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Cross-trimester repeated measures testing for Down's syndrome screening: an assessment

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Abstract

Cross-trimester repeated measures testing for Down's syndrome screening: an assessment

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Objectives: To provide estimates and confidence intervals for the performance (detection and false-positive rates) of screening for Down's syndrome using repeated measures of biochemical markers from first and second trimester maternal serum samples taken from the same woman.

Design: Stored serum on Down's syndrome cases and controls was used to provide independent test data for the assessment of screening performance of published risk algorithms and for the development and testing of new risk assessment algorithms.

Setting: 15 screening centres across the USA, and at the North York General Hospital, Toronto, Canada.

Participants: 78 women with pregnancy affected by Down's syndrome and 390 matched unaffected controls, with maternal blood samples obtained at 11–13 and 15–18 weeks' gestation, and women who received integrated prenatal screening at North York General Hospital at two time intervals: between 1 December 1999 and 31 October 2003, and between 1 October 2006 and 23 November 2007.

Interventions: Repeated measurements (first and second trimester) of maternal serum levels of human chorionic gonadotrophin (hCG), unconjugated estriol (uE3) and pregnancy-associated plasma protein A (PAPP-A) together with alpha-fetoprotein (AFP) in the second trimester.

Main outcome measures: Detection and false-positive rates for screening with a threshold risk of 1 in 200 at term, and the detection rate achieved for a false-positive rate of 2%.

Results: Published distributional models for Down's syndrome were inconsistent with the test data. When these test data were classified using these models, screening performance deteriorated substantially through the addition of repeated measures. This contradicts the very optimistic results obtained from predictive modelling of performance. Simplified distributional assumptions showed some evidence of benefit from the use of repeated measures of PAPP-A but not for repeated measures of uE3 or hCG. Each of the two test data sets was used to create new parameter estimates against which screening test performance was assessed using the other data set. The results were equivocal but there was evidence suggesting improvement in screening performance through the use of repeated measures of PAPP-A when the first trimester sample was collected before 13 weeks' gestation. A Bayesian analysis of the combined data from the two test data sets showed that adding a second trimester repeated measurement of PAPP-A to the base test increased detection rates and reduced false-positive rates. The benefit decreased with increasing gestational age at the time of the first

sample. There was no evidence of any benefit from repeated measures of hCG or uE3.

Conclusions: If realised, a reduction of 1% in false-positive rate with no loss in detection rate would give important benefits in terms of health service provision and the large number of invasive tests avoided. The Bayesian analysis, which shows evidence of benefit, is based on strong distributional assumptions and should not be regarded as confirmatory. The evidence of potential benefit suggests the need for a prospective study of repeated measurements of PAPP-A with samples from early in the first trimester. A formal clinical effectiveness and cost-effectiveness analysis should be undertaken. This study has shown that the established modelling methodology for assessing screening performance may be optimistically biased and should be interpreted with caution.

Contents

Glossary and list of abbreviations

Glossary

Affected pregnancy A pregnancy with a fetus that is affected with Down's syndrome.

Detection rate Proportion of affected pregnancies with a positive test result.

False-positive Unaffected pregnancy that has a positive test result.

False-positive rate Proportion of unaffected pregnancies with a positive test result.

First trimester Prior to 14 weeks' gestation.

Reference maternal age distribution The assumed maternal age distribution against which screening performance is assessed.

Risk threshold or risk cut-off Level of risk above which a test is reported as screen positive.

Second trimester After 14 weeks' gestation.

Screen negative Given risk is below specified risk cut-off.

Screen positive Given risk is above specified risk cut-off.

Weeks' gestation For example, week 11 gestation means between 11 weeks + 0 days and 11 weeks + 6 days inclusive.

List of abbreviations

AFP	alpha-fetoprotein (denoted in tables and figures by $a1$ and $a2$ for first and second trimester respectively)
CI	confidence interval
FaSTER	First and Second Trimester Evaluation of Risk study
hCG	human chorionic gonadotrophin (denoted in tables and figures by $h1$ and $h2$ for first and second trimester respectively)
β-hCG	free beta-human chorionic gonadotrophin
LL	log likelihood
MoM	multiple of the median
NT	nuchal translucency
PAPP-A	pregnancy-associated plasma protein A (denoted in tables and figures by $p1$ and $p2$ for first and second trimester respectively)
ROC	receiver operating characteristic
STARD	STAndards for the Reporting of Diagnostic accuracy studies
SURUSS	Serum Urine and Ultrasound Screening Study
uE3	unconjugated estriol (denoted in tables and figures by $u1$ and $u2$ for first and second trimester respectively)

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Objective

To provide estimates and confidence intervals (CIs) for the performance (detection and false-positive rates) of screening for Down's syndrome using repeated measures of biochemical markers from first and second trimester maternal serum samples taken from the same woman.

Design

Stored serum on Down's syndrome cases and controls was used to provide independent test data for the assessment of screening performance of published risk algorithms and for the development and testing of new risk assessment algorithms.

Setting

Two independent test data sets, including data on a total of 121 cases of Down's syndrome, were used in the study:

- The First and Second Trimester Evaluation of Risk (FaSTER) repeated measures study, in which samples were obtained from 15 screening centres across the USA between October 1999 and December 2002.
- The North York repeated measures study, in which samples were obtained from women who received integrated prenatal screening at the North York General Hospital, Toronto, Canada between December 1999 and November 2007.

Measurements

Repeated measurements (first and second trimester) of maternal serum levels of human chorionic gonadotrophin (hCG), unconjugated estriol (uE3) and pregnancy-associated plasma protein A (PAPP-A) together with alpha-fetoprotein (AFP) in the second trimester.

Outcomes

1. Detection and false-positive rates for screening with a threshold risk of 1 in 200 at term.
2. Detection rate achieved for a false-positive rate of 2%.

Rates were standardised to the distribution of maternal ages in England and Wales for the 3-year period from 2000 to 2002.

Results

Published distributional models for Down's syndrome cases were inconsistent with the test data. When these test data were classified using these models, screening performance deteriorated substantially through the addition of repeated measures. This contradicts the very optimistic results obtained from predictive modelling of performance. Simplified distributional assumptions, based on the principles of linear discriminant analysis, improved model fit and showed some evidence of benefit from the use of repeated measures of PAPP-A but not for repeated measures of uE3 or hCG.

Each of the two test data sets was used to create new parameter estimates against which screening test performance was assessed using the other data set. The results were equivocal, but there was suggestive evidence of improvement in screening performance through the use of repeated measures of PAPP-A when the first trimester sample was collected before 13 weeks' gestation.

A Bayesian analysis of the combined data from the two test data sets showed that adding a second trimester repeated measurement of PAPP-A to the base test (PAPP-A in the first trimester with AFP, hCG and uE3 in the second) increased detection rates and reduced false-positive rates. The benefit decreased with increasing gestational age at the time of the first sample. At 11 weeks' gestation, the repeated measurement of PAPP-A reduced the

false-positive rate by an estimated 1% (95% CI 0.6% to 1.5%) from 3.5% to 2.5%, and increases the detection rate by an estimated 3% (95% CI 1% to 6%) from 89% to 92%. There was no evidence of any benefit from repeated measures of hCG or uE3.

Conclusions

If realised, a reduction of 1% in false-positive rate with no loss in detection rate would give important benefits in terms of health service provision and the large number of invasive tests avoided. The Bayesian analysis, which showed evidence of benefit, was based on strong distributional assumptions and should not be regarded as confirmatory. The evidence of potential benefit suggests the need for a prospective study of repeated measurements of PAPP-A with samples from early in the first trimester. A formal clinical effectiveness and cost-effectiveness analysis should be undertaken. A secondary objective of this prospective study should be to investigate the potential value of other repeated measures markers including ADAM metallopeptidase domain 12 (ADAM-12) and Inhibin-A. The additional complexity arising from the need to obtain serum samples in the first and second trimester should be assessed in terms of its cost-effectiveness and impact on screening services.

This study has shown that the established modelling methodology for assessing screening performance may be optimistically biased and should be interpreted with caution. Multivariate methods for assessment of goodness of fit and Bayesian methods for inference have been used in the analysis presented in this report and should be used more widely in the field of screening. Guidance on the use of these methods should be produced and software should be made available for their implementation.

Chapter 1
Introduction

Prenatal screening for Down's syndrome is now offered routinely in many countries including those in the UK (see Appendix 1 for National Screening Committee criteria for appraising screening programmes). However, the gestational age when testing is carried out and the combinations of markers used vary widely.[1,2] The use of three or four second trimester maternal serum measurements is common but, increasingly, women are being offered first trimester testing based on ultrasound and biochemical markers. In some areas, markers obtained in the first and second trimesters are being interpreted together as the integrated test.[3–5] Variants such as sequential or contingent screening are also being considered.[6–8] Combined testing using measures of the biochemical markers, pregnancy associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotrophin (β-hCG) with the ultrasound marker nuchal translucency (NT),[9] is being adopted by the NHS. There is good evidence from a number of sources[10,11] that, with appropriate methodology,[12] this meets the current NHS standard of a detection rate of 75% or more for a false-positive rate of 3% or less. However, it fails to meet the standard for 2010 of a detection rate of 90% or higher for a false-positive rate of 2% or less.

The choice of markers in screening tests has been influenced by the extent to which they provide 'independent information' as characterised by low correlations between markers and the properties of markers when viewed individually. The prevailing view has been that combining markers with low correlations that individually have good discriminatory power produces screening tests with the best performance. Against this background, the integrated test[3] was obtained by combining the best markers from the first trimester with the best markers from the second trimester. The Serum Urine and Ultrasound Screening Study (SURUSS) report[4] concluded that the integrated test, based on this choice of markers, offers the most effective and safe current method of screening.

From the statistical perspective, however, the thinking behind the combination of the 'best' markers from the first trimester with the 'best' markers from the second trimester is misguided. This was demonstrated in the paper of Wright and Bradbury[13] which showed, using parameter estimates taken from SURUSS, that highly correlated repeated measures of markers, some of which, individually, have poor discriminatory power, may have substantial benefits over the established combinations of markers used in the integrated test. Wald and colleagues[14] have carried out further work on repeated measures testing, and have reached the same general conclusions about its benefit over the integrated test.

As Wright and Bradbury[13] emphasise, there is a need for further research because of uncertainty in parameter estimates, departures from model assumptions and inherent optimistic bias in the established methods used to assess screening performance. The primary aim of the research reported here is to provide estimates and confidence intervals (CIs) for the performance (detection rates and false-positive rates) of screening tests that use repeated measures. This is based on two independent test data sets incorporating a total of 121 Down's syndrome pregnancies. Results are obtained for tests involving repeated measures of combinations of PAPP-A, human chorionic gonadotrophin (hCG) and unconjugated estriol (uE3). In addition to the data available on repeated measures of PAPP-A, uE3 and hCG, measurements of alpha-fetoprotein (AFP) from the second trimester blood sample were available in both data sets. Data on NT and Inhibin-A were also available in one of the test data sets. The analysis presented here focuses on screening using tests that include combinations of cross-trimester repeated measures of PAPP-A, uE3 and hCG with second trimester AFP.

This report examines the use of repeated measures of PAPP-A, uE3 and hCG, using the standard Gaussian algorithm. Estimates of screening test performance are presented, the goodness of fit of the Gaussian models for the test data sets is assessed and a revised screening algorithm suggested. In order to provide robust evidence of the potential benefits of repeated measures, each of the test data sets is used to create new parameter estimates against which screening test performance is assessed using the other test data

set. The two data sets are then pooled to produce a single screening algorithm which is assessed using Gaussian modelling within a Bayesian framework taking account of uncertainty about parameters. In accordance with the STAndards for the Reporting of Diagnostic accuracy studies (STARD) guidelines[15] (see checklist in Appendix 2), estimates of screening performance are accompanied by 95% CIs.

Chapter 2
Methods

General

Screening for Down's syndrome involves the calculation of a risk based on maternal age, previous history of Down's syndrome, measurements of biochemical markers obtained from maternal serum samples, and possibly ultrasound images. The resultant risks are compared with a threshold and, in cases where the risk is at or above the threshold, the test is deemed screen-positive. Otherwise, it is deemed screen-negative. The current policy in the NHS is to use a risk threshold of 1 in 150 for risk assessment in the first trimester of pregnancy. A risk threshold of 1 in 200 is used in the second trimester. In general, both false-positive and detection rates increase with maternal age when a screening test is applied with a fixed risk threshold. For unambiguous comparisons, it is necessary to produce estimates of standardised detection rates and false-positive rates that apply to a specific reference maternal age distribution. This report presents results for screening tests applied to the maternal age distribution of England and Wales for the 3 years from 2000 to 2002.[16] Results for this reference distribution are presented for false-positive rates and detection rates obtained using a risk cut-off of 1 in 200, and for detection rates for a fixed false-positive rate of 2%.

Risk calculation

The calculation of risk in Down's syndrome screening is an application of Bayes' theorem[17] to combine prior information on the maternal age-specific risk[18,19] with likelihoods obtained from appropriately transformed measurements of marker concentrations from maternal serum and sometimes ultrasound markers such as NT. Almost invariably the transformation involves two steps. Firstly, the measurement is expressed as a multiple of the median (MoM) value for unaffected pregnancies, standardising for gestational age and other variables such as maternal weight, smoking status and ethnicity that have effects on the marker concentrations.[20] Secondly, a log transformation is used to produce a log (MoM) value. The likelihoods are calculated under the assumption that log (MoM) values follow different multivariate Gaussian distributions[21] in unaffected and in Down's syndrome pregnancies. For first trimester markers, it has been established that the mean log (MoM) in Down's syndrome changes with gestational age.[22] This is accommodated in the model by a linear regression relationship. In practice, the unknown parameters defining the multivariate Gaussian distributions are replaced by estimates obtained from fitting multivariate Gaussian models to data such as those collected in the SURUSS study. To deal with departures from the Gaussian form in the tails of the distribution, truncation is applied to values beyond a specified range. The established approach is to apply truncation separately to each dimension. We have explored an alternative multivariate approach, based on the Mahalanobis distance,[21] truncating values that are atypical of both Down's syndrome and unaffected distributions.[23] This avoids the production of extreme risks for atypical pregnancies.

It is notable that the so-called estimative approach[24] of substituting estimates for unknown parameters takes no account of the uncertainty in the parameter estimates. A formal way of dealing with this uncertainty is to use Bayesian predictive distributions.[24] However, we restrict this report to the estimative approach.

Assessing screening performance

The conventional 'modelling' methodology[25] for assessing screening performance assumes that the class conditional distributions fitted to unaffected and Down's syndrome log (MoM) values perfectly match the true population distributions. In practice, the fitted distributions will differ from the population distributions to some degree because the populations are not perfectly Gaussian and the fitted parameter estimates are subject to sampling error and biases. This means that assessment of screening performance under ideal modelling assumptions is optimistically biased. This is dealt with in this report as follows:

1. By assessing the performance of existing models for risk assessment on two independent test data sets. This avoids the optimistic bias associated with assuming the same Gaussian class conditional distributions in the population and in the risk calculation.
2. Each of two test data sets is used to create new parameter estimates against which screening test performance is assessed using the other data set. This provides robust estimates of screening performance that do not rely on assumptions that the distributions are Gaussian and enables us to provide estimates of the screening parameters from the two test data sets.
3. Distributions are fitted to the combined data from the two test data sets. Point and interval estimates are obtained under the Gaussian model adopting a Bayesian approach to inference that takes account of uncertainty concerning unknown parameters.[26,27]

Parameters

To date, three sets of parameter estimates, (I)–(III) below, have been published that can be used as a basis for screening tests with repeated measures of PAPP-A, hCG and uE3. All of these are based on secondary data published in appendices of the SURUSS report,[4] and give very similar results when applied to the test data sets. This report also includes a fourth set of parameters obtained from the North York routine data and published meta-analysis.

(I) The original SURUSS parameter estimates[4] with corrections.[28]
(II) The cross-trimester ratios parameter estimates obtained from SURUSS published by Wald and colleagues.[14]
(III) The SURUSS parameter estimates incorporating the modifications associated with measurements of PAPP-A in the second trimester reported by Palomaki and colleagues[23] in 2006.
(IV) The model for the means of log (MoM) values taken from published meta-analyses.[22] Covariance matrices, or equivalently standard deviations and correlations, are estimated from routine data collected at North York General Hospital.

Parameter estimates for (I)–(IV) are given in Appendix 3.

In (II), measures of PAPP-A in the first trimester and uE3 and hCG in the second trimester were included as log (MoM) values. Measures of PAPP-A in the second trimester and uE3 and hCG in the first trimester were included indirectly in terms of log-transformed cross-trimester ratios of second to first trimester MoM values. The screening algorithm that results, apart from the effect of truncation, is in fact equivalent to (I).[29] However, because of the methods of estimation used, the cross-trimester ratios formulation gives different estimates of means, standard deviations and correlations.[30]

With the exception of parameters involving second trimester PAPP-A, the estimates used for (III) in the validation study of Palomaki and colleagues[23] were taken from SURUSS. Parameter estimates for PAPP-A were obtained from a meta-analysis and from a consecutive series of 838 women using appropriately adjusted assays. A data set comprising 34 Down's syndrome pregnancies and 514 unaffected pregnancies was used as an independent test data set. These data were obtained from North York and the cases are a subset of those comprising our test data set. New measurements of uE3 and hCG were made on first trimester samples for this *Health Technology Assessment* report.

The fourth set of parameters estimates (IV) was obtained from repeated measures made on routine samples from North York General Hospital. It should be emphasised that the North York test data were not used in the estimation of (IV). Estimation for (IV) was carried out using a Bayesian analysis implemented using WinBUGS.[31]

Assumptions regarding covariance structure

Some of the published correlation matrices are not positive definite[14] and others are near singular. The practical consequences are that it is impossible to compute risks in cases where the correlation matrix is not positive definite and that the computed risks are implausible when the correlation matrix is near singular. Furthermore, assessment of screening performance based on models using the estimated covariance matrix may be grossly optimistic. The near singular covariance matrices arise because of the sparseness of data from affected pregnancies and the methods employed in estimation. Using computer simulation, we have demonstrated that although the standard product moment estimators

are unbiased, the determinant, or generalised variance, of the covariance matrix is biased towards zero. This worsens with increasing numbers of markers and with novel combinations of markers. The approach we have taken to dealing with this is to impose structural assumptions relating the covariance matrix in Down's syndrome to that in unaffected pregnancies. Screening performance is assessed for the following assumptions regarding covariance matrices:

(i) Original covariance matrices – the covariance matrix for Down's syndrome taken directly from the original source publications.
(ii) Pooled covariance matrices – the population covariance matrices for Down's syndrome and unaffected pregnancies are assumed to be equal. A pooled estimate of the common covariance matrix is used.
(iii) Diagonally inflated covariance matrix – although there are some exceptions, the view is that the variances in Down's syndrome pregnancies are likely to be larger than those in unaffected pregnancies. A model where the off-diagonal elements of the covariance matrix in Down's syndrome are the same as those in unaffected pregnancies but the diagonal elements (i.e. the variances) are inflated in Down's syndrome is used to capture this.

For the North York routine samples training data set (IV) that is assumed to contain unaffected pregnancies only, the analysis is restricted to assumption (ii) above.

Assessment of population screening performance

Population detection rates and false-positive rates for the assumed reference distribution were estimated as follows. Likelihood ratios were computed for the assumed Gaussian model. These were used to estimate the age-specific detection rates and false-positive rates. This was achieved by computing the proportion of likelihood ratios for which the risk resulting from combining the maternal age risk with the likelihood ratio exceeded the risk threshold. Population false-positive and detection rates were obtained by taking the weighted average of these age-specific proportions with respect to the relative frequency distribution of maternal ages in the reference populations for unaffected and Down's syndrome pregnancies respectively. This methodology has the benefit of efficiency in the sense that all of the available data are used at each maternal age. An implicit assumption involved in this calculation is that conditionally on karyotype (unaffected or Down's syndrome), the log (MoM) values are independent of maternal age. This assumption is consistent with the available evidence. Moreover, the results we present are robust to moderate departures from this assumption. CIs were produced using non-parametric bootstrapping.

Assessment of goodness of fit

The fit of the various models to the independent test data sets was assessed using likelihood ratio-based test statistics. These were employed as a basis for comparing the goodness of fit of the different models; not as a formal hypothesis test of goodness of fit.

Model fitting

The model fitting presented in this report was carried out using Bayesian analysis implemented using WinBUGS. This approach enables missing data to be dealt with and, through the use of a mixture model with contamination, robust estimates of parameters to be obtained without the need to make arbitrary or subjective decisions about exclusion of outliers.[32] Assessment of screening performance under the Gaussian model fitted to the combined First and Second Trimester Evaluation of Risk (FaSTER) and North York data sets was carried out by sampling detection and false-positive rates from the posterior predictive distributions. Risks were calculated with the covariance matrices and means fixed at their posterior mean.

Test data

The FaSTER repeated measures data arise from a nested case–control study consisting of 78 Down's syndrome cases and 390 matched unaffected controls, with maternal blood samples obtained at 11–13 and 15–18 weeks' gestation. Measurements of the integrated test markers (NT and PAPP-A in the first trimester and AFP, uE3, hCG and Inhibin-A in the second trimester) were augmented by measures of PAPP-A in the second trimester and of hCG and uE3 in the first trimester. In the original FaSTER study,[2] samples were obtained from 15 screening centres across the USA between October 1999 and December 2002 and analysed

centrally. All centres and the central laboratory obtained institutional review board approval, and all patients provided informed consent. Outcomes were obtained in 97% of all pregnancies. Of the 117 cases of Down's syndrome identified in this study, 25 were identified by first trimester ultrasound findings and did not have serum samples collected. Second trimester serum samples were obtained from 87 cases of Down's syndrome. The case–control study is based on 78 of these 87 cases for which there was sufficient serum to carry out the repeated measurements. Each of the cases of Down's syndrome was matched to five controls for gestational ages at the times of serum sampling, ethnicity, maternal age and storage duration. Serum samples were stored at –80°C. The first trimester sera were thawed and tested for uE3 and hCG. The second trimester sera were thawed and tested for PAPP-A. All measurements were made without knowledge of whether the sample was from a case or control pregnancy.

The North York repeated measures data arise from a case–control study in which cases were identified from women who received integrated prenatal screening at North York General Hospital at two time intervals: (1) between 1 December 1999 and 31 October 2003, and (2) between 1 October 2006 and 23 November 2007. Institutional review board approval was obtained for the study. After testing, first and second trimester serum samples were stored at –20°C. Demographic and pregnancy-related information, such as maternal age, gestational age, maternal weight and pregnancy outcome, including if the pregnancy was affected by Down's syndrome, was available from the Ontario Multiple Marker Screening Database. Ultrasound-based gestational age was between 11 and 13 completed weeks for the first trimester samples and 14 and 20 completed weeks for the second trimester samples. For each pair of samples obtained from a documented singleton Down's syndrome pregnancy (case), five paired sample sets from singleton pregnancies not known to be affected with any chromosomal abnormality were selected as controls. Cases and controls were matched for sample date, gestational age and maternal age. No data on NT and Inhibin-A were available in the database.

First trimester PAPP-A and second trimester AFP, uE3 and hCG measurements in maternal serum (PerkinElmer Life and Analytical Sciences, Woodbridge, Ontario, Canada) were already available in the Ontario Multiple Marker Screening Database. The first trimester sera were thawed and tested for uE3 and hCG. The second trimester sera were thawed and tested for PAPP-A. All measurements were made without knowledge of whether the sample was from a case or control pregnancy. The first trimester samples were tested for PAPP-A after a 1:5 dilution (according to package insert instructions). The matching second trimester samples were tested in the same manner, but at a dilution of 1:40. Measurements were converted to MoM values using medians derived from the control samples and were adjusted for maternal weight using existing equations. Because a relatively large proportion of samples was from Asian women, a separate adjustment was used for existing markers to ensure that the median MoM was 1.0 in both Asian and non-Asian women.

Training data sets

Data from two separate consecutive series screening tests from North York were used to provide evidence on the covariance matrices of marker panels involving repeated measures of PAPP-A, uE3 and hCG. Research Ethics Board approval was obtained for these studies. The same storage and assay methods as for the case–control samples were used for these samples.

Sample 1, which includes data on repeated measures of uE3, hCG and PAPP-A, was obtained from a consecutive series of 1050 women who received integrated screening between January and April 2007. The sample was restricted to singleton pregnancies with no known chromosomal anomaly for which data on maternal weights were available. Pregnancies associated with insulin-dependent diabetic mellitus were excluded. First trimester PAPP-A and second trimester AFP, uE3 and hCG measurements of these samples were already available in the Ontario Multiple Marker Screening Database. First trimester uE3 and hCG and second trimester PAPP-A concentrations were measured for this study.

Sample 2 includes repeated measures data on PAPP-A from an earlier consecutive series of 838 women. These data, reported by Palomaki and colleagues,[23] were collected on women who received integrated screening during March and April 2005, reported as having a singleton pregnancy, with maternal weight and ethnicity available.

Chapter 3
Results

Data

Data disposition for the FaSTER and North York test data sets are shown in *Table 1*. Summary statistics for these data are given in Appendix 4. As can be seen, there are a number of pregnancies in the North York test data for which no second trimester sample data are available. These amount to 19% of cases of Down's syndrome and 12% of the controls. Measurements on first trimester uE3 were missing in 10 of the cases and 50 controls in the North York sample. These data were missing because there was insufficient serum available to complete the full panel of first trimester assays. Full marker information was available on 25 cases and 123 controls.

The design used in FaSTER means that cases and controls were restricted to women for whom first and second trimester data were available. In the FaSTER repeated measures data, there was insufficient serum for assays of hCG on 9 cases and 125 controls giving full marker information on 68 cases and 224 controls. The full information data sets were used as test data for comparison of different screening strategies. Bayesian model fitting in WinBUGS used all available data.

Model data fit

The fit of the various fitted models, described in Chapter 2, was assessed using a likelihood ratio-based test statistic (see Appendix 5). This was obtained from a test of the null hypothesis that the training data arise from the specific multivariate distribution with parameters taken from Appendix 3. Under the alternative hypothesis, the data arise from a distribution with a different mean and covariance matrix. As described in Appendix 5, this statistic is partitioned into two additive components representing the lack of fit of means and of covariance matrices. The departure from the mean was represented by a linear trend with gestational age to allow for a gestational age-dependent error in mean log (MoM) values. To remove the effect of gross outliers, the likelihood ratio test statistic was computed after truncation of observations falling outside of the 99.9th contour of the fitted distribution. The results, values of –2 log likelihood ratio, are presented in *Table 2*.

For a situation involving p markers, under the assumption that the data arise from the particular model, the statistics presented in *Table 2* are asymptotically chi-squared distributed with degrees of freedom: $\nu = 2p$ for the fit statistic for the mean and $\nu = p(p + 1)/2$ for the fit statistic for the covariance matrix. Of course, in this analysis, the model parameters were estimated from training data and would be expected to show some departure from the true parameters, thus inflating this test statistic. Moreover, some degree of departure from a Gaussian distribution would be expected and this would further inflate the fit statistic. With $p = 7$ in this situation, values of $2p = 14$ and $p(p + 1)/2 = 28$ provide a guide to interpretation, but it is the differences in the fit statistics across the different models and assumptions regarding covariance matrices that are important in the interpretation of *Table 2*.

The most notable feature of *Table 2* is the relatively poor fit of the data from Down's syndrome cases to the covariance matrices from the original sources (i). For parameter sets (I)–(III), the pooled covariance matrix, which is dominated by data from unaffected pregnancies, provides a better fit to the data in Down's syndrome than the Down's covariance matrix from the original source. It is also notable from *Table 2* that the parameter sets (I)–(IV) are similar in terms of their goodness of fit to the test data. This is reflected in the similarity in screening performance when applied to the test data sets. In this report we present results of screening performance for parameter set I using truncation limits on MoM values from SURUSS.

Under assumptions (i) original covariance matrices and (ii) pooled covariance matrices, *Figure 1* shows the distribution of squared Mahalanobis distances from the mean for the Down's syndrome pregnancies. Points with the same Mahalanobis distance have the same Gaussian probability density and fall on the same contour of the probability distribution, so can be considered to be statistically equidistant from the mean. Under the Gaussian model the squared Mahalanobis distances

TABLE 1 *Gestational ages (completed weeks) for cases and controls in the FaSTER and North York (NY) test data sets and the two North York training data sets (NY1, NY2). For the FaSTER test data set, complete data were available on 68 cases and 224 controls. For the North York test data set, complete data were available on 25 cases and 123 controls*

First sample								
Weeks		*10*	*11*	*12*	*13*	*14*		*Total*
FaSTER	Cases	0	17	36	25	0		78
	Controls	0	85	180	125	0		390
NY	Cases	1	4	32	5	1		43
	Controls	5	20	141	30	0		196
NY1	Controls	9	114	483	232	0		838
NY2	Controls	0	420	420	210	0		1050
Second sample								
Weeks		*15*	*16*	*17*	*18*	*19*		*Total*
FaSTER	Cases	39	34	5	0	0		78
	Controls	195	170	25	0	0		390
NY	Cases	16	15	2	1	1		35
	Controls	55	82	19	17	0		173
NY1	Controls	212	439	124	60	3		838
NY2	Controls	337	475	148	90			1050
Difference								
Weeks		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*Total*
FaSTER	Cases	1	20	34	21	2			78
	Controls	9	77	193	102	9			390
NY	Cases	2	4	15	9	2	2	1	35
	Controls	3	9	80	53	18	10	0	173
NY1	Controls	5	92	329	291	93	24	4	838
NY2	Controls	5	99	354	379	140	59	14	1050

should follow a chi-squared distribution with $\nu = 7$ degrees of freedom as shown by the smooth curve. Under assumption (i) it is clear that the training data are generally atypical of the assumed Gaussian distribution. Under assumption (ii) the degree of lack of fit is much less pronounced. *Figure 2* shows the distribution of squared Mahalanobis distances for unaffected pregnancies. This indicates that, under both sets of assumptions (i) and (ii), the fitted covariance matrices are consistent with the test data.

Estimation of screening performance using independent test data

Table 3 gives standardised detection rates for the two repeated measures test data sets for a 2% false-positive rate using the SURUSS screening model under the three different assumptions regarding the covariance matrix in Down's syndrome pregnancies. *Table 4* shows the marginal increase in standardised detection rates over the base test comprising PAPP-A in the first trimester, and AFP, hCG and uE3 in the second trimester. The 2% false-positive rate was chosen as it is the 2010 target set by the NHS National Programme (see Appendix 1 for National Screening Committee criteria for screening programmes). *Table 5* presents standardised false-positive and detection rates using the term risk threshold of 1 in 200 to define a screen positive group. This risk threshold was chosen because it is the current threshold adopted by the NHS National Programme. *Table 6* shows the marginal increases in standardised false-positive and detection rates over the base model that result from the inclusion of repeated measures markers.

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TABLE 2 *–2 log likelihood ratio fit statistics for means and covariance matrices for different training data sets under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The total log likelihood ratio statistic (LL) is partitioned additively into components for the mean (LL.mean) and the covariance (LL.cov)*

	Training data I: SURUSS								
	Assumptions (i): original			**Assumptions (ii): pooled**			**Assumptions (iii): diagonally inflated**		
Goodness of fit	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**
Controls									
FaSTER	111.93	20.06	91.88	116.53	19.34	97.18	111.93	20.06	91.88
NY	100.13	8.46	91.67	97.59	8.66	88.94	100.13	8.46	91.67
Cases									
FaSTER	337.06	89.28	247.78	122.53	77.82	44.71	151.48	93.38	58.1
NY	156.06	50.91	105.15	103.52	40.2	63.32	114.77	38.58	76.19
	Training data II: CT ratios[a]								
	Assumptions (i): original			**Assumptions (ii): pooled**			**Assumptions (iii): diagonally inflated**		
Goodness of fit	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**
Controls									
FaSTER	106.36	20.94	85.42	97.41	20.14	77.28	106.36	20.94	85.42
NY	79.06	8.47	70.58	77.64	8.68	68.95	79.06	8.47	70.58
Cases									
FaSTER	305.73	85.04	220.69	129.40	92.93	36.47	201.07	140.11	60.96
NY	139.15	45.12	94.04	96.32	41.79	54.53	96.84	35.28	61.56

continued

TABLE 2 *–2 log likelihood ratio fit statistics for means and covariance matrices for different training data sets under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The total log likelihood ratio statistic (LL) is partitioned additively into components for the mean (LL.mean) and the covariance (LL.cov) (continued)*

	Training data III: Palomaki *et al.* (2006)								
	Assumptions (i): original			**Assumptions (ii): pooled**			**Assumptions (iii): diagonally inflated**		
Goodness of fit	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**
Controls									
FaSTER	103.61	20.84	82.77	97.89	19.36	78.52	103.61	20.84	82.77
NY	74.05	8.44	65.62	79.59	8.34	71.25	74.05	8.44	65.62
Cases									
FaSTER	211.81	69.51	142.30	98.12	55.08	43.04	102.64	48.55	54.09
NY	110.63	40.34	70.29	99.59	34.36	65.23	107.46	30.77	76.68
	Training data IV: NY training data								
	Assumptions (i): original			**Assumptions (ii): pooled**			**Assumptions (iii): diagonally inflated**		
Goodness of fit	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**	**LL**	**LL.mean**	**LL.cov**
Controls									
FaSTER				136.5	23.3	113.2			
NY				99.8	8.8	91.0			
Cases									
FaSTER				114.4	62.5	51.7			
NY				104.6	29.4	75.2			

[a]Means were taken from the SURUSS model.
CT, cross-trimester; NY, North York.

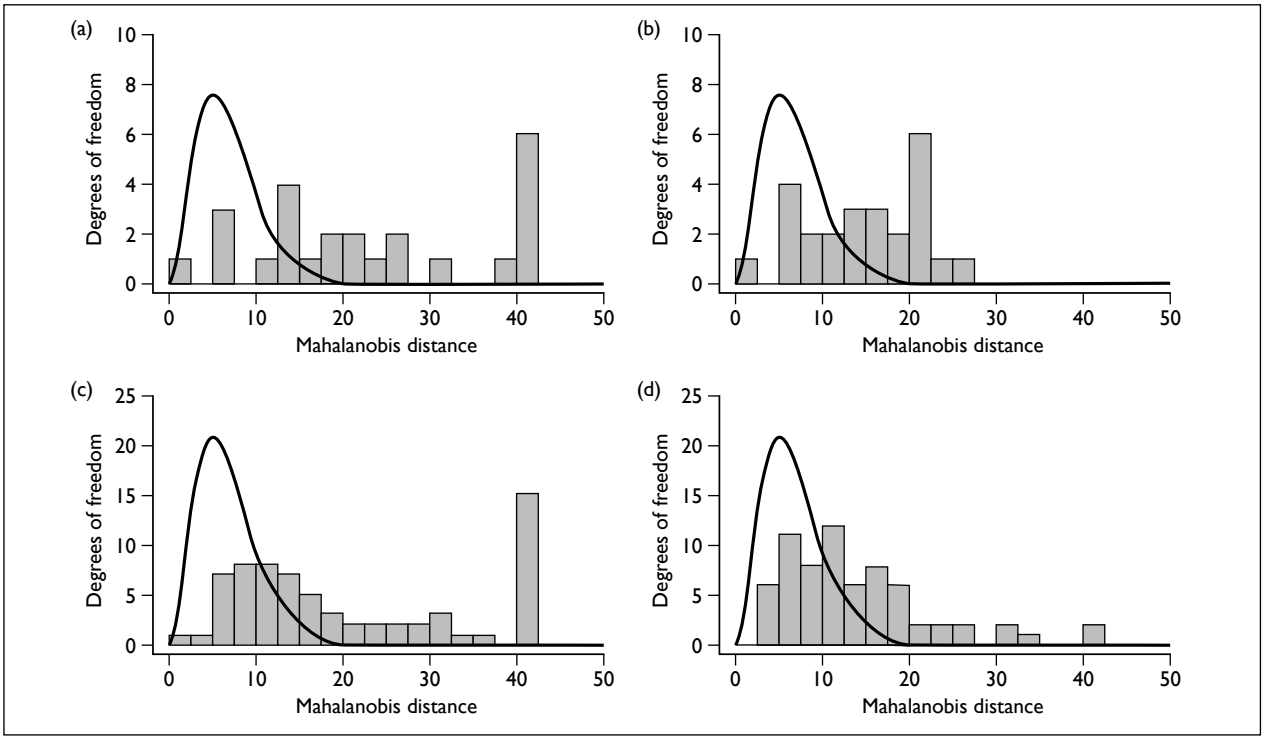

FIGURE 1 *Histograms of squared Mahalanobis distances of log (MoM) values of* h*1*, p*1*, u*1*, a2, u2, h2 *and* p2 *for Down's syndrome pregnancies. Under the Gaussian model, the squared Mahalanobis distances should follow the chi-squared distribution with 7 degrees of freedom shown by the smooth curve. (a) North York data using SURUSS parameters with original covariance matrix; (b) North York data using SURUSS parameters with pooled covariance matrix; (c) FaSTER repeated measures data using SURUSS parameters with original covariance matrix; (d) FaSTER data using SURUSS parameters with pooled covariance matrix. Values are truncated at the 99.99th percentile.*

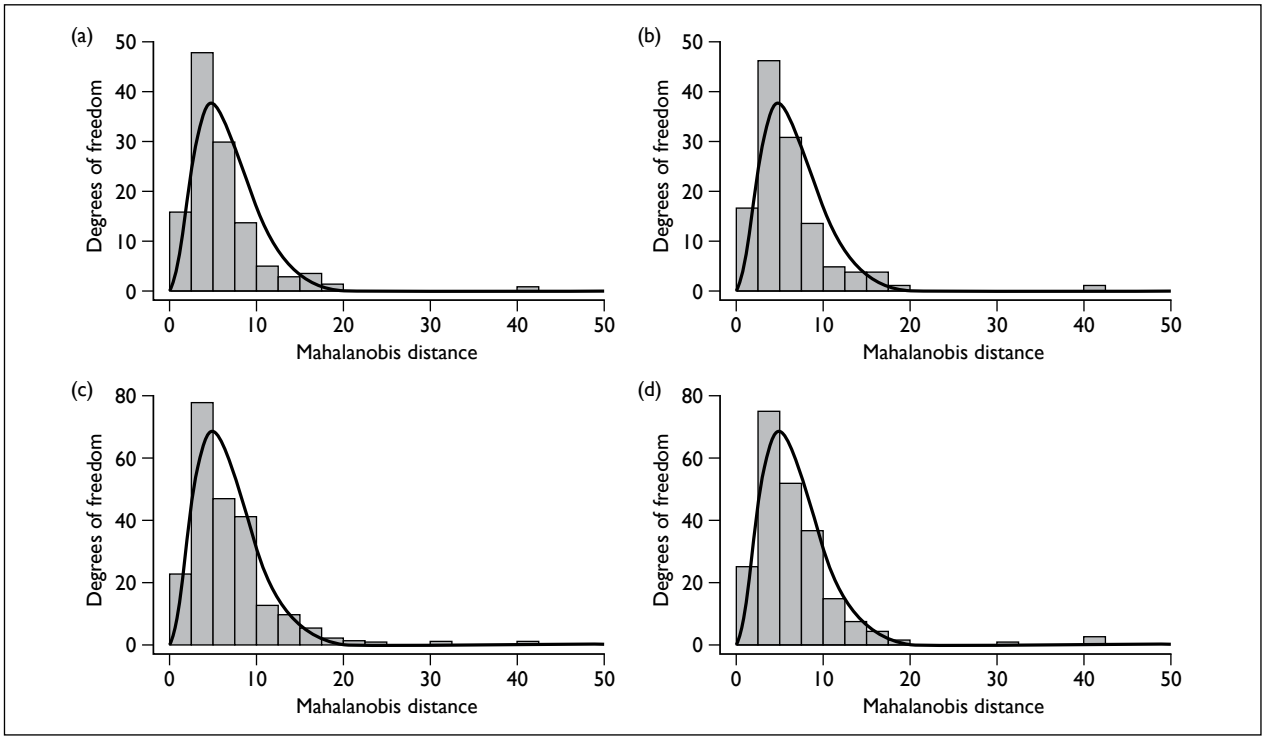

FIGURE 2 *Histograms of squared Mahalanobis distances of log (MoM) values of* h*1*, p*1*, u*1*, a2, u2, h2 *and* p2 *for unaffected pregnancies. Under the Gaussian model, the squared Mahalanobis distances should follow the chi-squared distribution with 7 degrees of freedom shown by the smooth curve. (a) North York data using SURUSS parameters with original covariance matrix; (b) North York data using SURUSS parameters with pooled covariance matrix; (c) FaSTER repeated measures data using SURUSS parameters with original covariance matrix; (d) FaSTER data using SURUSS parameters with pooled covariance matrix. Values are truncated at the 99.99th percentile.*

TABLE 3 *Standardised detection rates (%) for a 2% false-positive rate from the FaSTER and North York test data using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. In this and subsequent tables abbreviations* p1 *and* p2*, for example, are used to denote PAPP-A in the first and second trimesters respectively*

	Assumptions (i): original	Assumptions (ii): pooled	Assumptions (iii): diagonally inflated
FaSTER			
*p*1 + *a*2 + *u*2 + *h*2	73 (62 to 84)	72 (61 to 83)	72 (61 to 82)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	70 (58 to 82)	72 (61 to 84)	70 (59 to 82)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	71 (59 to 83)	70 (59 to 81)	71 (60 to 81)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	66 (53 to 79)	72 (61 to 83)	72 (60 to 83)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	41 (30 to 52)	71 (59 to 82)	71 (59 to 82)
North York			
*p*1 + *a*2 + *u*2 + *h*2	85 (74 to 97)	85 (70 to 99)	85 (69 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	86 (75 to 97)	93 (86 to 99)	91 (84 to 99)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	84 (73 to 96)	87 (76 to 98)	85 (69 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	81 (67 to 94)	84 (69 to 100)	84 (67 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	55 (41 to 70)	93 (86 to 99)	86 (71 to 100)

TABLE 4 *Marginal increase in standardised detection rates (%) for a 2% false-positive rate from the FaSTER and North York test data using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The detection rates and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original	Assumptions (ii): pooled	Assumptions (iii): diagonally inflated
FaSTER			
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–3 (–12 to 5)	0 (–4 to 4)	–1 (–6 to 4)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	–3 (–7 to 2)	–2 (–6 to 2)	–1 (–4 to 2)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	–7 (–12 to –2)	0 (–2 to 2)	0 (–4 to 5)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–32 (–43 to –21)	–2 (–8 to 4)	–1 (–7 to 5)
North York			
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	1 (–10 to 11)	8 (–4 to 20)	6 (–9 to 22)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	–1 (–4 to 2)	2 (–5 to 10)	0 (–1 to 2)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	–5 (–11 to 2)	0 (–2 to 1)	–1 (–3 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–30 (–46 to –14)	8 (–4 to 20)	1 (–7 to 9)

Whilst *Tables 2* and *3* serve as a useful basis for comparing screening tests, in practice, screening is usually operated with a fixed risk threshold, so *Tables 5* and *6* give a better indication of the practical consequence of incorporating repeated measures.

The most notable feature of *Tables 3–6* is the very poor performance associated with repeated measures with the original Down's syndrome covariance matrix. The addition of repeated measures of uE3, hCG and PAPP-A to the base test, comprising PAPP-A in the first trimester and AFP, uE3 and hCG in the second, reduces the detection rate for a fixed 2% false-positive rate by around 30% in both FaSTER and North York data sets. This is very different from the results obtained from modelling using the fitted Gaussian model from SURUSS as presented by Wright and

TABLE 5 *Standardised detection rates and false-positive rates (%) for a term risk cut-off of 1 in 200 for the FaSTER and North York test data using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original		Assumptions (ii): pooled		Assumptions (iii): diagonally inflated	
	FPR (%)	DR (%)	FPR (%)	DR (%)	FPR (%)	DR (%)
FaSTER						
*p*1 + *a*2 + *u*2 + *h*2	3.6 (1.5 to 5.7)	79 (72 to 86)	4.3 (2.0 to 6.6)	80 (73 to 86)	4.8 (2.4 to 7.2)	80 (74 to 87)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	2.4 (0.9 to 4.0)	71 (62 to 80)	3.1 (0.9 to 5.3)	78 (71 to 85)	3.4 (1.1 to 5.7)	78 (71 to 84)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	3.7 (1.5 to 5.9)	76 (69 to 84)	4.4 (2.0 to 6.8)	78 (71 to 85)	4.7 (2.2 to 7.1)	79 (72 to 85)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	4.0 (1.7 to 6.3)	75 (68 to 83)	4.1 (1.8 to 6.4)	78 (72 to 85)	4.2 (1.9 to 6.4)	79 (73 to 85)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	1.9 (0.7 to 3.2)	41 (31 to 51)	3.0 (0.8 to 5.1)	76 (68 to 84)	3.2 (1.1 to 5.3)	75 (68 to 81)
North York						
*p*1 + *a*2 + *u*2 + *h*2	3.0 (1.5 to 4.6)	89 (78 to 100)	2.6 (0.6 to 4.6)	90 (80 to 99)	2.7 (0.7 to 4.8)	91 (82 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	1.4 (0.0 to 2.8)	91 (82 to 100)	1.2 (0.4 to 1.9)	94 (87 to 100)	2.1 (0.1 to 4.0)	97 (93 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	3.1 (1.3 to 4.8)	88 (76 to 99)	2.9 (0.8 to 4.9)	89 (80 to 99)	2.7 (0.6 to 4.7)	90 (81 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	3.2 (1.4 to 5.0)	89 (77 to 100)	2.6 (0.7 to 4.6)	90 (81 to 100)	2.5 (0.5 to 4.5)	90 (80 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	1.5 (0.0 to 2.9)	63 (46 to 80)	1.7 (0.6 to 2.7)	95 (87 to 100)	2.0 (0.0 to 4.0)	96 (89 to 100)

DR, detection rate; FPR, false-positive rate.

Bradbury[13] and Wald and colleagues.[14] The poor performance, which reflects the poor fit observed in *Table 2* and illustrated in *Figure 1*, was explored by examining the determinants of the correlation matrices of the various models given in *Table 7*.

These determinants provide summary measures of the multivariate spread of the fitted distribution of the standardised log (MoM) values. The smaller determinants for Down's syndrome pregnancies relative to unaffected pregnancies means that the fitted multivariate Gaussian distribution in Down's syndrome pregnancies is concentrated in a relatively small region of the sample space. In practice, Down's syndrome pregnancies for which observations fall outside this region are assigned low risks. Consequently, whilst modelled performance is very good because the population distributions are assumed to be the same as the fitted distributions, performance on test data is poor. Indeed, *Tables 3–6* show deterioration in performance from the addition of repeated measures when using the original covariance matrix (i) for Down's syndrome pregnancies. This is illustrated in *Figure 3*, which shows the modelled receiver operating characteristic (ROC) curves with the estimates and 95% CIs for the false-positive and detection rates obtained from the test data sets with a risk threshold of 1 in 200. The evidence from the two test data sets is that screening performance in practice is likely to be much worse than that suggested by the modelling.

Turning to the performance with pooled or diagonally inflated covariance matrices, the results from the North York and FaSTER test data sets are somewhat equivocal. Referring to *Table 4*, with the FaSTER test data, the addition of repeated measures of PAPP-A produces a marginal decrease

TABLE 6 *Marginal increase in standardised detection rates and false-positive rates (%) relative to the base model* p*1* + a2 + u2 + h2 *for a term risk cut-off of 1 in 200 for the FaSTER and North York test data. Risks were computed using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original		**Assumptions (ii): pooled**		**Assumptions (iii): diagonally inflated**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
FaSTER						
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–1.2 (–2.6 to 0.2)	–8 (–14 to –2)	–1.2 (–2.5 to 0.2)	–2 (–5 to 2)	–1.4 (–3.1 to 0.3)	–3 (–7 to 2)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	0.1 (–0.8 to 1.0)	–3 (–5 to 0)	0.1 (–0.7 to 1.0)	–2 (–4 to 0)	–0.1 (–1.0 to 0.7)	–1 (–3 to 0)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0.4 (–0.4 to 1.2)	–4 (–6 to –1)	–0.2 (–0.6 to 0.1)	–1 (–2 to 0)	–0.7 (–1.7 to 0.4)	–1 (–3 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–1.7 (–3.9 to 0.6)	–38 (–48 to –29)	–1.3 (–2.9 to 0.2)	–4 (–8 to 1)	–1.6 (–3.4 to 0.3)	–5 (–10 to –1)
North York						
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–1.7 (–2.6 to –0.7)	2 (–7 to 11)	–1.4 (–3.6 to 0.8)	5 (–4 to 14)	–0.7 (–1.2 to –0.1)	6 (–1 to 13)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	0.0 (–0.7 to 0.8)	–1 (–3 to 0)	0.3 (–0.1 to 0.6)	0 (–1 to 1)	–0.1 (–0.5 to 0.3)	–1 (–2 to 0)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0.1 (–0.9 to 1.2)	0 (–3 to 3)	0.0 (–0.1 to 0.2)	1 (0 to 1)	–0.2 (–0.6 to 0.2)	–1 (–3 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–1.6 (–2.7 to –0.5)	–26 (–42 to –10)	–0.9 (–3.3 to 1.4)	6 (–3 to 14)	–0.8 (–1.5 to –0.1)	5 (–2 to 12)

DR, detection rate; FPR, false-positive rate.

TABLE 7 *Determinants of correlation matrices in unaffected and Down's syndrome pregnancies*

		Assumptions regarding covariance matrix		
Training data		**(i) Original**	**(ii) Pooled**	**(iii) Diagonally inflated**
I. SURUSS	Controls	0.116	0.108	0.116
	Cases	0.009	0.108	0.162
II. Palomaki *et al.* (2006)[23]	Controls	0.080	0.085	0.080
	Cases	0.042	0.085	0.127
III. Cross-trimester ratios	Controls	0.072	0.071	0.072
	Cases	0.012	0.071	0.086

in estimated detection rates for the fixed 2% false-positive rate. However, the 95% CI contains zero. For the North York test data the estimate shows a potentially important benefit for repeated measures of PAPP-A but, again, the CIs for the marginal increase in detection rates all contain zero.

The improvement in performance from assuming equal covariance matrices echoes results presented by Williams and colleagues[33] in 1999, who found that, with smaller training samples, even the performance of tests with relatively few dimensions was improved by making the assumption of equal covariance matrices.

Modelling screening performance[23] shows that any benefit of repeated measures diminishes as the gestational age for the first sample increases

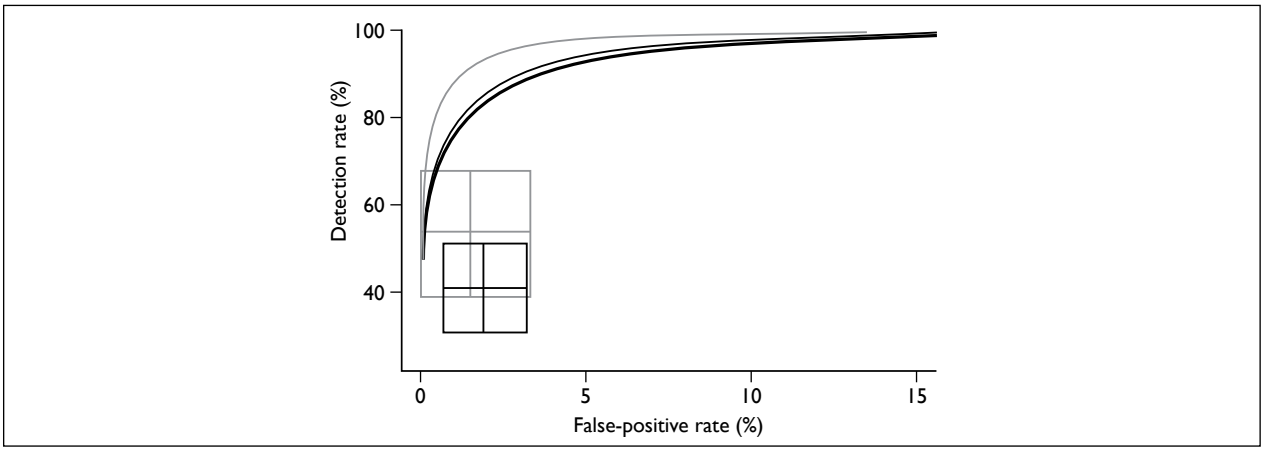

FIGURE 3 *Modelled receiver operating characteristics curves for screening with u1 + h1 + p1 + a2 + u2 + h2 + p2 using SURUSS parameters at 11 weeks' (—), 12 weeks'(—) and 13 weeks' (▬) gestation with 95% CIs for false-positive and detection rates from the North York (—) and FaSTER (—) test data with a risk threshold of 1 in 200. The rectangles are the 95% CIs. The vertical and horizontal lines within these rectangles are the estimated false-positive rate and detection rate respectively for a risk threshold of 1 in 200.*

and that the modelled benefits are negligible for gestational ages of 13 weeks or older. The intuitive explanation for this is that the benefit of repeated measures depends on the difference between the means of the repeated measures. In situations where the first measurement is taken late in the first trimester, the means across the two trimesters are closer together and the discriminatory power is reduced. *Tables 8–11* show screening performance for the two test data sets where the gestational age at the time of the first sample is younger than 13 weeks. Again, the original Down's syndrome covariance matrix is associated with worsening screening performance with the addition of repeated measures. In contrast, the pooled and diagonally inflated covariance matrices show improvements, especially for repeated measures of PAPP-A.

Using the pooled covariance matrix for both FaSTER and North York data sets (see *Tables 8* and *9*), the use of repeated measures of PAPP-A increases the estimated detection rate for a fixed 2% false-positive rate by an estimated 5% (95% CI –2% to 13%) in the FaSTER data set and an estimated 10% (95% CI –5% to 24%) in the North York data set. Similarly, the estimates shown in *Tables 10* and *11* indicate that repeated measures of PAPP-A have the potential to produce an important reduction in false-positive rates whilst maintaining or even increasing detection rates. However, because of the uncertainly reflected in the wide CIs associated with the relatively small samples of Down's syndrome cases in the test data sets, the evidence cannot be considered conclusive.

TABLE 8 *Standardised detection rates (%) for a 2% false-positive rate from the FaSTER and North York test data with first sample gestations below 13 weeks. Screening using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original	Assumptions (ii): pooled	Assumptions (iii): diagonally inflated
FaSTER			
*p*1 + *a*2 + *u*2 + *h*2	75 (62 to 89)	75 (62 to 88)	75 (62 to 88)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	72 (59 to 85)	81 (69 to 92)	77 (65 to 89)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	74 (59 to 88)	74 (60 to 87)	74 (61 to 87)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	66 (50 to 82)	75 (61 to 89)	75 (60 to 90)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	41 (22 to 60)	79 (67 to 91)	76 (63 to 88)
North York			
*p*1 + *a*2 + *u*2 + *h*2	85 (71 to 98)	83 (65 to 100)	84 (64 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	86 (74 to 97)	93 (87 to 99)	91 (84 to 99)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	84 (69 to 99)	86 (72 to 100)	84 (64 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	80 (67 to 94)	83 (64 to 100)	82 (62 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	59 (46 to 73)	93 (87 to 98)	85 (62 to 100)

TABLE 9 *Marginal increase in standardised detection rates (%) for a 2% false-positive rate from the FaSTER and North York test data with first sample gestations below 13 weeks. Screening using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original	Assumptions (ii): pooled	Assumptions (iii): diagonally inflated
FaSTER			
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–3 (–17 to 11)	5 (–2 to 13)	2 (–7 to 11)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	–2 (–6 to 3)	–1 (–5 to 2)	–1 (–5 to 3)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	–9 (–15 to –3)	0 (–3 to 3)	0 (–9 to 8)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–34 (–59 to –10)	4 (–4 to 12)	1 (–9 to 11)
North York			
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	1 (–17 to 19)	10 (–5 to 24)	8 (–10 to 26)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	–1 (–4 to 2)	3 (–6 to 11)	0 (–2 to 3)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	–5 (–10 to 1)	–1 (–2 to 1)	–1 (–4 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–26 (–44 to –7)	9 (–5 to 24)	1 (–12 to 14)

TABLE 10 *Standardised detection and false-positive rates (%) for a term risk cut-off of 1 in 200 for the FaSTER and North York test data with first sample gestations below 13 weeks. Screening using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original		**Assumptions (ii): pooled**		**Assumptions (iii): diagonally inflated**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
FaSTER						
*p*1 + *a*2 + *u*2 + *h*2	3.5 (0.0 to 7.6)	81 (71 to 91)	3.6 (0.9 to 6.4)	81 (72 to 91)	4.0 (1.8 to 6.2)	81 (72 to 91)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	1.3 (0.0 to 3.8)	72 (64 to 79)	1.8 (0.9 to 2.7)	80 (76 to 84)	2.0 (1.1 to 3.0)	78 (73 to 82)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	3.6 (0.0 to 9.0)	80 (68 to 92)	4.1 (1.7 to 6.5)	80 (73 to 87)	4.0 (1.7 to 6.2)	80 (71 to 90)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	4.1 (0.0 to 9.4)	78 (66 to 89)	3.8 (1.6 to 6.0)	81 (72 to 90)	3.3 (1.0 to 5.5)	83 (72 to 93)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	1.5 (0.1 to 4.0)	36 (21 to 52)	2.0 (1.0 to 2.9)	79 (75 to 83)	1.8 (0.0 to 4.0)	76 (65 to 88)
North York						
*p*1 + *a*2 + *u*2 + *h*2	3.1 (1.1 to 5.1)	88 (77 to 99)	2.7 (0.5 to 4.9)	89 (79 to 99)	2.9 (0.7 to 5.1)	91 (81 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	1.5 (0.0 to 3.1)	84 (74 to 94)	1.1 (0.2 to 2.0)	93 (86 to 100)	1.4 (0.3 to 2.5)	93 (87 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	3.0 (0.8 to 5.3)	87 (76 to 98)	2.9 (0.7 to 5.1)	89 (79 to 98)	2.8 (0.5 to 5.0)	90 (79 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	3.3 (0.7 to 5.8)	88 (77 to 100)	2.7 (0.6 to 4.9)	90 (80 to 100)	2.7 (0.4 to 5.0)	90 (80 to 99)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	1.2 (0.0 to 2.8)	56 (40 to 72)	1.2 (0.1 to 2.4)	94 (88 to 100)	2.2 (0.0 to 4.5)	90 (82 to 98)

DR, detection rate; FPR, false-positive rate.

TABLE 11 *Marginal increase in standardised detection and false-positive rates (%) relative to the base model* p*1* + a2 + u2 + h2 *for a term risk cut-off of 1 in 200 for the FaSTER and North York test data with first sample gestations below 13 weeks. Risks were computed using the SURUSS model under assumptions (i) original covariance matrices, (ii) pooled covariance matrices and (iii) diagonally inflated covariance matrices. Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs*

	Assumptions (i): original		**Assumptions (ii): pooled**		**Assumptions (iii): diagonally inflated**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
FaSTER						
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–2.2 (–6.5 to 2.1)	–10 (–21 to 1)	–1.9 (–4.1 to 0.3)	–1 (–10 to 7)	–2.0 (–3.9 to –0.1)	–4 (–12 to 4)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	0.1 (–1.6 to 1.8)	–2 (–5 to 2)	0.5 (–0.9 to 1.8)	–1 (–5 to 3)	–0.1 (–0.3 to 0.2)	–1 (–2 to 0)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0.6 (–1.4 to 2.6)	–4 (–9 to 1)	0.1 (–0.9 to 1.1)	–1 (–3 to 1)	–0.8 (–1.1 to –0.4)	1 (–1 to 3)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–2.0 (–6.3 to 2.3)	–45 (–62 to –28)	–1.7 (–3.8 to 0.5)	–2 (–10 to 6)	–2.2 (–4.0 to –0.4)	–5 (–13 to 3)
North York						
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–1.6 (–2.7 to –0.6)	–4 (–16 to 8)	–1.6 (–3.8 to 0.5)	4 (–1 to 10)	–1.5 (–3.7 to 0.7)	3 (–4 to 9)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	–0.1 (–0.9 to 0.8)	–2 (–3 to 0)	0.2 (–0.2 to 0.5)	0 (–2 to 1)	–0.1 (–0.5 to 0.2)	–1 (–2 to 0)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0.2 (–1.0 to 1.4)	0 (–4 to 4)	0.0 (–0.1 to 0.2)	1 (0 to 2)	–0.2 (–0.8 to 0.4)	–1 (–3 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–1.9 (–3.2 to –0.6)	–33 (–50 to –16)	–1.5 (–3.8 to 0.8)	5 (–2 to 12)	–0.7 (–1.8 to 0.4)	–1 (–10 to 8)

DR, detection rate; FPR, false-positive rate.

Chapter 4

Development of a new screening algorithm for use in repeated measures screening

Model fitting

The assessment of goodness of fit and screening performance with published parameters has demonstrated the limitations of the existing evidence for risk assessment using repeated measures. In particular, the correlation matrices for Down's syndrome for training data sets (I)–(III) have unrealistically small determinants, they are a poor fit to the test data sets and produce poor screening performance. The pooled estimates provide a better fit and show some improvement in screening performance with repeated measures of PAPP-A, especially when the first sample is taken early in the first trimester. However, with the relatively small sample sizes, there is considerable uncertainty associated with these estimates. The purpose of this chapter is to show how new models were developed using the evidence available from the North York and FaSTER data sets. Three models, all based on pooled covariance matrices, were fitted within the Bayesian framework implemented using WinBUGS. One model was fitted to each of the two test data sets separately so that the other test data set could be used for independent cross-validation. A third model was fitted to the combined data set. The fitted model parameters are presented in Appendix 6.

Cross-validation

Tables 12–17 show the results of a cross-validation study using separate models fitted to each of the two test data sets using the other test data set for validation. These show similar performance to that achieved using the SURUSS data. These tables also provide estimates of screening performance when the same data set is used for training and testing. It is notable that the different results from a particular test data set are similar for the two choices of training data. The degree of optimistic bias encountered in these data is therefore small. *Figure 4* shows the ROC curve produced from the model fitted to the combined data, together with estimates of screening performance from the cross-validation using the data at 12 weeks or earlier (*Table 16*). This shows that the estimates from the cross-validation are broadly consistent with the modelled performance. *Tables 16* and *17* show that for both FaSTER and North York samples, the evidence is that repeated measures of PAPP-A improve screening performance when the first trimester sample is taken at 12 weeks' gestation or earlier.

Bayesian inference under a Gaussian model fitted to the combined data

Table 18 shows screening performance under the Gaussian model fitted to the combined test data sets from FaSTER and North York. Point estimates, together with 95% CIs, were obtained by sampling from the posterior predictive distribution of screening performance. *Table 19* shows the marginal benefits of adding the sequence of repeated measures of PAPP-A (second trimester), hCG (first trimester) and then uE3 (first trimester) to the base test, comprising PAPP-A in the first trimester and AFP, hCG and uE3 in the second trimester. The evidence is that PAPP-A is the most promising marker for repeated measures. However, the benefit of this and other repeated measures markers diminishes with gestational age at the time of the first trimester sample. By 13 weeks there is no evidence of any benefit.

Figures 5–7 show ROC curves (bold) obtained from the model fitted to the combined data at 11, 12 and 13 weeks respectively for a test using first trimester PAPP-A and second trimester AFP, uE3, hCG and PAPP-A. Estimates (posterior means) and 95% credibility intervals for this test, with a risk threshold of 1 in 200, are superimposed on *Figures 5–7*. These were obtained from the posterior distribution under the Gaussian model. For comparison, the ROC curves of the base test (first trimester PAPP-A and second trimester AFP, hCG and uE3) are also shown.

TABLE 12 *Standardised detection rates (%) for a screen positive rate of 2% with different combinations of FaSTER and North York data as test and training data. Results are presented for test data with the first sample gestations younger than 13 weeks and for the full range of gestations. Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. No CIs are given for situations where the same data are used for training and testing the risk algorithm*

	Test: FaSTER				**Test: North York**			
	Training: FaSTER		**Training: North York**		**Training: North York**		**Training: FaSTER**	
	< 13 weeks	**All**	**< 13 weeks**	**All**	**< 13 weeks**	**All**	**< 13 weeks**	**All**
*p*1 + *a*2 + *u*2 + *h*2	76	72	75 (62 to 88)	73 (63 to 83)	85	87	85 (66 to 100)	86 (71 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	82	68	78 (67 to 89)	76 (65 to 86)	94	95	95 (89 to 100)	95 (89 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	75	68	73 (60 to 87)	72 (61 to 82)	85	86	84 (69 to 98)	85 (74 to 95)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	76	71	73 (59 to 87)	73 (63 to 83)	80	82	84 (65 to 100)	85 (69 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	81	65	75 (64 to 87)	73 (62 to 84)	93	95	95 (89 to 100)	95 (86 to 100)

TABLE 13 *Marginal increases in standardised detection rates (%) relative to the base model* p*1* + a2 + u2 + h2 *for a screen positive rate of 2% with different combinations of FaSTER and North York data as test and training data. Results are presented for test data with the first sample gestations younger than 13 weeks and for the full range of gestations. Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. No CIs are given for situations in which the same data are used for training and testing the risk algorithm*

	Test: FaSTER				**Test: North York**			
	Training: FaSTER		**Training: North York**		**Training: North York**		**Training: FaSTER**	
	< 13 weeks	**All**	**< 13 weeks**	**All**	**< 13 weeks**	**All**	**< 13 weeks**	**All**
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	6	3	4 (–3 to 11)	–3 (–8 to 1)	9	8	13 (–8 to 34)	9 (–3 to 21)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	–1	–2	–2 (–6 to 2)	–3 (–6 to 0)	0	0	–5 (–19 to 10)	–1 (–9 to 6)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0	0	–2 (–4 to 1)	–1 (–2 to 0)	–6	–5	–2 (–5 to 1)	–1 (–3 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	4	0	1 (–7 to 8)	–7 (–13 to 0)	7	6	12 (–8 to 33)	9 (–3 to 21)

TABLE 14 *Standardised detection rates and false-positive rates (%) for a term risk cut-off of 1 in 200 for different combinations of FaSTER and North York data as test and training sets. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. No CIs are given for situations in which the same data are used for training and testing the risk algorithm*

	Test: FaSTER				**Test: North York**			
	Training: FaSTER		**Training: North York**		**Training: North York**		**Training: FaSTER**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
*p*1 + *a*2 + *u*2 + *h*2	4.1	80	3.9 (1.7 to 6.0)	80 (73 to 88)	3.0	90	2.6 (0.6 to 4.7)	89 (78 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	3.7	82	3.3 (1.5 to 5.0)	78 (71 to 85)	2.3	97	2.2 (0.4 to 3.9)	93 (85 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	4.4	79	4.1 (1.7 to 6.5)	78 (70 to 85)	3.0	90	2.7 (0.7 to 4.6)	89 (78 to 99)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	4.1	79	3.6 (1.7 to 5.4)	79 (71 to 86)	3.0	90	2.6 (0.6 to 4.7)	89 (78 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	4.0	82	3.1 (1.4 to 4.8)	75 (68 to 83)	2.5	96	2.5 (0.7 to 4.3)	94 (86 to 100)

DR, detection rate; FPR, false-positive rate.

TABLE 15 *Marginal increases in standardised detection and false-positive rates (%) relative to the base model* p*1* + a2 + u2 + h2 *for a term risk cut-off of 1 in 200 for different combinations of FaSTER and North York data as test and training data sets. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. No CIs are given for situations in which the same data are used for training and testing the risk algorithm*

	Test: FaSTER				**Test: North York**			
	Training: FaSTER		**Training: North York**		**Training: North York**		**Training: FaSTER**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–0.4	3	–0.6 (–2.2 to 0.9)	–3 (–8 to 3)	–0.7	7	–0.5 (–2.5 to 1.5)	4 (1 to 8)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	0.3	–1	0.2 (–0.7 to 1.0)	–3 (–4 to –1)	0.0	0	0.0 (–0.2 to 0.3)	0 (–2 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0	–1	–0.3 (–1.0 to 0.4)	–2 (–4 to 0)	0.1	0	0.0 (0.0 to 0.1)	0 (0 to 0)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–0.1	2	–0.8 (–2.6 to 1.0)	–5 (–11 to 1)	–0.5	7	–0.1 (–2.3 to 2.0)	5 (1 to 10)

DR, detection rate; FPR, false-positive rate.

TABLE 16 *Standardised detection and false-positive rates (%) for a term risk cut-off of 1 in 200 for different combinations of FaSTER and North York data as test and training data sets for first sample gestations of 11 and 12 weeks or first sample gestations below 13 weeks. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. No CIs are given for situations in which the same data are used for training and testing the risk algorithm*

	Test: FaSTER				**Test: North York**			
	Training: FaSTER		**Training: North York**		**Training: North York**		**Training: FaSTER**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
*p*1 + *a*2 + *u*2 + *h*2	3.6	82	3.2 (0.7 to 5.7)	81 (73 to 90)	3.2	89	2.8 (0.9 to 4.6)	89 (79 to 98)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	2.6	85	1.7 (0.0 to 3.7)	78 (70 to 85)	2.4	97	2.3 (0.7 to 3.9)	93 (86 to 100)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	3.8	81	3.8 (0.7 to 6.9)	80 (70 to 89)	3.1	89	2.7 (0.8 to 4.6)	88 (79 to 97)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	3.6	82	3.5 (0.9 to 6.1)	80 (72 to 88)	3.2	90	2.8 (0.9 to 4.6)	89 (79 to 98)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	3.0	85	1.9 (0.0 to 4.2)	78 (70 to 85)	2.2	96	2.4 (0.7 to 4.1)	94 (88 to 100)

DR, detection rate; FPR, false-positive rate.

TABLE 17 *Marginal increases in standardised detection and false-positive rates (%) relative to the base model* p*1* + a2 + u2 + h2 *for a term risk cut-off of 1 in 200 for different combinations of FaSTER and North York data as test and training data sets for first sample gestations of 11 and 12 weeks or first sample gestations below 13 weeks. The detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002. Figures in brackets are 95% CIs. No CIs are given for situations in which the same data are used for training and testing the risk algorithm*

	Test: FaSTER				**Test: North York**			
	Training: FaSTER		**Training: North York**		**Training: North York**		**Training: FaSTER**	
	FPR (%)	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**
*p*1 + *a*2 + *u*2 + *h*2 + *p*2	–1.0	3	–1.5 (–2.9 to –0.1)	–4 (–12 to 4)	–0.7	8	–0.5 (–2.5 to 1.6)	5 (0 to 9)
*p*1 + *a*2 + *u*2 + *h*2 + *h*1	0.2	–1	0.6 (–0.4 to 1.5)	–2 (–4 to 1)	–0.1	0	–0.1 (–0.2 to 0.1)	0 (–2 to 1)
*p*1 + *a*2 + *u*2 + *h*2 + *u*1	0.0	–1	0.2 (–0.3 to 0.8)	–1 (–4 to 1)	0.0	0	0 (–0.0 to 0.1)	0 (0 to 0)
*p*1 + *a*2 + *u*2 + *h*2 + *p*2 + *u*1 + *h*1	–0.6	3	–1.3 (–2.5 to –0.2)	–4 (–11 to 3)	–0.9	7	–0.3 (–2.4 to 1.7)	6 (0 to 11)

DR, detection rate; FPR, false-positive rate.

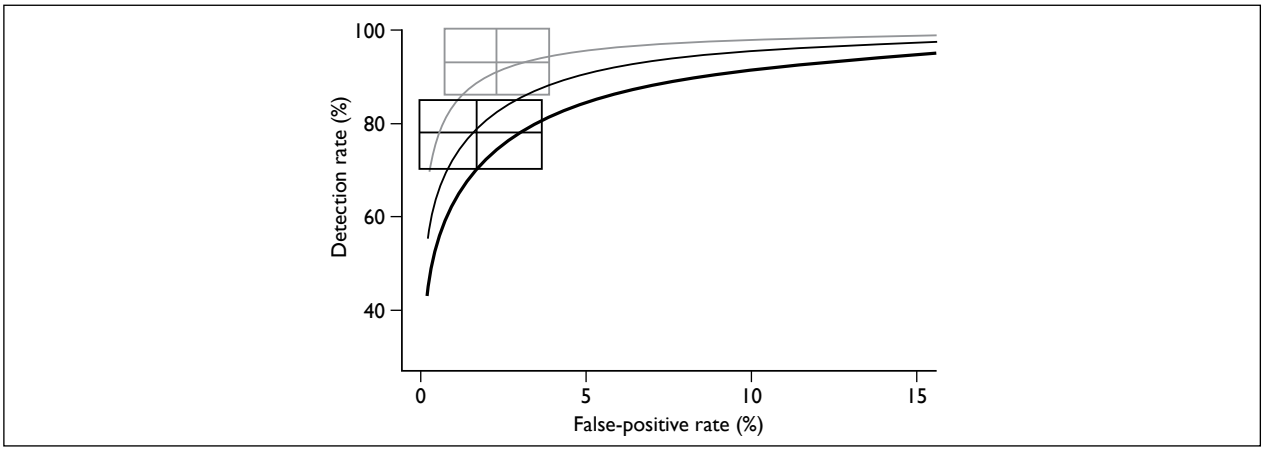

FIGURE 4 *Modelled receiver operating characteristics curves for screening with* p*1* + a2 + u2 + h2 + p2 *at 11 weeks' (—), 12 weeks' (—) and 13 weeks' (—) gestation. The rectangles are the 95% CIs for false-positive and detection rates from the North York (—) and FaSTER (—) test data using a risk threshold of 1 in 200. The vertical and horizontal lines within these rectangles are the estimated false-positive rate and detection rate respectively. The estimates and CIs were obtained using cross-validation. For example, the estimates and CIs for the North York test data were obtained from screening using the model fitted to the FaSTER test data.*

TABLE 18 *Screening performance of repeated measures tests relative to the base test (p1 + a2 + h2 + u2) under the Gaussian model. Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002 assuming a risk threshold of 1 in 200. Figures in brackets are 95% CIs*

	Week 11		**Week 12**		**Week 13**	
	DR (%)	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**
(i) Base (i.e. *p*1 + *a*2 + *h*2 + *u*2)	88.6 (83.8 to 93.5)	3.5 (2.8 to 4.2)	85.7 (81.2 to 90.2)	4.4 (3.7 to 5.2)	82.8 (78.2 to 87.4)	5.3 (4.4 to 6.1)
(ii) Base + *p*2	91.7 (86.9 to 96.6)	2.5 (1.8 to 3.1)	87.6 (83.6 to 91.6)	3.8 (3.0 to 4.6)	83.2 (78.4 to 88.0)	5.1 (4.2 to 6.0)
(ii)–(i)	3.1 (0.7 to 5.5)	–1.1 (–1.5 to –0.6)	1.9 (0.0 to 3.7)	–0.6 (–1.1 to –0.2)	0.4 (–1.0 to 1.9)	–0.1 (–0.5 to 0.2)
(iii) Base + *h*1	89.6 (85.0 to 94.1)	3.2 (2.5 to 3.9)	85.7 (81.2 to 90.2)	4.4 (3.7 to 5.2	83.9 (79.1 to 88.8)	4.9 (4.0 to 5.7)
(iii)–(i)	0.9 (–0.9 to 2.8)	–0.3 (–0.6 to –0.0)	0.0 (–0.4 to 0.4)	0.0 (–0.2 to 0.2)	1.2 (–1.6 to 3.9)	–0.4 (–0.9 to 0.1)
(iv) Base + *u*1	88.8 (83.9 to 93.7)	3.5 (2.8 to 4.2)	85.7 (81.3 to 90.2)	4.4 (3.7 to 5.2)	82.4 (77.9 to 87.0)	5.1 (4.3 to 6.0)
(iv)–(i)	0.1 (–0.8 to 1.0	–0.1 (–0.3 to 0.2)	0.0 (–0.4 to 0.4)	0.0 (–0.2 to 0.2)	–0.4 (–1.8 to 1.1)	–0.1 (–0.4 to 0.1)
(v) Base + *p*2 + *h*1 + *u*1	92.6 (87.9 to 97.3)	2.2 (1.5 to 2.9)	87.6 (83.6 to 91.6)	3.8 (3.0 to 4.7)	84.0 (79.4 to 88.6)	4.5 (3.7 to 5.3)
(v)–(i)	4.0 (1.0 to 6.9)	–1.3 (–1.8 to –0.8)	1.9 (0.1 to 3.7)	–0.6 (–1.0 to –0.1)	1.2 (–1.9 to 4.3)	–0.7 (–1.3 to –0.2)

DR, detection rate; FPR, false-positive rate.

TABLE 19 *Screening performance of repeated measures showing incremental changes from the addition of markers* p2, h*1 and* u*1. Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002 assuming a risk threshold of 1 in 200. Figures in brackets are 95% CIs*

	Week 11		Week 12		Week 13	
	DR (%)	**FPR (%)**	**DR (%)**	**FPR (%)**	**DR (%)**	**FPR (%)**
(i) Base (i.e. *p*1 + *a*2 + *h*2 + *u*2)	88.6 (83.8 to 93.5)	3.5 (2.8 to 4.2)	85.7 (81.2 to 90.2)	4.4 (3.7 to 5.2)	82.8 (78.2 to 87.4)	5.3 (4.4 to 6.1)
(ii) Base + *p*2	91.7 (86.9 to 96.6)	2.5 (1.8 to 3.1)	87.6 (83.6 to 91.6)	3.8 (3.0 to 4.6)	83.2 (78.4 to 88.0)	5.2 (4.2 to 6.0)
(ii)–(i)	3.1 (0.7 to 5.5)	–1.1 (–1.5 to –0.6)	1.9 (0.0 to 3.7)	–0.6 (–1.1 to –0.2)	0.4 (–1.0 to 1.9)	–0.1 (–0.5 to 0.2)
(iii) Base + *p*2 + *h*1	92.3 (87.6 to 97.1)	2.3 (1.6 to 2.9)	87.7 (83.7 to 91.6)	3.8 (3.0 to 4.7)	84.3 (79.4 to 89.1)	4.7 (3.8 to 5.5)
(iii)–(ii)	0.6 (–0.9 to 2.1)	–0.2 (–0.2 to 0.1)	0.1 (–0.4 to 0.5)	0.0 (–0.3 to 0.4)	1.0 (–1.5 to 3.6)	–0.5 (–1.0 to 0.1)
(iv) Base + *p*2 + *h*1 + *u*1	92.6 (87.9 to 97.3)	2.2 (2.8 to 4.2)	87.6 (83.6 to 91.6)	3.8 (3.0 to 4.7)	84.0 (79.4 to 89.1)	4.5 (3.7 to 5.3)
(iv)–(iii)	0.3 (–0.5 to 1.0)	–0.1 (–0.4 to 0.2)	0.0 (–0.4 to 0.4)	0.0 (–0.4 to 0.4)	–0.3 (–2.0 to 1.4)	–0.1 (–0.5 to 0.2)

DR, detection rate; FPR, false-positive rate.

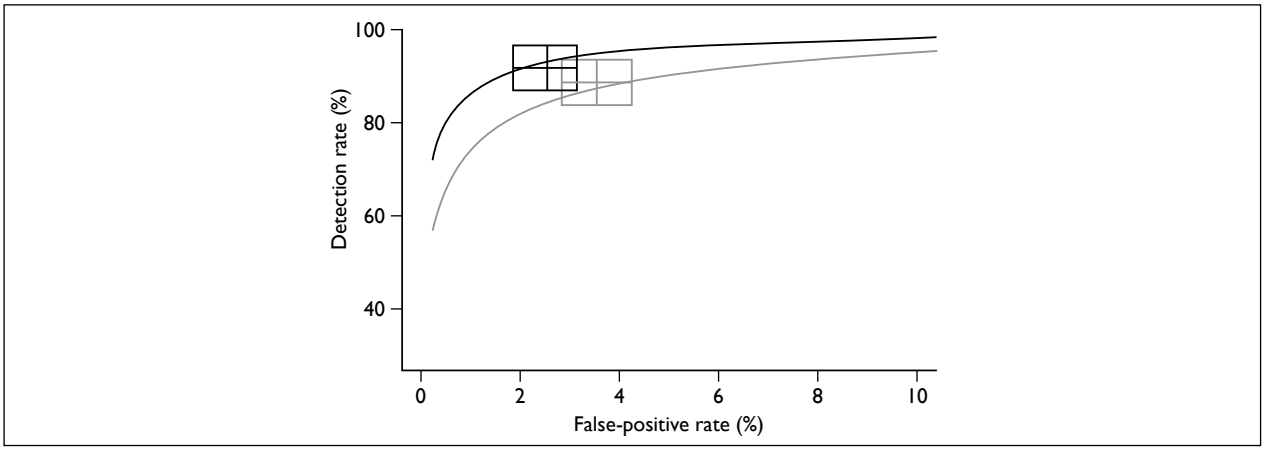

FIGURE 5 *Receiver operating characteristic curve for the base test* p*1* + a*2* + h*2* + u*2 and for the base test* + p*2 (bold) when the first trimester sample is taken at 11 weeks' gestation. The rectangles show 95% credibility intervals for standardised detection rates and false-positive rates for a risk threshold of 1 in 200. These were obtained from the posterior distribution under the Gaussian model.*

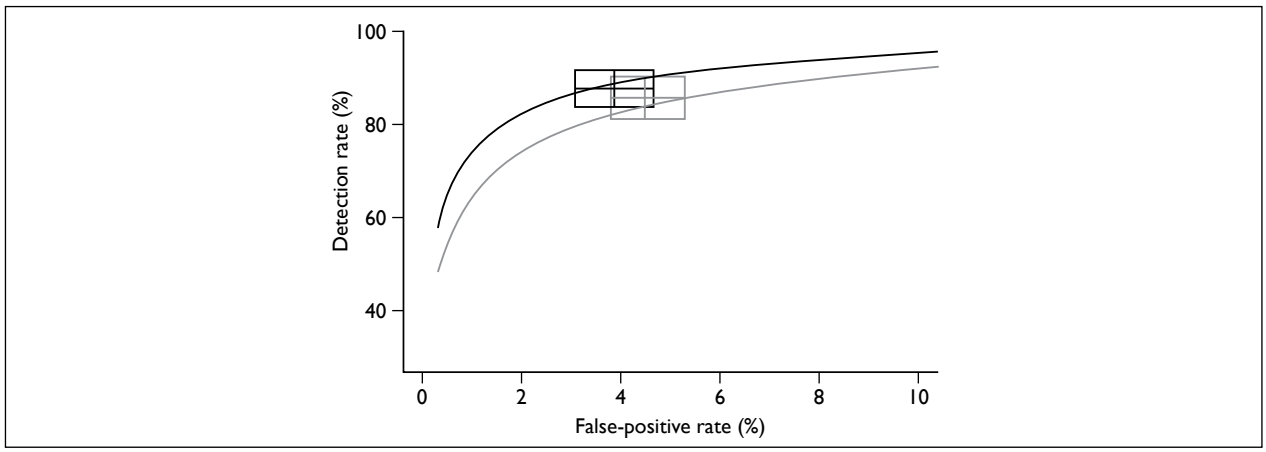

FIGURE 6 *Receiver operating characteristic curve for the base test* p*1* + a2 + h2 + u2 *and for the base test* + p2 *(bold) when the first trimester sample is taken at 12 weeks' gestation. The rectangles show 95% credibility intervals for standardised detection rates and false-positive rates for a risk threshold of 1 in 200. These were obtained from the posterior distribution under the Gaussian model.*

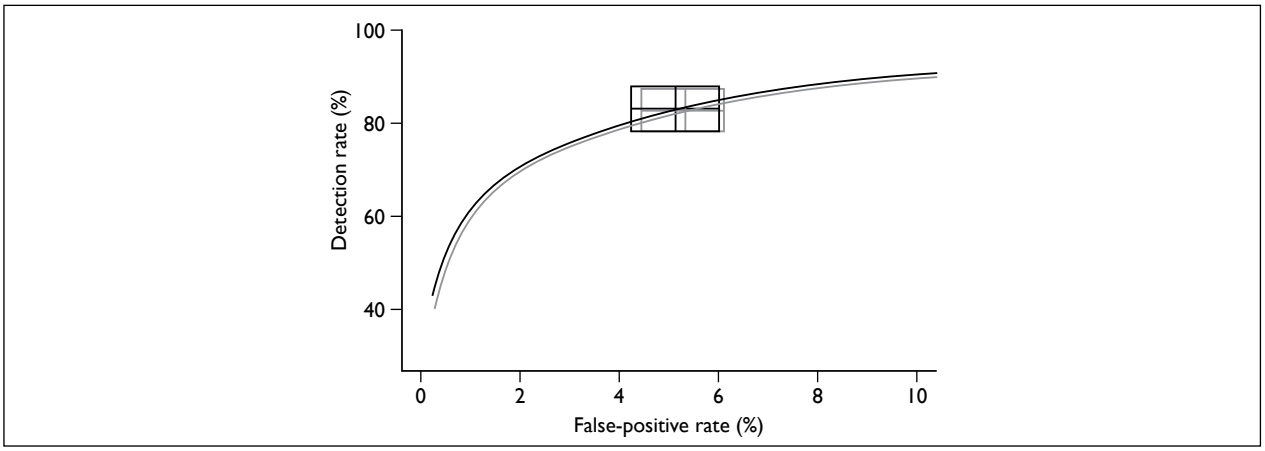

FIGURE 7 *Receiver operating characteristic curve for the base test* p*1* + a2 + h2 + u2 *and for the base test* + p2 *(bold) when the first trimester sample is taken at 13 weeks' gestation. The rectangles show 95% credibility intervals for standardised detection rates and false-positive rates for a risk threshold of 1 in 200. These were obtained from the posterior distribution under the Gaussian model.*

TABLE 20 *Screening performance of repeated measures showing incremental changes from the addition of PAPP-A in the second trimester over the combined and quadruple test markers (first trimester NT, β–hCG, PAPP-A and second trimester AFP, uE3, hCG and Inhibin-A). Detection and false-positive rates are for the maternal age distribution of England and Wales for the 3-year period 2000–2002 using a risk cut-off of 1 in 200*

	Week 11		Week 12		Week 13	
	DR (%)	FPR (%)	DR (%)	FPR (%)	DR (%)	FPR (%)
(i) Combined + quadruple test	95	1.5	93	1.9	92	2.2
(ii) Combined + quadruple test + *p*2	97	1.1	94	1.7	92	2.2
(ii)–(i)	1	–0.4	1	–0.2	0	0

DR, detection rate; FPR, false-positive rate.

From a practical perspective, first trimester combined screening using NT, PAPP-A and β-hCG at 11–13 weeks' gestation is the standard being adopted in the UK and elsewhere. The quadruple test comprising AFP, uE3, hCG and Inhibin-A is being adopted for women screened in the second trimester. It is therefore important to determine the role of repeated measures in tests incorporating markers from the combined test and the quadruple tests. Specific questions are:

- What is the benefit of second trimester PAPP-A when added to the markers in the combined and quadruple tests?
- What is the best subset of markers?

Using the estimates from Appendix 6 in conjunction with the mixture model for NT,[34] the performance of screening using second trimester measurement of PAPP-A with the markers from the combined and quadruple tests was assessed. The results are presented in *Table 20*. With the inclusion of NT, the modelling produces detection rates well in excess of 90% for false-positive rates of less than 2%. The addition of PAPP-A in the second trimester increases detection rates marginally and reduces false-positive rates by 0.4% when the first trimester sample is taken at 11 weeks' gestation and 0.2% when the first trimester sample is taken at 12 weeks. The addition of the second trimester measurement of PAPP-A is of no benefit when the first trimester sample is taken at 13 weeks' gestation.

Chapter 5
Discussion

Although modelling using published parameter estimates demonstrated substantial benefits in terms of detection rates and false-positive rates for repeated measures,[13,14] we have shown that when applied to independent test data sets, screening using published parameter estimates performs very poorly when repeated measures are included. This contradiction between the model predictions and the results from real data can be explained by the unrealistically small determinants of the published correlation matrices for Down's syndrome pregnancies. These small determinants mean that the fitted distribution for Down's syndrome pregnancies is concentrated in a relatively small region. Under the modelling assumption, where the population reflects the model and measurements on Down's syndrome pregnancies arise from this highly concentrated distribution, screening performance is exceptionally good. However, in reality, data on Down's syndrome pregnancies exhibit more variability than the fitted model and so risks computed from the model are unrealistically low in many cases.

Evidence has been presented that, when risks are computed from models based on structured covariance matrices, screening performance can be improved using repeated measures of PAPP-A. In these models, the covariance matrix for Down's syndrome pregnancies is constrained so that it is linked to the covariance matrix for unaffected pregnancies. The simplest constraint is to make the covariance matrix in Down's syndrome pregnancies the same as that in unaffected pregnancies. This assumption leads to the use of linear discriminant analysis,[21] as previously suggested by Williams and colleagues.[33] This assumption has benefits in terms of simplicity and ensures that the likelihood ratio is a monotonic function of the MoM values.

The evidence comes from three analyses of the marginal benefit of adding a repeated measurement of PAPP-A in the second trimester to a base test comprising PAPP-A in the first trimester and AFP, uE3 and hCG in the second.

Firstly, using bootstrapping to provide CIs, we have used the FaSTER and North York data sets to carry out independent validation studies of the performance of screening using published parameters. The strength of this approach is its robustness. Although the risks are computed under the assumptions of a Gaussian model, no parametric assumptions are involved in the assessment of screening performance. The weakness of this approach is the lack of precision as reflected by relatively wide CIs.

Secondly, using a Bayesian approach, separate models have been fitted to the FaSTER and North York data sets, and a cross-validation study, using the same non-parametric bootstrapping approach to obtain CIs, has been applied.

Thirdly, adopting a Bayesian approach, we have obtained credibility intervals for screening performance under the Gaussian model fitted to the combined test data sets from FaSTER and North York.

The Bayesian analysis shows evidence of substantial benefits from the use of repeated measures of PAPP-A in situations where the first trimester sample is taken at 11 weeks' gestation. These model-based results are generally consistent with the cross-validation studies but show greater precision. At 11 weeks, the repeated measurement of PAPP-A reduced the false-positive rate by an estimated 1% (95% CI 0.6% to 1.5%) from 3.5% to 2.5% and increased the detection rate by an estimated 3% (95% CI 1% to 6%) from 89% to 92%. There is little evidence of benefit from repeated measures of hCG or uE3. The evidence also suggests that any benefit from repeated measures of PAPP-A diminishes with increases in gestation of the first trimester sample, and by 13 weeks' gestation the repeated measurement of PAPP-A has little to add to screening performance.

The evidence of a reduction of around 1% in false-positive rate, with no loss in detection rate, has important benefits in terms of health service provision and the large number of invasive tests avoided. For example, in a screened population of 100,000, an expected 1000 invasive tests and 10 fetal losses would be avoided. The results from this study therefore provide evidence to support a prospective study of repeated measurements of

PAPP-A. They also suggest that any such study should focus on samples taken early (between 8 and 12 weeks) during the first trimester. A formal clinical effectiveness and cost-effectiveness analysis should be undertaken. A secondary objective of any such prospective study should be to investigate the potential value of other repeated measures markers including ADAM-12 and Inhibin-A. The additional complexity arising from the need to obtain serum samples in the first and second trimester is an important practical consideration. The use of contingent screening[6,7] with intermediate risks can be used to reduce the need for the second sample in around 80% of women with very little impact on screening performance. There is a need to assess effectiveness of repeated measures screening policies, including those that make use of contingent strategies, from the perspectives of women, service provision and health economics.

First trimester combined screening using NT, PAPP-A and β-hCG at 11–13 weeks' gestation is the standard being adopted in the UK and elsewhere. The quadruple test comprising AFP, uE3, hCG and Inhibin-A is being adopted for women screened in the second trimester. The results presented in this report suggest that, if the first trimester sample is taken at 11 weeks, adding repeated measures of PAPP-A to the combined test and quadruple test markers reduces false-positive rates by an estimated 0.4% from 1.5% to 1.1% with no loss in detection rate. It is envisaged that any prospective studies of repeated measures of PAPP-A would involve its inclusion in a panel of second trimester markers from the quadruple test following the combined test, either as an integrated test or a contingent screening test.[6,7] This would enable the benefits of adding second trimester PAPP-A to the combined test and quadruple test markers to be assessed prospectively and the different marker combinations to be compared.

The results presented in this report are based on the use of multivariate methods for assessment of goodness of fit and bootstrapping and Bayesian methods for inference. The possibility of using a predictive approach to account for uncertainty in parameters in assessment of risk has also been discussed. Further methodological work of this kind would be of great benefit in terms of improvements in service provision and policy making.

The development and evaluation of risk assessment and screening tests for Down's syndrome and other maternal and fetal conditions requires samples from large numbers of affected pregnancies. Where centres are able to collect blood at two different stages of pregnancy and separate and store serum samples under controlled conditions until the outcome of pregnancy is known, it would be of considerable value if an aliquot of these samples along with suitable matched control sera could be donated to a central serum bank for long-term storage. This would provide a valuable resource facilitating further research to improve prenatal care across a range of maternal and fetal conditions.

Acknowledgements

Sadly, Dr Summers, who helped instigate this project, provided data from the Ontario screening program and contributed to the planning of the work, died before the project was completed. She was a tremendously supportive colleague and friend, who contributed greatly to research and practice in this field over many years.

Contribution of authors

The data which made this study possible were provided from the FaSTER study, represented by F Malone and M D'Alton, and North York General Hospital, Toronto, by A Summers and T Huang. The analysis was conducted by D Wright and I Bradbury, with S Ball and A Baker assisting with the analysis. The report was drafted by D Wright and I Bradbury. B Nix, D Aitken, J Crossley, H Cuckle and K Spencer worked on the design of the study. All authors contributed to the writing of the report.

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Appendix 1

National Screening Committee criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Ideally all the following criteria should be met before screening for a condition is initiated:

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood, including the psychological implications.

The test

1. There should be a simple, safe, precise and validated screening test.
2. The distribution of test values in the target population should be known, and a suitable cut-off level defined and agreed.
3. The test should be acceptable to the population.
4. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
5. If the test is for mutations, the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

The treatment

1. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
2. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
3. Clinical management of the condition and patient outcomes should be optimised in all health-care providers prior to participation in a screening programme.

The screening programme

1. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.
2. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
3. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.
4. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
5. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).
6. There should be a plan for managing and monitoring the screening programme, and an agreed set of quality assurance standards.

7. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.
8. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
9. Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.
10. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
11. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members.

References

1. Department of Health. *Screening of pregnant women for hepatitis B and immunization of babies at risk.* London: Department of Health, 1998 (Health Service Circular: HSC 1998/127).

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5. Wald NJ (editor). *Antenatal and neonatal screening.* Oxford: Oxford University Press, 1984.

6. Holland WW, Stewart S. *Screening in healthcare.* London: The Nuffield Provincial Hospitals Trust, 1990.

7. Grey JAM. *Dimensions and definitions of screening.* Milton Keynes: NHS Executive Anglia and Oxford, Research and Development Directorate, 1996.

Appendix 2

STARD checklist for reporting of studies of diagnostic accuracy (version January 2009)

Section and topic	Item		On pages
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity')	i, iii–iv
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups	1–2
METHODS			3–6
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected	
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected	
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	
Test methods	7	The reference standard and its rationale	
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cited references for index tests and reference standard	
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard	
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard	
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers	
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals)	
	13	Methods for calculating test reproducibility, if done	
RESULTS			7–18
Participants	14	When study was performed, including beginning and end dates of recruitment	
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms)	
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended)	
Test results	17	Time interval between the index tests and the reference standard, and any treatment administered in between	
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition	
	19	A cross-tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard	
	20	Any adverse events from performing the index tests or the reference standard	

Section and topic	Item		On pages
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals)	
	22	How indeterminate results, missing data and outliers of the index tests were handled	
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if done	
	24	Estimates of test reproducibility, if done.	
DISCUSSION	25	Discuss the clinical applicability of the study findings	27–28

MeSH, medical subject headings.

Appendix 3

Parameter estimates from training data sets I–IV

TABLE 21 *Mean log MoM values in Down's syndrome pregnancies by week*

	Mean log MoM in Down's syndrome pregnancies							
	SURUSS				CT ratios			
Parameter	Week 10	Week 11	Week 12	Week 13	Week 10	Week 11	Week 12	Week 13
First trimester								
NT	0.3820	0.3367	0.2913	0.2460	0.3820	0.3367	0.2913	0.2460
AFP	–0.0655	–0.0655	–0.0655	–0.0655	–0.2380	–0.1839	–0.1264	–0.0703
uE3	–0.0044	–0.0605	–0.1024	–0.1427	–0.0182	–0.0525	–0.0843	–0.1187
hCG	–0.0177	0.1038	0.1875	0.2742	0.0565	0.0970	0.1357	0.1751
β-hCG	0.2095	0.2878	0.3404	0.3944	0.2850	0.3076	0.3280	0.3494
Inhibin-A	–0.0269	0.1303	0.2380	0.3384	0.1131	0.1453	0.1770	0.2113
PAPP-A	–0.4685	–0.3768	–0.3010	–0.2366	–0.4685	–0.3768	–0.3010	–0.2366
Second trimester								
AFP	–0.1308	–0.1308	–0.1308	–0.1308	–0.1308	–0.1308	–0.1308	–0.1308
uE3	–0.1549	–0.1549	–0.1549	–0.1549	–0.1549	–0.1549	–0.1549	–0.1549
hCG	0.3118	0.3118	0.3118	0.3118	0.3118	0.3118	0.3118	0.3118
β-hCG	0.4249	0.4249	0.4249	0.4249	0.4249	0.4249	0.4249	0.4249
Inhibin-A	0.3384	0.3384	0.3384	0.3384	0.3384	0.3384	0.3384	0.3384
PAPP-A	0.0453	0.0453	0.0453	0.0453	–0.0740	–0.0344	–0.0087	0.0039

CT, cross-trimester.

TABLE 22 *Standard deviations of log MoM values in Down's syndrome and unaffected pregnancies. The SURUSS estimates were obtained from Wald* et al. *(2003)[4,5] incorporating changes from Wald* et al. *(2004)[35] and Wald* et al. *(2006).[28] Palomaki* et al. *(2006)[23] use a standard deviation of 0.243 for second-trimester PAPP-A in unaffected pregnancies. All other standard deviations are as published in the SURUSS report*

		Standard deviations of log MoM in unaffected pregnancies		Standard deviations of log MoM in Down's syndrome pregnancies		Estimated common SD from the North York training data
Parameter	**Week**	**SURUSS**	**CT ratios**	**SURUSS**	**CT ratios**	
First trimester						
NT	10	0.1732	0.1732	0.2313	0.2313	
	11	0.1439	0.1439			
	12–13	0.1329	0.1329			
AFP		0.1818	0.1788	0.1672	0.1832	
uE3		0.1204	0.1183	0.1720	0.1708	0.1190
hCG		0.1950	0.1999	0.2069	0.1817	0.2007
β-hCG		0.2651	0.2605	0.2569	0.2417	
Inhibin-A		0.2191	0.2057	0.2343	0.2112	
PAPP-A		0.2495	0.2495	0.2802	0.2802	0.2421
Second trimester						
AFP		0.1399	0.1399	0.1398	0.1398	0.1355
uE3		0.1142	0.1142	0.1238	0.1238	0.1066
hCG		0.2276	0.2276	0.2395	0.2395	0.2186
β-hCG		0.2577	0.2577	0.2965	0.2965	
Inhibin-A		0.2078	0.2078	0.2679	0.2679	
PAPP-A		0.2549	0.2451	0.2203	0.2227	0.2408

CT, cross-trimester; SD, standard deviation.

TABLE 23 *Estimated correlation matrix for unaffected pregnancies from SURUSS*

	First trimester										Second trimester					
	NT															
Parameter	**10 weeks**	**11 weeks**	**12 weeks**	**13 weeks**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester																
AFP	0.0227	0.0273	0.0296	0.0296	1	0.1632	–0.0232	–0.0346	0.0400	0.0114	0.5587	0.1318	0.0199	0.0031	0.1344	0.0722
uE3	0.0550	0.0662	0.0717	0.0717	0.1632	1	0.1010	0.0422	–0.0374	0.1009	0.1515	0.5803	0.0512	0.0308	–0.0307	0.0821
hCG	–0.0630	–0.0758	–0.0821	–0.0821	–0.0232	0.101	1	0.7178	0.5771	0.2198	0.0675	0.0306	0.7191	0.7236	0.3167	0.3891
β-hCG	–0.0325	–0.0391	–0.0423	–0.0423	–0.0346	0.0422	0.7178	1	0.4958	0.1395	0.0167	–0.0255	0.5606	0.7605	0.2937	0.2700
Inhibin-A	–0.0663	–0.0798	–0.0865	–0.0865	0.0400	–0.0374	0.5771	0.4958	1	0.238	0.0982	–0.0942	0.3956	0.4208	0.7003	0.3858
PAPP-A	–0.0429	–0.0516	–0.0559	–0.0559	0.0114	0.1009	0.2198	0.1395	0.2380	1	0.1160	0.1213	0.0624	0.0627	0.0237	0.6980
Second trimester																
AFP	–0.0079	–0.0095	–0.0103	–0.0103	0.5587	0.1515	0.0675	0.0167	0.0982	0.1160	1	0.1981	0.1535	0.0974	0.2033	0.1979
uE3	0.0495	0.0596	0.0645	0.0645	0.1318	0.5803	0.0306	–0.0255	–0.0942	0.1213	0.1981	1	–0.0416	–0.0585	–0.0875	0.0960
hCG	–0.0549	–0.0661	–0.0716	–0.0716	0.0199	0.0512	0.7191	0.5606	0.3956	0.0624	0.1535	–0.0416	1	0.8651	0.4293	0.2762
β-hCG	–0.0502	–0.0604	–0.0654	–0.0654	0.0031	0.0308	0.7236	0.7605	0.4208	0.0627	0.0974	–0.0585	0.8651	1	0.4092	0.2723
Inhibin-A	–0.0415	–0.0499	–0.0540	–0.0540	0.1344	–0.0307	0.3167	0.2937	0.7003	0.0237	0.2033	–0.0875	0.4293	0.4092	1	0.2554
PAPP-A	–0.0546	–0.0657	–0.0711	–0.0711	0.0722	0.0821	0.3891	0.2700	0.3858	0.6980	0.1979	0.0960	0.2762	0.2723	0.2554	1

TABLE 24 *Estimated correlation matrix for Down's syndrome pregnancies from SURUSS. Palomaki* et al. *(2006)[23] use a coefficient of 0.8146 for the correlation between PAPP-A in the first-trimester and PAPP-A in the second-trimester. This coefficient is used in both unaffected and Down's syndrome pregnancies. All other correlation coefficients in this configuration are as published in the SURUSS report*

	First trimester							**Second trimester**					
Parameter	**NT**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester													
AFP	0.0526	1	0.1626	–0.1808	0.2201	–0.1169	0.2374	0.5003	–0.0099	–0.2186	–0.2262	–0.0554	0.0248
uE3	0.1240	0.1626	1	–0.1200	–0.2588	–0.1942	0.3562	0.1036	0.7356	–0.1703	–0.1999	–0.0969	0.2427
hCG	–0.0819	–0.1808	–0.1200	1	0.5053	0.397	0.1284	0.1075	–0.1741	0.6912	0.5735	0.2493	0.1983
β-hCG	0.1080	–0.2201	–0.2588	0.5053	1	0.283	–0.0692	0.0697	–0.3666	0.4598	0.7797	0.2909	0.0117
Inhibin-A	–0.1292	–0.1169	–0.1942	0.3970	0.2830	1	0.1119	0.0374	–0.2557	0.2629	0.2291	0.6269	0.1944
PAPP-A	–0.1506	0.2374	0.3562	0.1284	–0.0692	0.1119	1	0.0660	0.3712	–0.2295	–0.3004	–0.1842	0.8263
Second trimester													
AFP	0.0809	0.5003	0.1036	0.1075	0.0697	0.0374	0.0660	1	–0.1093	0.1920	0.1981	0.1770	0.0877
uE3	0.0695	–0.0099	0.7356	–0.1741	–0.3666	–0.2557	0.3712	–0.1093	1	–0.3808	–0.4356	–0.3276	0.4914
hCG	0.0466	–0.2186	–0.1703	0.6912	0.4598	0.2629	–0.2295	0.1920	–0.3808	1	0.8178	0.4197	–0.0188
β-hCG	0.1471	–0.2262	–0.1999	0.5735	0.7797	0.2291	–0.3004	0.1981	–0.4356	0.8178	1	0.4384	–0.0756
Inhibin-A	0.1854	–0.0554	–0.0969	0.2493	0.2909	0.6269	–0.1842	0.1770	–0.3276	0.4197	0.4384	1	–0.0025
PAPP-A	0.0062	0.0248	0.2427	0.1983	0.0117	0.1944	0.8263	0.0877	0.4914	–0.0188	–0.0756	–0.0025	1

TABLE 25 *Estimated correlation matrix for unaffected pregnancies from cross-trimester ratios*

	First trimester										Second trimester					
	NT															
Parameter	10 weeks	11 weeks	12 weeks	13 weeks	AFP	uE3	hCG	β-hCG	Inhibin-A	PAPP-A	AFP	uE3	hCG	β-hCG	Inhibin-A	PAPP-A
First trimester																
AFP	0.0140	0.0169	0.0183	–0.0966	1	0.1765	–0.0123	–0.0260	0.0469	0.0022	0.5612	0.1374	0.0259	0.0065	0.1462	0.0708
uE3	0.0536	0.0644	0.0698	0.0433	0.1765	1	0.1045	0.0360	–0.0435	0.0981	0.1440	0.5785	0.0627	0.0377	–0.0170	0.0799
hCG	–0.0676	–0.0814	–0.0882	0.0541	–0.0123	0.1045	1	0.7217	0.5988	0.2067	0.0661	0.0323	0.7700	0.7179	0.3208	0.3851
β-hCG	–0.0391	–0.0470	–0.0509	0.0048	–0.0260	0.0360	0.7217	1	0.5356	0.1315	0.0031	–0.0311	0.5821	0.7997	0.3010	0.2701
Inhibin-A	–0.0628	–0.0755	–0.0817	0.1612	0.0469	–0.0435	0.5988	0.5356	1	0.2396	0.1020	–0.0951	0.4194	0.4436	0.6345	0.4074
PAPP-A	–0.0429	–0.0516	–0.0559	–0.0559	0.0022	0.0981	0.2067	0.1315	0.2396	1	0.1160	0.1213	0.0624	0.0627	0.0237	0.7543
Second trimester																
AFP	–0.0079	–0.0095	–0.0103	–0.0103	0.5612	0.1440	0.0661	0.0031	0.1020	0.1160	1	0.1981	0.1535	0.0974	0.2033	0.2061
uE3	0.0495	0.0596	0.0645	0.0645	0.1374	0.5785	0.0323	–0.0311	–0.0951	0.1213	0.1981	1	–0.0416	–0.0585	–0.0875	0.0934
hCG	–0.0549	–0.0661	–0.0716	–0.0716	0.0259	0.0627	0.7700	0.5821	0.4194	0.0624	0.1535	–0.0416	1	0.8651	0.4293	0.2845
β-hCG	–0.0502	–0.0604	–0.0654	–0.0654	0.0065	0.0377	0.7179	0.7997	0.4436	0.0627	0.0974	–0.0585	0.8651	1	0.4092	0.2763
Inhibin-A	–0.0415	–0.0499	–0.0540	–0.0540	0.1462	–0.0170	0.3208	0.3010	0.6345	0.0237	0.2033	–0.0875	0.4293	0.4092	1	0.2598
PAPP-A	–0.0543	–0.0653	–0.0708	–0.3204	0.0708	0.0799	0.3851	0.2701	0.4074	0.7543	0.2061	0.0934	0.2845	0.2763	0.2598	1

TABLE 26 *Estimated correlation matrix for Down's syndrome pregnancies from cross-trimester ratios*

	First trimester							Second trimester					
Parameter	**NT**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester													
AFP	0.0476	1	0.1840	–0.2474	–0.2720	–0.1382	0.2156	0.5696	–0.0090	–0.1977	–0.2069	–0.0511	0.0384
uE3	0.1249	0.1840	1	–0.0779	–0.2083	–0.1542	0.3591	0.1035	0.5435	–0.1707	–0.2020	–0.0979	0.1847
hCG	–0.0937	–0.2474	–0.0779	1	0.5865	0.4684	0.1491	0.1254	–0.1970	0.8170	0.6539	0.2849	0.2805
β-hCG	0.1146	–0.2720	–0.2083	0.5865	1	0.3144	–0.0744	0.0734	–0.3895	0.4895	0.8087	0.3086	0.0220
Inhibin-A	–0.1438	–0.1382	–0.1542	0.4684	0.3144	1	0.1224	0.0385	–0.2824	0.2922	0.2541	0.7161	0.1702
PAPP-A	–0.1506	0.2156	0.3591	0.1491	–0.0744	0.1224	1	0.0660	0.3712	–0.2295	–0.3004	–0.1842	0.5711
Second trimester													
AFP	0.0809	0.5696	0.1035	0.1254	0.0734	0.0385	0.0660	1	–0.1093	0.1920	0.1981	0.1770	0.0868
uE3	0.0695	–0.0090	0.5435	–0.1970	–0.3895	–0.2824	0.3712	–0.1093	1	–0.3808	–0.4356	–0.3276	0.4862
hCG	0.0466	–0.1977	–0.1707	0.8170	0.4895	0.2922	–0.2295	0.1920	–0.3808	1	0.8178	0.4197	–0.0186
β-hCG	0.1471	–0.2069	–0.2020	0.6539	0.8087	0.2541	–0.3004	0.1981	–0.4356	0.8178	1	0.4384	–0.0747
Inhibin-A	0.1854	–0.0511	–0.0979	0.2849	0.3086	0.7161	–0.1842	0.1770	–0.3276	0.4197	0.4384	1	–0.0024
PAPP-A	0.0061	0.0384	0.1847	0.2805	0.0220	0.1702	0.5711	0.0868	0.4862	–0.0186	–0.0747	–0.0024	1

TABLE 27 *Estimated common correlation matrix for unaffected and Down's syndrome pregnancies from the North York training data*

	First trimester						Second trimester					
Parameter	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester												
AFP												
uE3		1.0000	0.1870			0.1368	0.1338	0.4602	0.0418			0.1291
hCG		0.1870	1.0000			0.2634	0.0819	–0.0481	0.7242			0.3868
β-hCG												
Inhibin-A												
PAPP-A		0.1368	0.2634			1.0000	0.0733	0.1460	0.1204			0.7112
Second trimester												
AFP		0.1338	0.0819			0.0733	1.0000	0.1151	0.1866			0.1171
uE3		0.4602	–0.0481			0.1460	0.1151	1.0000	–0.0663			0.0786
hCG		0.0418	0.7242			0.1204	0.1866	–0.0663	1.0000			0.2597
β-hCG												
Inhibin-A												
PAPP-A		0.1291	0.3868			0.7112	0.1171	0.0786	0.2597			1.0000

Appendix 4

Summary statistics for sample data

TABLE 28 *Distribution of ethnic origin in FaSTER and North York samples. Figures in brackets are percentages*

FaSTER	***Caucasian***	***Asian***	***Oriental***	***American Indian***	***Hispanic***	***Black***	***Other***
Cases	49 (63)	3 (4)	0 (0)	0 (0)	17 (22)	4 (5)	5 (6)
Controls	263 (67)	14 (4)	2 (1)	1 (0)	65 (17)	20 (5)	25 (6)
North York	***Caucasian***	***Asian***	***Other***	***Unknown***			
Cases	19 (44)	19 (44)	3 (7)	2 (5)			
Controls	95 (44)	95 (44)	15 (7)	10 (5)			
North York routine	***Caucasian***	***Asian***	***Other***	***Unknown***	***Aboriginal***	***Black***	
NY1	570 (54)	340 (32)	46 (4)	17 (2)	3 (0)	74 (7)	
NY2	485 (58)	258 (31)	20 (2)	19 (2)	0 (0)	56 (7)	

TABLE 29 *Distribution of maternal ages (years) in FaSTER and North York data sets*

	n	**Minimum**	**Maximum**	**Mean**	**Standard deviation**
FaSTER					
Cases	78	19	46.7	37.3	5.1
Controls	390	16.9	45.2	32.5	5.53
North York					
Cases	43	23.05	46.06	36.4	4.9
Controls	215	18.51	49.11	31.8	4.9
North York routine					
NY1	1050	16	45	31.2	4.8
NY2	838	16	45	31.3	4.5

TABLE 30 *Distribution of maternal weights (lb) in FaSTER and North York data sets*

	n	**Minimum**	**Maximum**	**Mean**	**Standard deviation**
FaSTER					
Cases	78	98	259	147	30.7
Controls	390	95	308	143	27.5
North York					
Cases	37[a]	104	208	144	25.4
Controls	215	100	235	141	22.4
North York routine					
NY1	1050	89	321	147	34.1
NY2	838	92	395	145	34.5

a Six cases with missing maternal weights.

Appendix 5

Likelihood ratio test statistics

As a numerical measure of lack of fit between the published parameters and the data, we consider a generalised likelihood ratio test of the null hypothesis:

$$H_0: \delta = 0 \text{ and } \Sigma = \Sigma_0$$

where δ denotes the difference between the mean log multiple of the median (MoM) from the data and the published mean. In general, the mean log MoM is zero in unaffected pregnancies and is dependent on gestational age in pregnancies affected by Down's syndrome. Σ denotes the covariance matrix of the vector x of log MoM values, and Σ_0 denotes the covariance matrix obtained from the published standard deviations and correlations.

The aim is to quantify departures from the model in terms of the way the covariance differs from Σ_0 and δ may differ from zero. We assume departures from zero according to a simple linear regression model on gestational age.

The generalised likelihood ratio test statistic, based on the likelihood l_0 under the published model and the likelihood l_1 under the model fitted to the log MoM values $x_1, x_2, \ldots x_n$ is given by:

$$-2\log\left(\frac{l_0}{l_1}\right) = n\ln(|\Sigma_0|) + \sum_i x_i \Sigma_0^{-1} x_i^T - n\ln(|S|) - \sum_i (x_i - \hat{\delta}_i) S^{-1} (x_i - \hat{\delta}_i)^T$$

where $\hat{\delta}_i$ is the estimated value of δ from a linear regression on gestational age and S is the sample covariance matrix. A total of $2p$ parameters are involved in the regression model and $p(p + 1)/2$ are involved in the covariance matrix.

Under H_0, this likelihood ratio test statistic is approximately χ^2 distributed with $p(p + 5)/2$ degrees of freedom. This can be partitioned into two additive components:

$$\sum_i \hat{\delta}_i \Sigma_0^{-1} \hat{\delta}_i^T$$

and

$$n\ln(|\Sigma_0|) + \sum_i (x_i - \hat{\delta}_i)\Sigma_0^{-1}(x_i - \hat{\delta}_i)^T$$
$$-n\ln(|S_0|) - \sum_i (x_i - \hat{\delta}_i) S^{-1} (x_i - \hat{\delta}_i)^T$$

The first component represents the deviation of δ_i from 0, while the second measures the deviation of Σ from Σ_0. Under H_0, these components are approximately independently χ^2 distributed with $2p$ and $p(p + 1)/2$ degrees of freedom respectively. We use these test statistics not for formal hypothesis tests but as measures of the lack of fit between the published parameters and the data. If the published parameters explain the data well, then the statistics above should be close to the respective degrees of freedom. Large values of these tests statistics are indicative of lack of fit.

Appendix 6

Models fitted to FaSTER and North York test data

TABLE 31 *Fitted regression models for mean log MoM values in Down's syndrome pregnancies*

	FaSTER		North York		Combined	
Marker	α	β	α	β	α	β
First trimester						
AFP						
uE3	–0.08836	–0.002313	–0.066	–0.008899	–0.07718	–0.005606
hCG	0.1463	0.01065	0.2441	0.01556	0.1952	0.013105
β-hCG						
Inhibin-A						
PAPP-A	–0.3144	0.01016	–0.3431	0.01927	–0.32875	0.014715
Second trimester						
AFP	–0.1337	0	–0.09654	0	–0.11512	0
uE3	–0.1845	0	–0.1325	0	–0.1585	0
hCG	0.2980	0	0.4011	0	0.34955	0
β-hCG		0		0		0
Inhibin-A		0		0		0
PAPP-A	–0.08962	0	–0.008819	0	–0.04922	0

Fitted model: mean log MoM = α + β(GA – 87). GA denotes gestational age in days.

TABLE 32 *Standard deviations of log MoM values – the standard deviations are assumed to be the same in Down's syndrome and unaffected pregnancies*

Marker	FaSTER	North York	Combined
First trimester			
AFP			
uE3	0.1347	0.1212	0.1306
hCG	0.1804	0.1861	0.1835
β-hCG			
Inhibin-A			
PAPP-A	0.2399	0.2518	0.2436
Second trimester			
AFP	0.1397	0.1342	0.1381
uE3	0.1350	0.1125	0.1286
hCG	0.2203	0.2172	0.2201
β-hCG			
Inhibin-A			
PAPP-A	0.2141	0.2257	0.2181

TABLE 33 *Estimated correlation matrix for FaSTER data – the correlation matrices are assumed to be the same in Down's syndrome and unaffected pregnancies*

	First trimester							Second trimester					
Parameter	**NT**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester													
AFP													
uE3			1.0000	0.1720			0.0387	0.1069	0.5988	0.0784			0.1300
hCG			0.1720	1.0000			0.2482	0.0249	–0.0223	0.7677			0.3322
β-hCG													
Inhibin-A													
PAPP-A			0.0387	0.2482			1.0000	0.1066	0.0333	0.0897			0.7783
Second trimester													
AFP			0.1069	0.0249			0.1066	1.0000	0.0963	0.1270			0.1074
uE3			0.5988	–0.0223			0.0333	0.0963	1.0000	–0.0848			0.1226
hCG			0.0784	0.7677			0.0897	0.1270	–0.0848	1.0000			0.2393
β-hCG													
Inhibin-A													
PAPP-A			0.1300	0.3322			0.7783	0.1074	0.1226	0.2393			1.0000

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Table 34 *Estimated correlation matrix for North York data – the correlation matrices are assumed to be the same in Down's syndrome and unaffected pregnancies*

	First trimester							Second trimester					
Parameter	**NT**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester													
AFP													
uE3			1.0000	0.1709			0.1982	0.0142	0.6279	0.0793			0.1749
hCG			0.1709	1.0000			0.2757	–0.0753	–0.0230	0.7823			0.3768
β-hCG													
Inhibin-A													
PAPP-A			0.1982	0.2757			1.0000	0.1398	0.0997	0.1601			0.8553
Second trimester													
AFP			0.0142	–0.0753			0.1398	1.0000	0.0430	0.0332			0.1873
uE3			0.6279	–0.0230			0.0997	0.0430	1.0000	–0.0576			0.0808
hCG			0.0793	0.7823			0.1601	0.0332	–0.0576	1.0000			0.3248
β-hCG													
Inhibin-A													
PAPP-A			0.1749	0.3768			0.8553	0.1873	0.0808	0.3248			1.0000

TABLE 35 *Estimated correlation matrix for combined data – the correlation matrices are assumed to be the same in Down's syndrome and unaffected pregnancies*

	First trimester							Second trimester					
Parameter	**NT**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**	**AFP**	**uE3**	**hCG**	**β-hCG**	**Inhibin-A**	**PAPP-A**
First trimester													
AFP													
uE3			1.0000	0.1726			0.0833	0.0874	0.5997	0.0840			0.1440
hCG			0.1726	1.0000			0.2471	–0.0039	–0.0191	0.7763			0.3485
β-hCG													
Inhibin-A													
PAPP-A			0.0833	0.2471			1.0000	0.1117	0.0524	0.1084			0.8001
Second trimester													
AFP			0.0874	–0.0039			0.1117	1.0000	0.0855	0.1041			0.1347
uE3			0.5997	–0.0191			0.0524	0.0855	1.0000	–0.0698			0.1125
hCG			0.0840	0.7763			0.1084	0.1041	–0.0698	1.0000			0.2719
β-hCG													
Inhibin-A													
PAPP-A			0.1440	0.3485			0.8001	0.1347	0.1125	0.2719			1.0000

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