0.2)	2	0.1 (0, 0.2)	1,669	99.6 (99.2, 91.3)	1,675
0.33% - 0.5%	5	0.2 (0.1, 300)	1	0 (0, 0.4)	1	0 (0, 0.2)	7	0.2 (0.1, 0.2)	1	0 (0, 0.5)	0	0 (0, 0.2)	4	0.1 (0, 0.1)	2,958	99.6 (99.3, 92)	2,970
0.2% - 0.33%	8	0.2 (0.1, 500)	0	0 (0, 0.3)	2	0 (0, 0.1)	10	0.2 (0.1, 0.1)	0	0 (0, 0.4)	0	0 (0, 0.1)	5	0.1 (0, 0.1)	4,842	99.7 (99.5, 92.2)	4,857
0.1% - 0.2%	8	0.1 (0.03, 1000)	1	0 (0, 0.16)	1	0 (0, 0.06)	10	0.1 (0.05, 0.06)	0	0 (0, 0.18)	1	0 (0, 0.04)	9	0.1 (0.04, 0.06)	10,007	99.8 (99.7, 92.8)	10,027
<0.1%	5	0.01 (0, 1E+22)	1	0 (0, 0.01)	1	0 (0, 0.01)	7	0.01 (0, 0.01)	0	0 (0, 0.02)	0	0 (0, 0)	29	0.04 (0.02, 0)	81724	100 (99.9, 93.7)	81,760

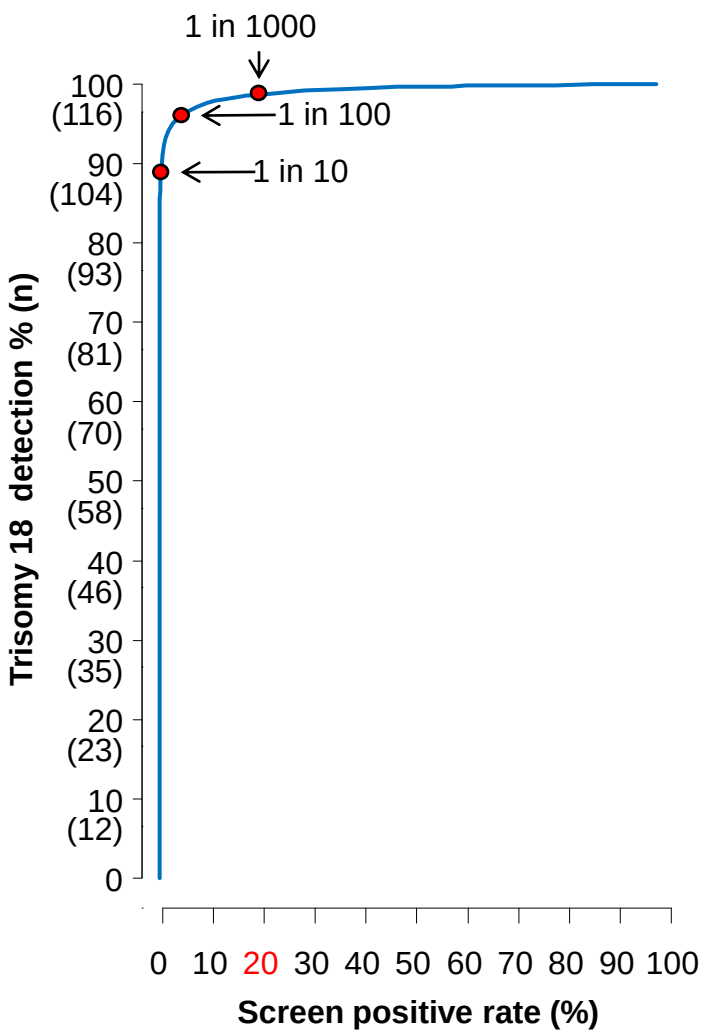
Supplementary Table 2. Standardized screen positive rate, with 95% confidence interval, of fetuses with abnormal and normal karyotype in screening by a combination of maternal age, fetal nuchal translucency thickness, serum free ß-hCG and PAPP-A at 11-13 weeks' gestation according to the method proposed by the UK National Screening Committee (NSC). In the upper part of the table are the rates derived from screening with fetal heart rate (FHR) and in the lower part are the rates without FHR. The rates were standardized according to the maternal age distribution in England and Wales in 2011. According to the recommendations of the NSC the high-risk group is defined by the risk cut-off of 1 in 150 at birth.

Risk cut-off	Trisomy				Normal karyotype/ phenotype
	21	18	13	21, 18 or 13	
With FHR					
1 in 2	46 (43, 50)	66 (59, 72)	61 (51, 72)	53 (50, 55)	0.08 (0.06, 0.09)
1 in 5	62 (58, 66)	78 (73, 84)	75 (65, 85)	67 (65, 70)	0.23 (0.21, 0.25)
1 in 10	70 (66, 74)	83 (78, 89)	80 (71, 90)	74 (72, 77)	0.42 (0.39, 0.45)
1 in 25	78 (75, 82)	88 (83, 93)	85 (76, 93)	81 (79, 84)	0.87 (0.82, 0.92)
1 in 50	84 (81, 87)	91 (86, 95)	87 (79, 95)	86 (83, 88)	1.49 (1.42, 1.55)
1 in 100	88 (85, 90)	93 (89, 97)	89 (82, 97)	89 (87, 91)	2.54 (2.46, 2.62)
1 in 150	**90 (88, 92)**	**94 (90, 97)**	**90 (83, 97)**	**91 (89, 93)**	**3.46 (3.37, 3.55)**
1 in 200	91 (89, 93)	94 (91, 98)	91 (84, 98)	92 (90, 94)	4.29 (4.18, 4.39)
1 in 300	93 (91, 95)	95 (92, 98)	92 (85, 98)	93 (92, 95)	5.77 (5.66, 5.89)
1 in 500	95 (93, 96)	96 (93, 99)	93 (87, 99)	95 (94, 96)	8.36 (8.22, 8.5)
1 in 1,000	97 (96, 98)	97 (95, 99)	94 (90, 99)	97 (96, 98)	13.48 (13.31, 13.66)
Without FHR					
1 in 2	44 (40, 48)	63 (57, 70)	40 (30, 51)	49 (45, 52)	0.06 (0.05, 0.08)
1 in 5	60 (56, 64)	78 (72, 83)	56 (46, 66)	64 (61, 67)	0.20 (0.18, 0.22)
1 in 10	68 (65, 72)	83 (78, 88)	64 (54, 73)	72 (69, 74)	0.38 (0.35, 0.41)
1 in 25	77 (74, 81)	88 (83, 93)	72 (63, 80)	79 (77, 82)	0.83 (0.78, 0.88)
1 in 50	83 (80, 86)	91 (87, 95)	77 (68, 85)	84 (82, 87)	1.44 (1.37, 1.5)
1 in 100	87 (85, 90)	93 (89, 97)	81 (74, 89)	88 (86, 90)	2.48 (2.4, 2.57)
1 in 150	**90 (87, 92)**	**94 (90, 98)**	**84 (77, 91)**	**90 (88, 92)**	**3.40 (3.31, 3.5)**
1 in 200	91 (89, 93)	95 (91, 98)	86 (79, 93)	91 (90, 93)	4.24 (4.14, 4.34)
1 in 300	93 (91, 94)	95 (92, 98)	88 (82, 95)	93 (91, 94)	5.75 (5.64, 5.87)
1 in 500	95 (93, 96)	96 (94, 99)	91 (85, 97)	95 (93, 96)	8.35 (8.21, 8.5)
1 in 1,000	97 (95, 98)	97 (95, 99)	94 (89, 99)	97 (95, 98)	13.56 (13.38, 13.73)

Supplementary Table 1. Observed screen positive rate, with 95% confidence interval, of fetuses with abnormal and normal karyotype in screening by a combination of maternal age, fetal nuchal translucency thickness, serum free ß-hCG and PAPP-A at 11-13 weeks' gestation according to the method proposed by the UK National Screening Committee (NSC). In the upper part of the table are the rates derived from screening with fetal heart rate (FHR) and in the lower part are the rates without FHR. According to the recommendations of the NSC the high-risk group is defined by the risk cut-off of 1 in 150 at birth.

Risk cut-off	Abnormal karyotype														Normal karyotype/ phenotype (n=108,112)	
	Trisomy 21 (n=432)		Trisomy 18 (n=166)		Trisomy 13 (n=56)		Trisomy 21, 18, 13 (n=654)		45XO (n= 63)		Triploidy (n=35)		Other (n=118)			
With FHR																
1 in 2	207	47.9 (43.1, 52.7)	114	68.7 (61, 75.6)	33	58.9 (45, 71.9)	354	54.1 (50.2, 58)	30	47.6 (34.9, 60.6)	26	74.3 (56.7, 87.5)	12	10.2 (5.4, 17.1)	110	0.1 (0.1, 0.1)
1 in 5	271	62.7 (58, 67.3)	130	78.3 (71.3, 84.3)	42	75.0 (61.6, 85.6)	443	67.7 (64, 71.3)	47	74.6 (62.1, 84.7)	28	80 (63.1, 91.6)		18.6 (12.1, 26.9)	290	0.3 (0.2, 0.3)
1 in 10	309	71.5 (67, 75.7)	139	83.7 (77.2, 89)	42	75.0 (61.6, 85.6)	490	74.9 (71.4, 78.2)	54	85.7 (74.6, 93.3)	30	85.7 (69.7, 95.2)	27	22.9 (15.7, 31.5)	518	0.5 (0.4, 0.5)
1 in 25	347	80.3 (76.3, 84)	149	89.8 (84.1, 93.9)	47	83.9 (71.7, 92.4)	543	83 (79.9, 85.8)	58	92.1 (82.4, 97.4)	31	88.6 (73.3, 96.8)	43	36.4 (27.8, 45.8)	1,110	1 (1, 1.1)
1 in 50	363	84 (80.2, 87.4)	151	91 (85.5, 94.9)	50	89.3 (78.1, 96.0)	564	86.2 (83.4, 88.8)	60	95.2 (86.7, 99)	33	94.3 (80.8, 99.3)	56	47.5 (38.2, 56.9)	1,885	1.7 (1.7, 1.8)
1 in 100	385	89.1 (85.8, 91.9)	155	93.4 (88.5, 96.6)	51	91.1 (80.4, 97.0)	591	90.4 (87.8, 92.5)	62	98.4 (91.5, 99.96)	33	94.3 (80.8, 99.3)	61	51.7 (42.3, 61)	3,268	3 (2.9, 3.1)
1 in 150	**399**	**92.4 (89.4, 94.7)**	**155**	**93.4 (88.5, 96.6)**	**51**	**91.1 (80.4, 97.0)**	**605**	**92.5 (90.2, 94.4)**	**62**	**98.4 (91.5, 99.96)**	**34**	**97.1 (85.1, 99.9)**	**63**	**53.4 (44, 62.6)**	**4,430**	**4.1 (4, 4.2)**
1 in 200	402	93.1 (90.2, 95.3)	155	93.4 (88.5, 96.6)	52	92.9 (82.7, 98.0)	609	93.1 (90.9, 94.9)	62	98.4 (91.5, 99.96)	34	97.1 (85.1, 99.9)	63	53.4 (44, 62.6)	5,465	5.1 (4.9, 5.2)
1 in 300	409	94.7 (92.1, 96.6)	157	94.6 (90, 97.5)	52	92.9 (82.7, 98.0)	618	94.5 (92.5, 96.1)	62	98.4 (91.5, 99.96)	34	97.1 (85.1, 99.9)	64	54.2 (44.8, 63.4)	7,455	6.9 (6.7, 7)
1 in 500	417	96.5 (94.3, 98)	159	95.8 (91.5, 98.3)	52	92.9 (82.7, 98.0)	628	96 (94.2, 97.4)	62	98.4 (91.5, 99.96)	34	97.1 (85.1, 99.9)	72	61 (51.6, 69.9)	10,695	9.9 (9.7, 10.1)
1 in 1,000	422	97.7 (95.8, 98.9)	161	97 (93.1, 99)	54	96.4 (87.7, 99.6)	637	97.4 (95.9, 98.5)	63	100 (94.3, 100)	34	97.1 (85.1, 99.9)	80	67.8 (58.6, 76.1)	17,177	15.9 (15.7, 16.1)
No FHR																
1 in 2	199	46.1 (41.3, 50.9)	107	64.5 (56.7, 71.7)	19	33.9 (21.8, 47.8)	325	49.7 (45.8, 53.6)	25	39.7 (27.6, 52.8)	22	62.9 (44.9, 78.5)	10	8.5 (4.1, 15.0)	93	0.1 (0.1, 0.1)
1 in 5	270	62.5 (57.7, 67.1)	129	77.7 (70.6, 83.8)	28	50.0 (36.3, 63.7)	427	65.3 (61.5, 68.9)	43	68.3 (55.3, 79.4)	27	77.1 (59.9, 89.6)	18	15.3 (9.3, 23.0)	204	0.2 (0.2, 0.3)
1 in 10	308	71.3 (66.8, 75.5)	140	84.3 (77.9, 89.5)	35	62.5 (48.5, 75.1)	483	73.9 (70.3, 77.2)	51	81.0 (69.1, 89.8)	29	82.9 (66.4, 93.4)	27	22.9 (15.7, 31.5)	506	0.5 (0.4, 0.5)
1 in 25	346	80.1 (76.0, 83.8)	148	89.2 (83.4, 93.4)	40	71.4 (57.8, 82.7)	534	81.7 (78.5, 84.5)	59	93.7 (84.5, 98.2)	30	85.7 (69.7, 95.2)	43	36.4 (27.8, 45.8)	1,093	1.0 (1.0, 1.1)
1 in 50	364	84.3 (80.5, 87.6)	153	92.2 (87.0, 95.8)	43	76.8 (63.6, 87.0)	560	85.6 (82.7, 88.2)	60	95.2 (86.7, 99.0)	32	91.4 (76.9, 98.2)	57	48.3 (39.0, 57.7)	1,866	1.7 (1.6, 1.8)
1 in 100	383	88.7 (85.3, 91.5)	154	92.8 (87.7, 96.2)	45	80.4 (67.6, 89.8)	582	89.0 (86.3, 91.3)	62	98.4 (91.5, 99.96)	33	94.3 (80.8, 99.3)	61	51.7 (42.3, 61.0)	3,227	3.0 (2.9, 3.1)
1 in 150	**395**	**91.4 (88.4, 93.9)**	**154**	**92.8 (87.7, 96.2)**	**48**	**85.7 (73.8, 93.6)**	**597**	**91.3 (88.9, 93.3)**	**62**	**98.4 (91.5, 99.96)**	**34**	**97.1 (85.1, 99.9)**	**61**	**51.7 (42.3, 61.0)**	**4,407**	**4.1 (4.0, 4.2)**
1 in 200	401	92.8 (90.0, 95.1)	155	93.4 (88.5, 96.6)	49	87.5 (75.9, 94.8)	605	92.5 (90.2, 94.4)	62	98.4 (91.5, 99.96)	34	97.1 (85.1, 99.9)	63	53.4 (44.0, 62.6)	5,523	5.1 (5.0, 5.2)
1 in 300	407	94.2 (91.6, 96.2)	156	94.0 (89.2, 97.1)	49	87.5 (75.9, 94.8)	612	93.6 (91.4, 95.3)	62	98.4 (91.5, 99.96)	34	97.1 (85.1, 99.9)	65	55.1 (45.7, 64.3)	7,548	7.0 (6.8, 7.1)
1 in 500	413	95.6 (93.2, 97.3)	160	96.4 (92.3, 98.7)	51	91.1 (80.4, 97.0)	624	95.4 (93.5, 96.9)	62	98.4 (91.5, 99.96)	34	97.1 (85.1, 99.9)	71	60.2 (50.7, 69.1)	10,898	10.1 (9.9, 10.3)
1 in 1,000	422	97.7 (95.8, 98.9)	162	97.6 (93.9, 99.3)	53	94.6 (85.1, 98.9)	637	97.4 (95.9, 98.5)	63	100 (94.3, 100)	34	97.1 (85.1, 99.9)	81	68.6 (59.5, 76.9)	17,457	16.1 (15.9, 16.4)


1 in 1000
1 in 100
1 in 10
Trisomy 21 detection % (n)
100 (271)
90 (244)
80 (217)
70 (190)
60 (163)
50 (136)
40 (108)
30 (81)
20 (54)
10 (27)
0
0 10 20 30 40 50 60 70 80 90 100
Screen positive rate (%)


1 in 1000
1 in 100
1 in 10
Trisomy 18 detection % (n)
100 (116)
90 (104)
80 (93)
70 (81)
60 (70)
50 (58)
40 (46)
30 (35)
20 (23)
10 (12)
0
0 10 20 30 40 50 60 70 80 90 100
Screen positive rate (%)

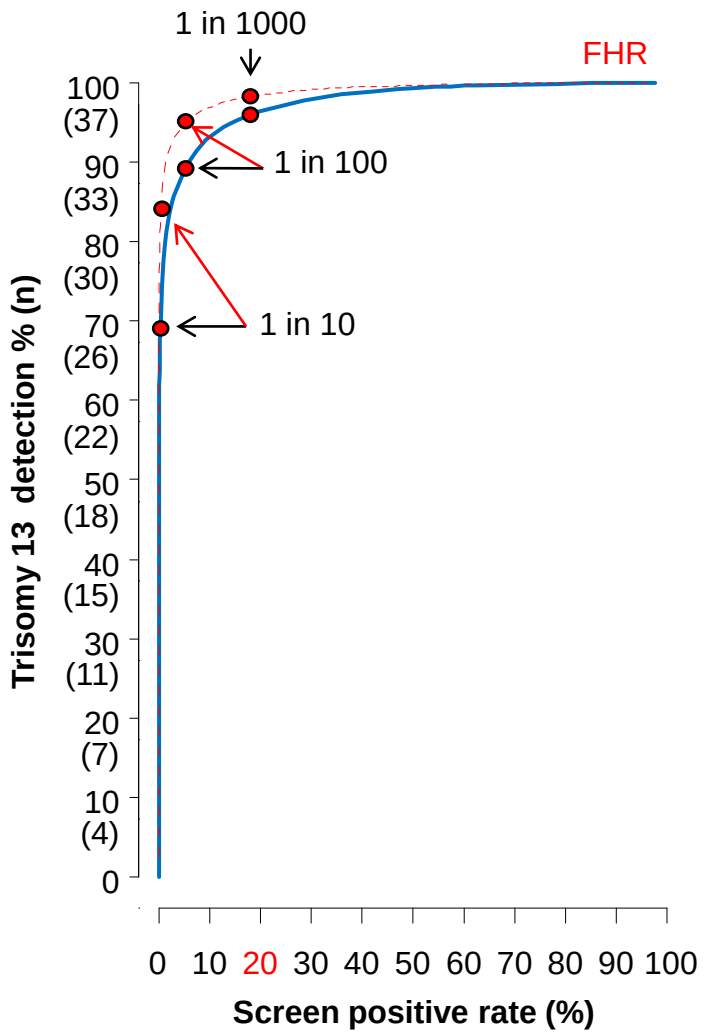

1 in 1000
FHR
1 in 100
1 in 10
Trisomy 13 detection % (n)
100 (37)
90 (33)
80 (30)
70 (26)
60 (22)
50 (18)
40 (15)
30 (11)
20 (7)
10 (4)
0
0 10 20 30 40 50 60 70 80 90 100
Screen positive rate (%)

Figure 1

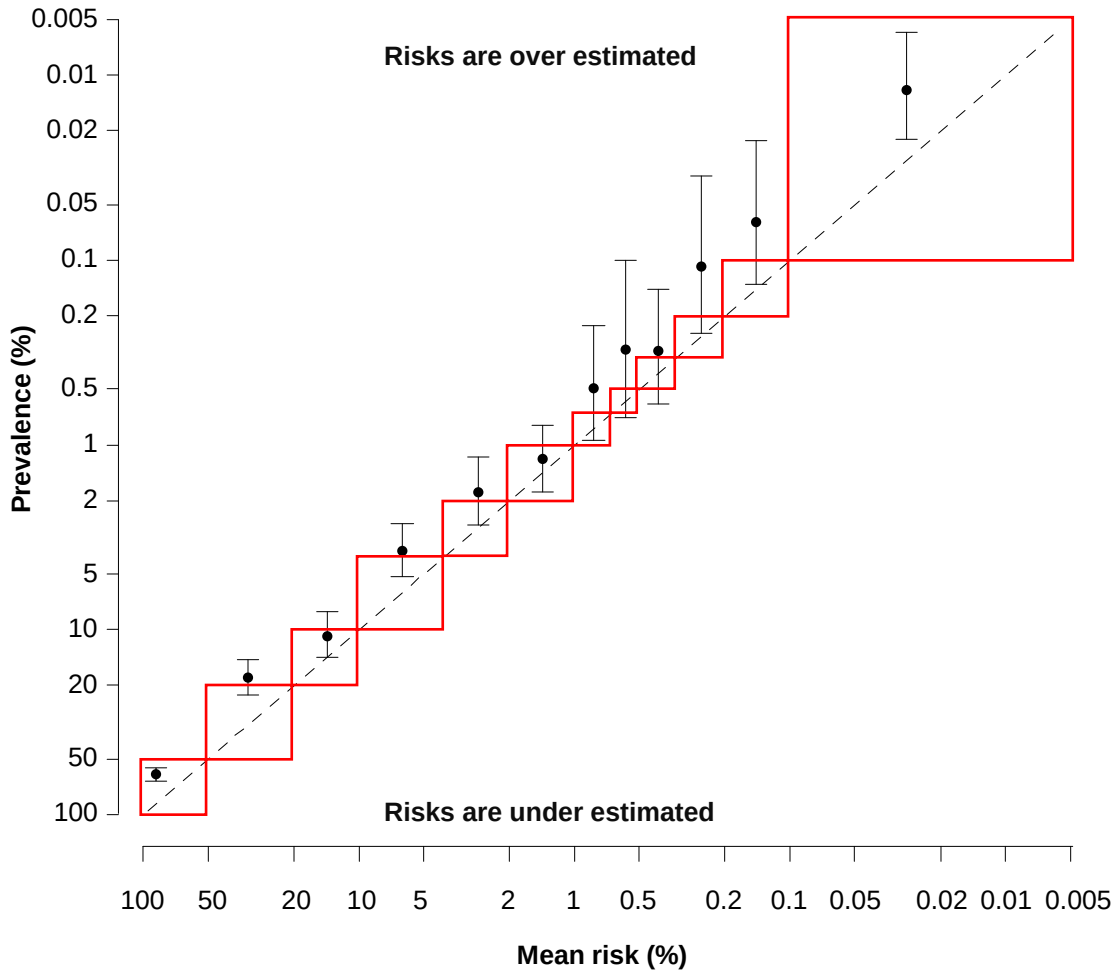

Risks are over estimated
Risks are under estimated
Prevalence (%)
0.005
0.01
0.02
0.05
0.1
0.2
0.5
1
2
5
10
20
50
100
100 50 20 10 5 2 1 0.5 0.2 0.1 0.05 0.02 0.01 0.005
Mean risk (%)

Figure 2