# ACGS audit of invasive prenatal samples received by NHS Regional Genetics Laboratories for confirmation of NIPT findings over a 5 year period

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## ABSTRACT

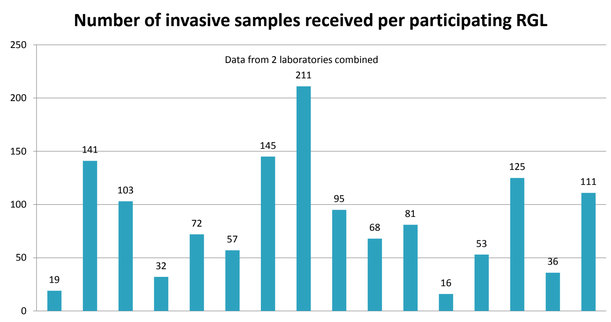
UK NHS Regional Genetics Laboratories were invited to share data on invasive prenatal samples sent for confirmation of non-invasive prenatal testing (NIPT) findings. Seventeen Laboratories submitted data representing 1365 NIPT results over a 5 year period with sample numbers increasing steadily across that time. The majority of samples received (92%) were for confirmation of high chance trisomy 13, 18 or 21. 66% of invasive samples received were amniotic fluid samples (AF) with the remaining 34% CVS.

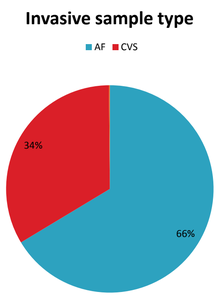
The results of invasive testing did not confirm the NIPT finding in 9% of cases; 2.5% for trisomy 21(25/1020), 11% for trisomy 18(19/171) and 41% for trisomy 13(32/78). Only 52% (37/71) of invasive samples received due to an increased chance of sex chromosome aneuploidy confirmed the result, the remainder being false positives. 92%(12/13) of samples referred following NIPT results indicating less common genomic imbalances; microdeletion syndromes, rare autosomal aneuploidies or triploidy went on to have normal invasive sampling results.

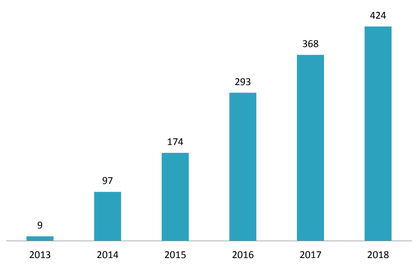
Data shows that, on the whole, invasive sampling is being performed appropriately. NIPT has a high positive predictive value (PPV) for trisomy 21 and trisomy 18, but a lower PPV for trisomy 13 in the combined population. A low PPV is also observed for sex chromosome aneuploidies and other genomic imbalance. PPVs increase in the presence of other clinical indications.

## PATIENT SAMPLES

- Data was received from 17 Regional Genetics Laboratories (RGL) representing 1365 invasive prenatal samples (906 AF and 457 CVS) taken following NIPT results indicating a high chance of genomic imbalance.
- There were just 9 invasive samples received nationally following NIPT studies in 2013, however that number rose to 424 in 2018.
- 66% of invasive samples taken across that time were amniotic fluid samples.

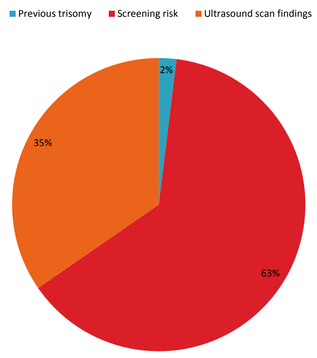


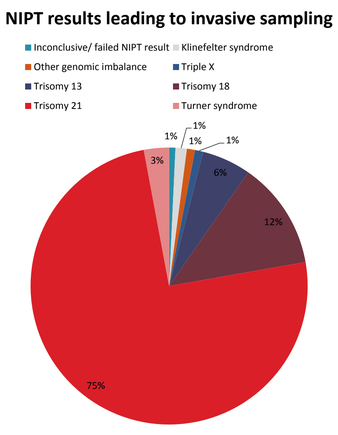




Clinical indication was stipulated for 514 samples; 63% had high biochemical screen risk results and 35% ultrasound scan findings.

No clinical reason for NIPT was given for 851 samples; many of these will be maternal request samples, with patients requesting NIPT as a first line screen (others will represent missing information at time of referral).

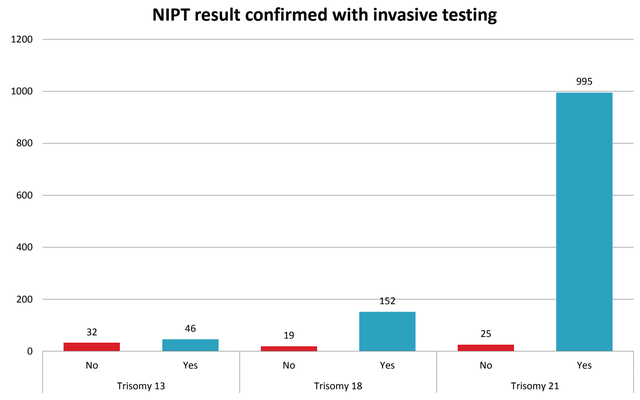


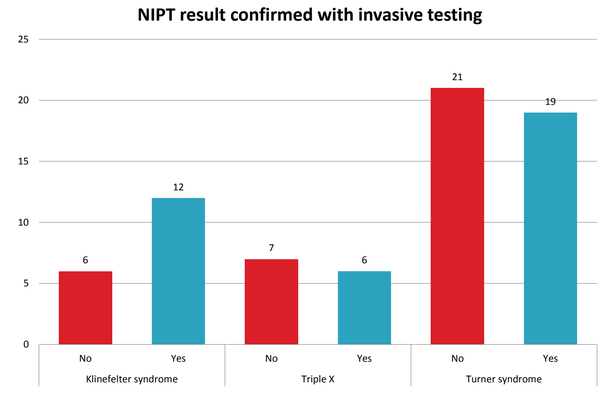



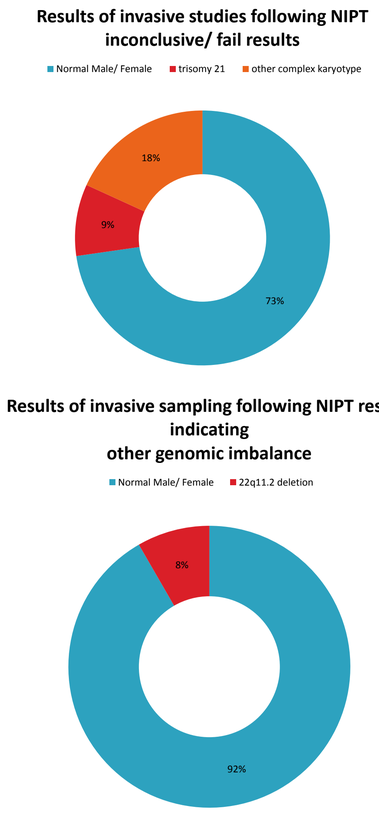

1269 invasive samples (93%) were taken following NIPT results showing a high chance of trisomy 13, 18 or 21.

## RESULTS

- 1020 invasive samples were taken following NIPT results showing a high chance of trisomy 21; this was confirmed in 995 of pregnancies by invasive sampling and just 2.5% of samples yielded normal results. 11% of invasive samples taken due to NIPT results indicating trisomy 18 yielded normal results and this figure rose to 41% for NIPT results indicating trisomy 13.
- 48% of invasive samples taken following NIPT results for a high chance of sex chromosome aneuploidy yielded euploid results .



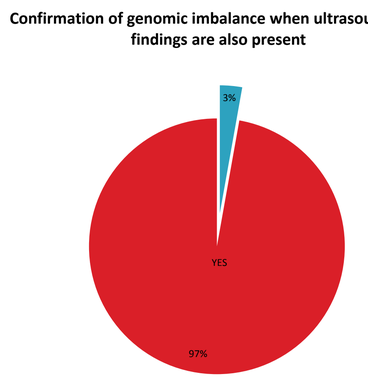



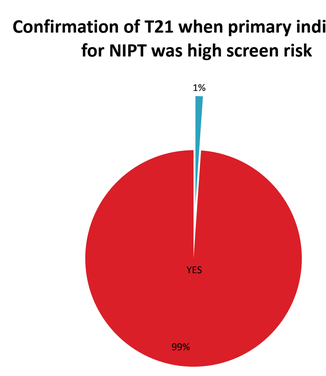




- 11 invasive samples were taken due to failed or inconclusive NIPT results
  - 8 of these samples yielded normal results.
  - 1 pregnancy was diagnosed with **trisomy 21** following invasive sampling, this sample failed NIPT due to a low fetal fraction caused by high maternal BMI.
  - 2 pregnancies showed other **complex karyotypes** following invasive sampling, NIPT had given inconclusive results.
- 12 invasive samples were taken following NIPT results which specified other genomic imbalance
  - 7 **amniotic fluid** samples were taken following NIPT results indicating less common aneuploidies
    - All of these samples yielded normal results
  - 2 samples were taken following NIPT results indicating triploidy
    - Both of these samples yielded normal results
  - 3 samples were taken due to NIPT results indicating microdeletion syndromes
    - A **22q11.2 deletion** was confirmed in one of these patient samples
- 1 amniotic fluid sample was taken due to sexing information from NIPT being discordant with scan findings and results of cytogenetic analysis showed an **X;Y translocation** which explained the finding.

178 patients had NIPT due to abnormal scan findings, genomic imbalance was confirmed following invasive sampling in 174 (97%).

- 3 patients with NIPT results indicating trisomy 21 were shown to have normal genomic results; in one of these trisomy 21 was detected in a sample taken from a twin, the remaining 2 samples had scan findings consistent with fetal hydrops.
- 1 patient with an isolated cardiac anomaly and NIPT result indicating trisomy 13 was shown to have a normal result.




271 patients with high chance trisomy 21 results from NIPT had requested NIPT following high screen risk results , trisomy 21 was confirmed in 99%. In 1 patient trisomy 21 was present in a twin, in another patient trisomy 18 was also detected by NIPT and this was present following invasive sampling.

## CONCLUSIONS

NIPT performs particularly well for trisomy 21 and trisomy 18. False positive rates in our combined data set of 2.5% and 11% for trisomies 21 and 18 respectively are lower than predicted in the Warwick Report for both general and high risk populations. Of particular note, the false positive rate of 2.5% observed here for trisomy 21 is apparently superior to the predicted 9-18% (Taylor-Phillips et al, 2016. BJM Open).

The majority of patients (92% in this dataset) having invasive sampling following a high chance NIPT results nationally are doing so following high chance NIPT results for trisomy 13, 18 or 21.

The PPVs of high chance NIPT sex chromosome aneuploidy results and other rare genomic imbalances are low.

A false positive rate close to 50% is observed for sex chromosome aneuploidies; given the mild phenotype of Triple X and Klinefelter syndromes and the high miscarriage rate and abnormal scan finding incidence observed in Turner syndrome, NIPT for these syndromes in the general population is not currently indicated.