Non-Invasive Prenatal Tests: Impact in a group of Portuguese pregnant population

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Background

Up until recently, the state of the art in prenatal screening was the 1st Trimester Combined Pre-Natal Test, a detection rate of 90-95% for a false-positive and false-negative rates of 5% and 5-10%, respectively. The invasive tests that may follow a positive screening test are accurate but can be expensive, and impose risks to both pregnant women and their fetuses. In the more recent years, a variety of cell-free DNA (cfDNA) methods were developed to test for fetal aneuploidies in maternal blood. In Portugal this new era in prenatal assessment risk began in 2013, and Centro de Medicina Laboratorial Germano de Sousa (CML-GS) introduced the Harmony Prenatal Test. This test uses directed DNA analysis. Compared to random sequencing, directed cfDNA analysis is simpler, less costly, and more precise. It also provides individualized prenatal test results for trisomy risk.

The authors want to evaluate the impact of this test in the risk assessment practice, compare the results obtained with the data published and analyze the foetal fraction in pregnancies with adverse outcome.

Methods

NIPT Screening analysis was carried out from January 2013 to March 2017. 7842 women were screened for trisomy 21, 18 and 13 by cffDNA testing from 10 weeks of gestation. Without any further processing, maternal blood samples were sent via courier to the USA for analysis using a direct DNA analysis (*Harmony Prenatal Test®*). Risk scores for trisomy 21, 18 and 13 were provided in the test report and were presented to each patient, with a expected turnaround time of 10-15 days. The risk scores were represented as a percentage, with ranges capped at >99% and <0.01%. The *Harmony Prenatal Test®* analyses the relative number of chromosomes in maternal blood to provide an objective individualized and dependable result with high sensitivity and specificity.

Results

Figure 1. Maternal Age (years) distribution in NIPT Population

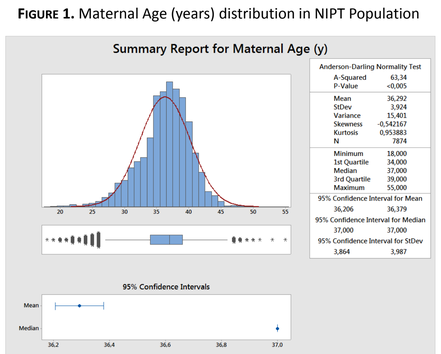


Figure 2. Gestational age (weeks) distribution in NIPT Population

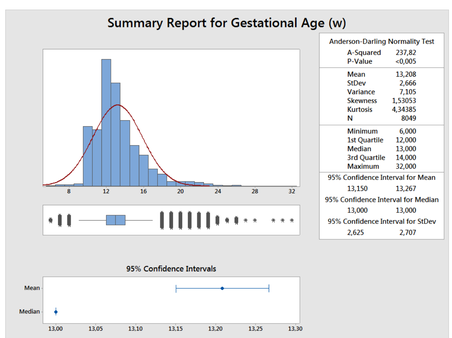


Figure 3. Fetal fraction distribution in NIPT Population

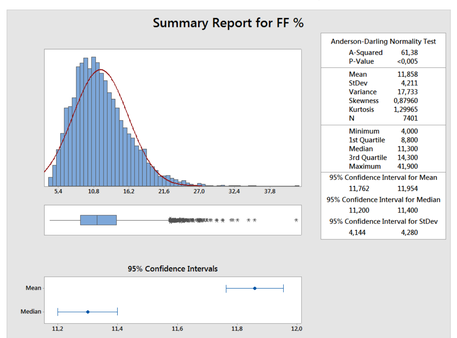


Figure 2. Characterization of Reason to perform NIPT – *Harmony Prenatal Test®*

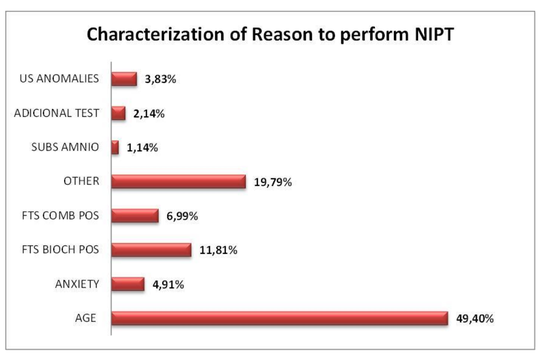


Figure 5. NIPT Redraw Rate and Redraw motive

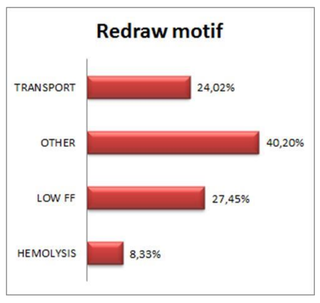


Figure 3. Foetal fraction mean by outcome and test result

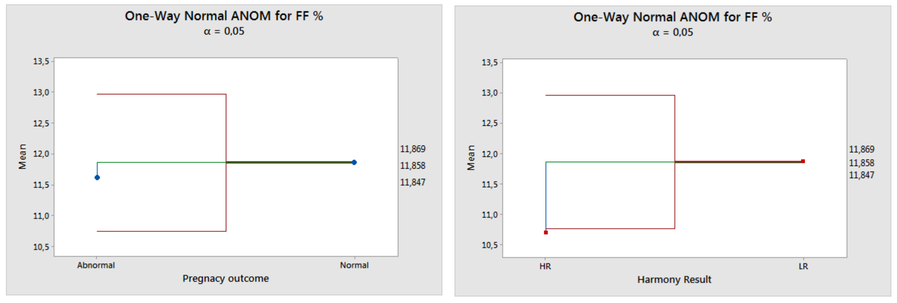
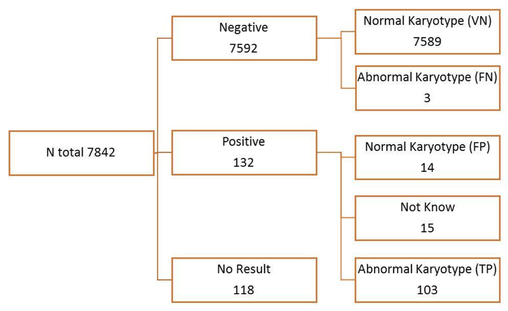


Figure 6. Performence details of NIPT – *Harmony Preenatal Test®* with XY analysis



	TAXA de DETECÇÃO (TD)	TAXA de FALSOS POSITIVOS (TFP)
Harmony Prenatal Test (T21, T18, T13, XY) DESEMPENHO	97,17%	0,18%
Harmony Prenatal Test (Tri 21, 18, 13) DESEMPENHO	97,06%	0,05%
TRISOMIA 21 DESEMPENHO	97,62%	0,02%
TRISOMIA 18 DESEMPENHO	90,00%	0,01%

Discussion

The NIPT impact in risk assessment management can be inferred from the results expressed above: since January 2013, CML GS has performed 7842 tests in a population with a mean maternal age of 36.3 years-old and 13.2 weeks as mean gestational age.

The main indication to perform this test was the maternal age (49.40%) and high risk first trimester combined screening (18.80%).

The estimated risks for fetal trisomies 21, 18 and 13 for a woman aged 20 years at 12 weeks of gestation are about 1 in 1000 (0.1%), 1 in 2500 (0.04%) and 1 in 8000 (0.01%), respectively. The respective risks for these aneuploidies for a woman aged 35 years at 12 weeks of gestation are about 1 in 250 (0.4%), 1 in 600 (0.17%) and 1 in 1800 (0.06%) [*Nicolaides, 2011*]. Among the 7842 participants (7724 with NIPT result), we found 84 cases (1.09%) with a high risk for trisomy 21 [DR: 97.62%, FPR: 0.02%], 22 cases (0.28%) showing a high risk for trisomy 18 [DR: 90.00%, FPR: 0.01%], 8 cases (0.10%) with a high risk for trisomy 13 [FPR: 0.03%], and 18 cases (0.23%) showing a high risk for sexual chromosomes aneuploidies [FPR: 0.12%], resulting in a 0.18% overall false positive rate (with XY analysis included). In the remaining participants, the results showed a low risk (<0.01%) for trisomies 21, 18 and 13.

In our centre, the redraw rate was 2.58%, mostly related with low foetal fraction of cfDNA (27.45% of all repetition). Factors leading to low foetal fraction of cfDNA were maternal weight, gestational age, or suboptimal blood collection and shipping. The mean foetal fraction was 11.86%, with no statistical significance difference detected between the two groups (normal and abnormal outcome). However the foetal fraction was lower in the high risk population (10.70%, p-value < 0.05).

The expected turnaround time was 10 to 15 days, with an average response time of 10.33 days (minimum 6 days and maximum of 21 days).

[Nicolaides, 2011. Screening for fetal aneuploidies at 11 to 13 weeks, *Prenat Diagn* 2011; 31: 7–15]

Conclusion

Until recently, the best available method of screening for trisomies 21, 18 and 13 has been the first-trimester combined test. The *Harmony Prenatal test®*, with a higher overall DR (97.17%) and a lower FPR (0.18%), and specifically for trissomies 21, a DR of 97.62% and FPR of 0.02%, may contribute to fill in the gap of the current available methods (maternal age, NT and biochemical markers). The low foetal fraction is correlated with high risks results, however not correlated with adverse outcomes. The reliability of the results, turnaround time and clear reports have contributed to acceptance of new algorithms in the Pre-Natal Diagnostic.