THE SAFE TEST:
Performance of non-invasive prenatal screening (NIPS) for high-risk pregnancies in the Southwest Thames Region

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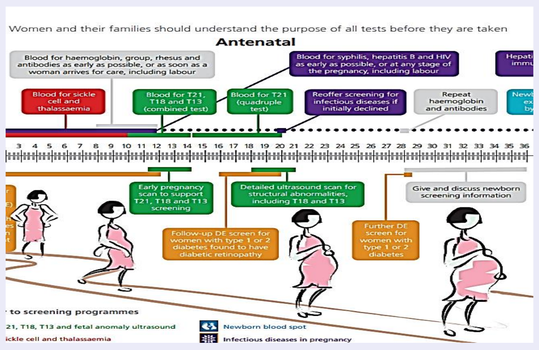
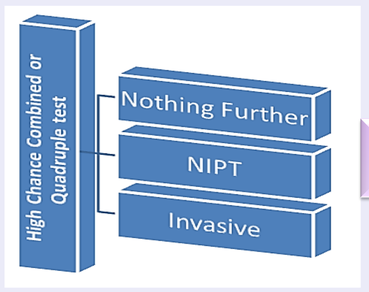
Introduction

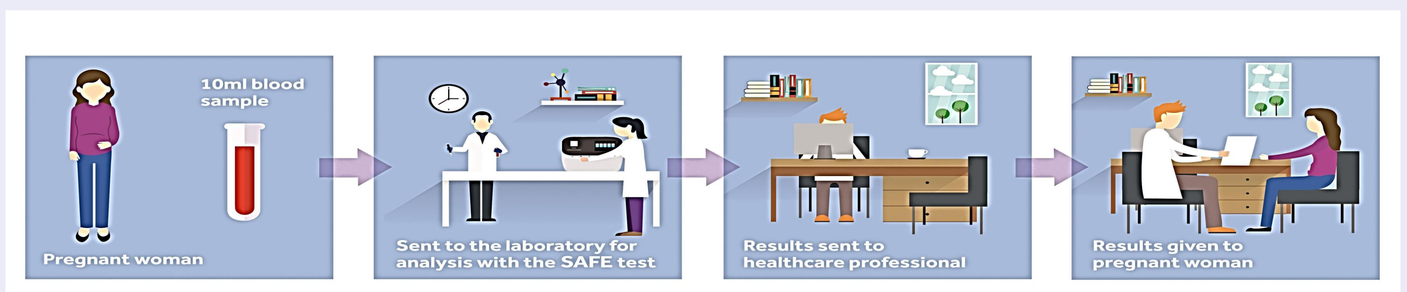


Women in the UK are currently offered screening for aneuploidies as part of the NHS screening pathway. Following on from the National Screening Committee's (NSC) recommendations, later this year (October 2018), Public Health England (PHE) will commence an evaluative roll out of non-invasive prenatal testing (NIPT) for trisomy 13, 18 and 21.

NHS England/PHE plan to introduce NIPT as an additional option to invasive testing or expectant management for women who receive a high chance result (>1:150) from the combined or quadruple test. This pathway has been in place at St George's Hospital since November 2015. Outcomes have been continuously monitored to ensure a high and maintained sensitivity for the test**.**

Clinical Process



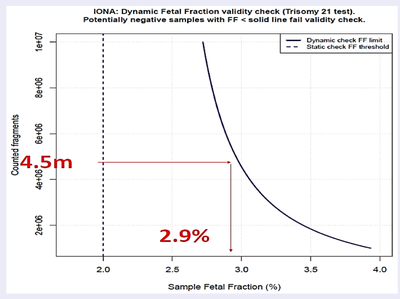


cfDNA samples were processed in a dedicated NHS laboratory using Next Generation Sequencing (NGS) technologies to sequence maternal and feto-placental cfDNA. A risk algorithm that integrates fetal fraction, modifiable a-priori risk, and data from DNA sequencing produces an individualised result for each patient.

Improving Performance

NIPT/NIPS is affected by the amount of fetal fraction in the maternal circulation. When the fetal fraction is above 8%, there is a clear separation between affected and unaffected pregnancies. Below this level of fetal fraction there are two ways in which detection rates can be improved:

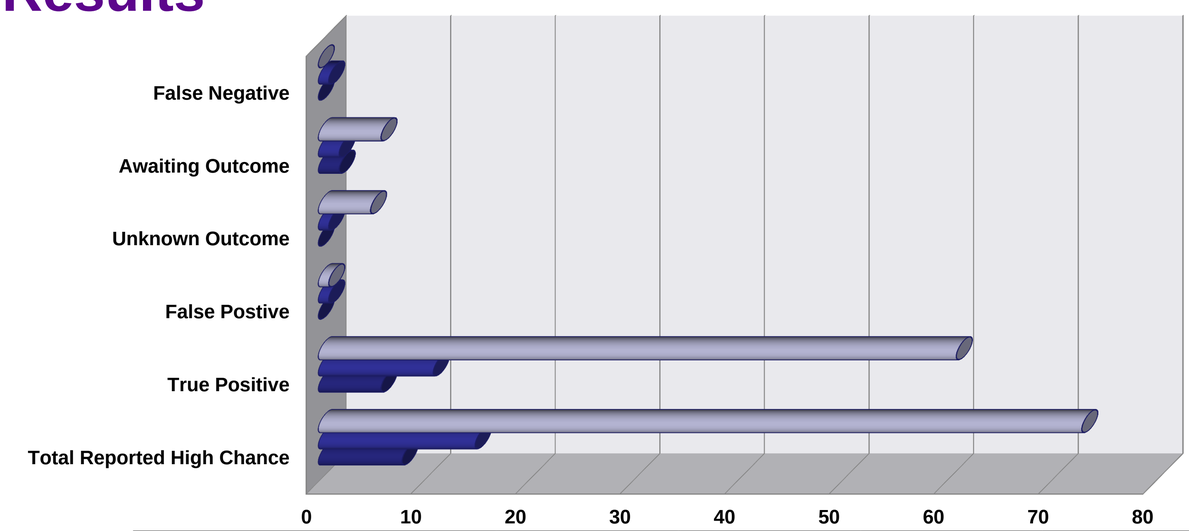
1. Dynamic Fetal Fraction (FF): incorporation of fetal fraction and sequencing data into the calculating algorithm when the fetal fraction is between 2-4%. This helps reduce false negatives in samples with low levels of fetal fraction.
2. A-priori risk: using a patient specific risk can make a result with a fetal fraction between 2-8% more comprehensive. Currently all NIPT tests use maternal age as the background risk, incorporating the combined or quadruple test results instead of maternal age, can improve the accuracy for the patient.



Objective

To evaluate the accuracy of routine NHS clinical provision of the SAFE test in women with high chance combined or maternal serum biochemistry test results.

Results



	Total Reported High Chance	True Positive	False Postive	Unknown Outcome	Awaiting Outcome	False Negative
Trisomy 21	73	61	1	5	6	0
Trisomy 18	15	11	1	1	2	1
Trisomy 13	8	6	0	0	2	0

Prenatal diagnosis and pregnancy outcome data were routinely collected for all singleton pregnancies.

- **3644 cfDNA samples were analysed up to August 2017. This included samples from private and NHS clinics.**
- **96 (2.6%) pregnancies were reported as high chance.**
- **The positive predictive values (PPV*) for T21, T18 and T13 were 98.3% (61/62), 91.6% (11/12) and 100% (6/6), respectively.**
- **Both false positive results were confirmed as confined placental mosaicism.**
- **The outcome of 10 high chance pregnancies are still pending as the parents opted to continue without invasive testing.**
- **Six pregnancies are reported lost to follow-up.**

***PPV is defined as the proportion of high chance pregnancies, that in fact are affected.**

Conclusion

This data demonstrates that NIPS can be used in a routine NHS pathway, as a safe and effective alternative to invasive prenatal diagnosis in high chance women. Integrating fetal fraction and modifiable a-priori risk into the risk algorithm, may have helped improve test performance and provide women with accurate patient-specific results.

References:
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The SAFE test is powered by the IONA® test from Premaitha Health

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