

Use of Maternal Age or First Trimester Screening risk results in the estimation of trisomy risk in an NIPT

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the IONA[®] test

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INTRODUCTION

The IONA[®] Test is a CE marked non-invasive prenatal screening test (NIPT) using proprietary reagents and fully validated IONA[®] Software to generate results. This screening test reports the probability of a fetus being affected with trisomy 13, 18 or 21 as either high or low risk based on the Test Risk Score. The probability risk score for the fetus being affected is assessed using an algorithm which incorporates a likelihood ratio calculated from the cell free DNA present in a maternal plasma sample combined with an *a priori* background risk. The *a priori* risk used is the maternal age-related background risk currently used in the United Kingdom National Health Service (UK NHS) (Wright *et al.*, 2015).

Several national screening committees have recommended offering NIPT as a contingent model where all women are first screened with the First Trimester Combined Test (FTCT) and high-risk women go on to receive NIPT. Based on this we wanted to see if it would be possible to use the resultant trisomy risks reported from FTCT as an alternative to the maternal age-related background prior to calculate the trisomy risk with the IONA[®] test.

OBJECTIVES

The primary objective of this study was to demonstrate the concordance, or lack thereof, of the IONA[®] test result calculated using the FTCT risk scores as an alternative background prior risk compared to using the current maternal age-related (MA) background prior based on the UK NHS standard cut-off for high and low risk of $\geq 1:150$ (*i.e.* a risk lower than 1:150 representing a low risk of the fetus being affected by a trisomy).

A secondary analysis was performed which repeated the analyses at other cut-off levels (*i.e.* $\geq 1:100$, $\geq 1:200$, $\geq 1:250$, $\geq 1:300$) to reflect cut-offs used in other countries.

INCLUSION CRITERIA

- All patient samples analysed in either the Premaitha Health Service Laboratory (PMH)(Sept 2015 to Sept 2016) or the SAFE Test laboratory at St. George's University Hospitals NHS Foundation Trust (SAFE) (Dec 2015 to June 2016) were considered for inclusion – during this period both laboratories were using the same version of the IONA[®] Software.
- All sample datasets had a valid IONA[®] test result and a FTCT risk score supplied for the same trisomy supplied on the Test Request and Consent form.
- All data was from patients who had given their written informed consent to allow their data to be used for future research.

For samples from twin pregnancies, each dataset was used either as one sample, where only one FTCT risk result was provided for a particular trisomy or as two sample datasets where two different FTCT results were given for the same trisomy (*i.e.* one for each fetus). Where two FTCT results were given they would have been calculated using different Nuchal Translucency measurements from the Ultrasound scan performed at the time the blood sample was taken for the FTCT, and hence two results calculated and reported.

METHOD

The analysis was performed as a blinded study. The FTCT risk results were collated for all appropriate samples and matched to the appropriate IONA[®] raw sample dataset. A Microsoft Excel spreadsheet equation was used to calculate the new test results, using the originally calculated likelihood ratios, while substituting the maternal age-related *a priori* risk with FTCT trisomy risk result as the background risk. Only then were the original IONA[®] test results un-blinded to allow comparison with those calculated using the FTCT risks to allow assessment of concordance for low and high risk.

SUMMARY OF SAMPLES ELIGIBLE FOR INCLUSION

Trisomy screened	PMH laboratory Number samples (twin samples)	SAFE laboratory Number samples (twin samples)	TOTAL NUMBER OF SAMPLES
13 (Patau's)	269 (113)	270 (7)	539 (120)
18 (Edwards')	258 (93)	261 (3)	519 (96)
21 (Down's)	507 (175)	395 (7)	902 (182)
Total	1034 (381)	929 (17)	1963 (398)

RESULTS

The primary analysis demonstrated 100% concordance for IONA[®] Risk Scores calculated using either MA or FTCT risk as the *a priori* background risk at a high and low risk cut-off of $\geq 1:150$ for trisomies 13, 18 and 21; likewise, at high and low risk cut-offs of $\geq 1:100$, $\geq 1:200$ and $\geq 1:250$.

At a cut-off of $\geq 1:300$, with risk scores less than 1 in 300 representing a low risk there was one discordant result for Trisomy 21. The sample was from a 40 year old women, whose MA risk was 1 in 89, compared to 1 in 3 from the FTCT. The Likelihood Ratio was 1:131. Thus, once combined with the background risks the resultant risk score was 1 in 11537 (*i.e.* low risk) using the MA and 1 in 264 using the FTCT (*i.e.* high risk) using a $\geq 1:300$ high/low cut-off risk. This result would have been a false positive since the women was followed up and gave birth to an unaffected neonate.

All of the data analysis conducted on samples from twin pregnancies gave correct and concordant results at all cut-offs analysed in both the primary and secondary analyses.

DISCUSSION

Using a continuous series of eligible sample datasets (*i.e.* a valid run on the IONA[®] test system using maternal age-related *a priori* risk to calculate the final IONA[®] Risk Score, and, a FTCT risk result being available for the trisomy being tested for, both types of *a priori* background risk were shown to be acceptable, producing concordant results up from $\geq 1:100$ to $\geq 1:250$ high and low risk cut-off.

CONCLUSION

Using the risk-score from the FTCT for trisomy 13, 18 and 21 is a suitable alternative to the maternal age-related background risk. Our study has demonstrated that the IONA[®] test can use FTCT results modified by the generated likelihood ratio, further tailoring the test results for the individual, and, allowing for contingent prenatal aneuploidy screening.

REFERENCE

Wright D, Wright A, Kypros H Nicolaidis. A unified approach to risk assessment for fetal aneuploidies. *Ultrasound Obstet Gynecol* (Impact Factor: 3.14). 01/2015; 45(1). DOI: 10.1002/uog.14694

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FURTHER INFORMATION

For further information on the IONA[®] test please visit www.premaitha.com or email iona@premaitha.com