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Non-Invasive Prenatal Testing (NIPT) – Utility Beyond Aneuploidies

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NIPT for significant dominant single gene disorders (Mohan et al., 2022)

This is the largest cohort study in clinical practice, which aimed to assess the performance of NIPT in 2208 women with singleton pregnancies, using a next generation sequencing (NGS) – based panel of 30 genes causing 25 clinically significant dominant single-gene disorders (SGDs). Sampling was done around 9 weeks of gestation. Only pathogenic and likely pathogenic variants based on the American College of Medical Genetics and Genomics (ACMG) guidelines were reported. A total of 125/2208 women (5.7%) screened positive. Of these, 104 pathogenic, 21 likely pathogenic and 15/125 novel variants were observed. No false positive results were found. The authors concluded that NIPT could assist in the early detection of a set of SGDs, particularly when either abnormal ultrasound findings or a family history was present. Despite its high degree of certainty, the authors did not regard NIPT-SGD as diagnostic and advocated confirmatory testing.

Cell–based NIPT following PGT–M (Toft et al., 2021)

This study assessed the use of cell-based non-invasive prenatal testing (cbNIPT) as an alternative to chorionic villus sampling (CVS) following preimplantation genetic testing for monogenic disorders (PGT-M). Eight patients were referred for PGT-M. Patients who opted for follow-up of PGT-M by CVS, had maternal blood sampled on the day of the CVS procedure, at 10-13 weeks of gestation. From this blood, potential fetal extra villus trophoblast cells were isolated and genetically tested by short tandem repeats (STR) marker analysis and direct mutation detection. Of the 24 fetal cell samples tested, 20 cell samples had an unaffected test result while four cells had a conditionally unaffected test result. All fetal cell samples had a genetic profile identical to that of the transferred embryo confirming a pregnancy with an unaffected fetus and verifying the PGT-M results. The cbNIPT results correlated with the CVS analysis in all cases. These findings showed that cbNIPT could be a promising alternative to CVS.

Genome wide NIPS for balanced translocation carriers (Flowers et al., 2020)

This study done in Australia aimed to determine if genome-wide cell-free DNA based non-invasive prenatal screening (gw-NIPS) could provide an alternative to prenatal diagnosis for carriers of balanced reciprocal chromosomal rearrangements. The study was done on 42 singleton pregnancies of 39 women, where one parent carried a balanced reciprocal translocation confirmed by karyotype. The cfDNA was analysed for sub-chromosomal changes associated with known parental translocations using WISECONDOR algorithm which assesses shallow genome-wide sequencing to detect imbalances of 10–20Mb.

Forty samples out of 42 (95%) pregnancies undergoing gw-NIPS returned an informative result. Seven out of the 40 pregnancies (17.5%) were high risk for an unbalanced translocation, which was confirmed after diagnostic prenatal testing. The remaining 33 informative pregnancies had low risk.

The sensitivity and specificity of gw-NIPS was 100% with no false positives or false negatives. The authors concluded that gw-NIPS was a potential option for most reciprocal translocation carriers and could be an alternative to prenatal diagnosis for couples who have undergone PGT-for structural rearrangements (PGT-SR).

NIPS for fetal CNVs (Wang et al., 2021))

The aim of this study was to evaluate the effectiveness of NIPS for detection of fetal pathogenic copy number variants (CNVs). In the prospective approach, they evaluated 24,613 pregnant women who underwent NIPS (low pass genome sequencing), 124 (0.50%) of whom

screened positive for fetal CNVs. Of these 124 women, 66 underwent prenatal diagnosis by CMA and 13 had true-positive results, giving a positive predictive value (PPV) of 19.7%.

Retrospectively, they also evaluated 47 women with 51 fetal pathogenic CNVs ranging in size from 0.5 to 26.5 Mb already detected by CMA and performed NIPS for them. Retesting with NIPS indicated that 24 of these 47 cases could be detected by NIPS, representing a detection rate (DR) of 51.1%. The authors acknowledged that the PPV and DR of their study was significantly lower than other clinical studies. Follow-up molecular prenatal diagnosis was strongly recommended in cases where NIPS suggests fetal CNVs.

International Society for Prenatal Diagnosis updated position statement on the use of genome wide sequencing for prenatal diagnosis (Van den Veyver et al., 2022)

This replaces the first position statement published in 2018 with updated information on the technologies, experience, and recommended practices. Genome wide DNA sequencing includes prenatal exome (pES), prenatal genome (pGS), clinical exome sequencing, and phenotype driven gene panels. The authors have listed the clinical indications for the use of genome wide sequencing for prenatal diagnosis. Diagnostic sequencing for fetal indications is best done as a trio analysis, where fetal and both parental samples are sequenced and analyzed together, with separate informed consents from both parents. Currently no consensus for reporting of secondary findings is available.Reporting is best focused on pathogenic and likely pathogenic variants in genes that are relevant to the fetal phenotype. Thorough pre test counselling and informed consent must address types of results possible, realistic expectations about the chance of finding a clinically significant result, timeframe for expecting a result, and possibility that no result is obtained.

References

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