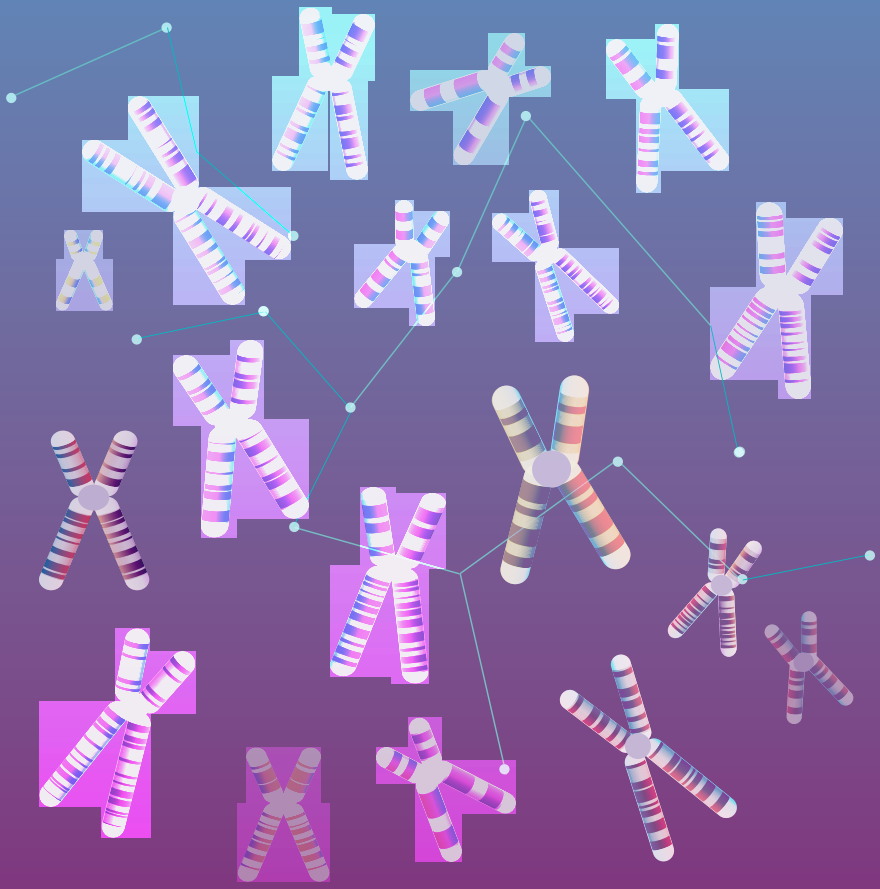
Claria
Reproductive Genetics

MEDGENOME

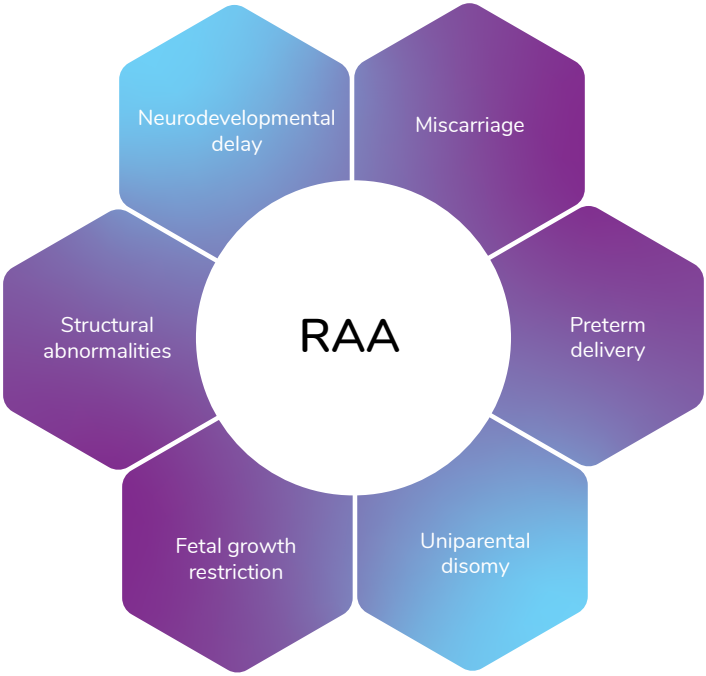
Claria NIPT Advanced

Screening for **Rare Autosomal Aneuploidies**



What are Rare Autosomal Aneuploidies?

Aneuploidies including monosomy and trisomy of chromosomes other than Trisomy 13, 18, 21 are called Rare autosomal aneuploidies (RAA). They are frequently associated with adverse pregnancy outcomes. RAA's can be identified by Genome-wide screening of cell-free DNA. About 30% - 75% of pregnancies that are high risk for RAAs on NIPT show clinically relevant abnormalities[1,2]. High risk results on genome wide NIPT warrants further investigations with confirmatory diagnostic tests to confirm the RAA findings using Karyotyping or Chromosomal Microarrays. In RAA positive pregnancies, it is recommended that the pregnancy is closely monitored [3,4].



Adverse pregnancy outcomes of Rare autosomal aneuploidies found in 60-75% of the pregnancies.

There is emerging evidence to support RAA screening using NIPT

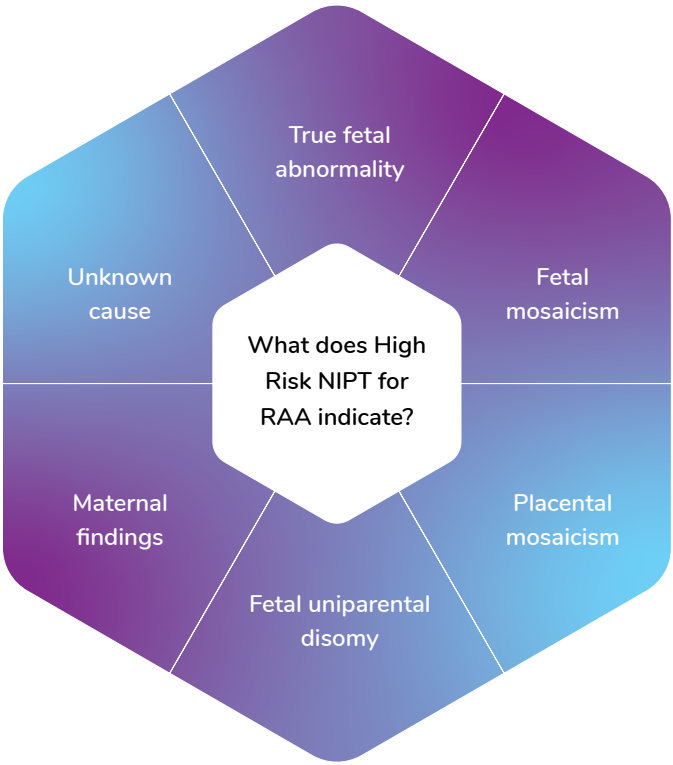
Study	Total Screened	Total RAT	Outcome Data	Fetal Loss	Confirmed Abnormal/ Significant UPD	Abnormal Pheno-type	FGR	Normal Outcome
Fiorentino et al. 2017	12,114	17	17	7	4	0	0	6
Pertile et al. 2017	16,885	58	50	26	6	1	2	14
van Opstal et al. 2018	2,527	26	25	0	4	5	8	10
Scott et al. 2018	23,388	30	30	6	2	5	8	9
Wan et al. 2018	15,362	53	21	2	1	0	NA	18
Chatron et al. 2018	1,617	10	10	0	1	0	3	6
	71,893	194	153 (78.%)	41/153 (26.8%)	18/153 (11.7%)	11/153 (7.2%)	21/153 (13.7%)	63/153 (41.2%)

Benn et al. Rare Autosomal trisomies: comparison detection through cell-free DNA analysys and direct chromosome preparation of chorionic villus samples. Ultrasound obsetet Gynecol 2019; 54: 458-467.

Literature	PPV for RAAs
Karuna R.M.van der Meij et al, 2019	6%
Van Opstal et al, 2018	15%
Desheng Liang et al, 2019	28.6%
Fiorentino et al, 2016	58.2%

MedGenome Labs Offers Validated RAA Screening

MedGenome's Claria NIPT screens for pregnancies from the 10th week of gestation. It uses whole genome sequencing which is a counting based technique. It can screen for numerical aneuploidies in all 23 chromosomes. We validated Claria NIPT for RAAs and 0.74% samples were found to be high risk for a rare autosomal aneuploidies



"VeriSeqTM NIPT Solution V2 Package Insert", Illumina Inc reported the following sensitivity and specificity for detection of genome wide screening (i.e., rare autosomal aneuploidies) by testing total of 2,307 singleton and twin samples were tested. Samples for the genome wide screen contained 28 samples with known mosaicism.

	Sensitivity	Specificity
Estimate % (n/N)	96.4% (27/28)	99.80% (2001/2005)

What Genetic Counselling must include?

- The test sensitivity, specificity, PPV and NPV along with prevalence of such rare autosomal aneuploidies should be communicated.
- Possible outcome of NIPT testing for genome wide screening and further management/steps in case of different result scenarios must be explained to the patients opting for the test.
- Implications of RAAs in pregnancies and post-natal life must be addressed. Educational tools and resources can be used for this purpose.

Case study

Patient information

A 27-year-old pregnant woman was offered basic NIPT at 16 weeks 4 days after her anomaly scan revealed unossified nasal bone.

Previous History

It was her first pregnancy, a spontaneous and singleton conception with no other gestational history.

Genetic Testing at MedGenome

Genome-wide NIPT

Results

The NIPT screen showed low risk for the tested chromosomes. However, on genome wide analysis, the sample revealed a high-risk for Trisomy 22.

Outcome

This was an incidental finding, and was conveyed to the clinician to follow up for the clinical outcome. The clinician shared that an anomaly scan at 16 weeks had revealed a slight left axis deviation of the heart. On receiving the information about incidental finding, another ultrasound scan was scheduled. Later, the clinician shared that the scan revealed a congenital heart defect - Tetralogy of Fallot. Due to unfavorable prognosis, the pregnancy was terminated after genetic counseling.

Product of Conception testing done at MedGenome confirmed ~30 % mosaic gain of chromosome 22 i.e. mosaic Trisomy 22 in the fetus. It included all the regions of chromosome 22 from 22q11.1 to qter region.

Discussion

Trisomy 22 is the second most common autosomal aneuploidy accounting for miscarriages. Full Trisomy 22 leads to non-viable gestation. In case of mosaic Trisomy 22, pregnancy can progress and even survive till term. However, it is known to cause fetal abnormalities such as dysmorphism, webbed neck, cardiac and renal anomalies. It can also cause intra uterine growth retardation or intra uterine fetal demise at later stages of pregnancy. The variability in the clinical features can be attributed to the percentage and type of mosaicism. Live born infants with mosaic Trisomy 22 do not survive past few months.

Conclusion:

Genome-wide NIPT was able to screen for clinically relevant information in this pregnancy for better pregnancy management.

References:

1. M. D. Pertile, M. Halks-Miller, N. Flowers, C. Barbacioru, S. L. Kinnings, D. Vavrek, W. K. Seltzer, D. W. Bianchi. (2017). Rare autosomal trisomies, revealed by maternal plasma DNA sequencing, suggest increased risk of feto-placental disease. Sci. Transl. Med. 9, eaan1240.
2. Benn, P., & Grati, F. R. (2018). Genome-wide non-invasive prenatal screening for all cytogenetically visible imbalances. Ultrasound in Obstetrics & Gynecology, 51(4), 429–433.
3. Benn, P., Malvestiti, F., Grimi, B., Maggi, F., Simoni, G., & Grati, F. R. (2019). Rare autosomal trisomies (RATs): a comparison of the detection through cell-free DNA and chorionic villus sampling. Ultrasound in Obstetrics & Gynecology.
4. VeriSeq NIPT Solution v2 Package Insert, May 2019 (Document No - Document # 1000000078751 v00) provided by Illumina.

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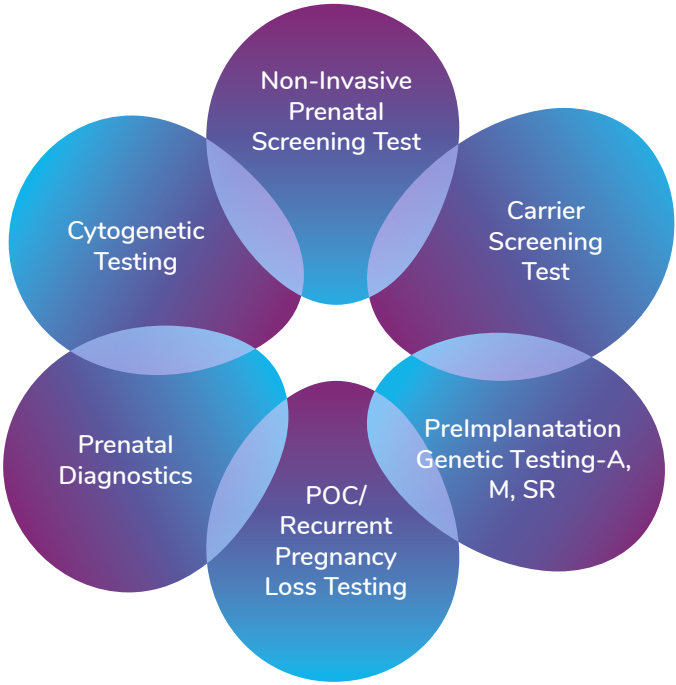
Claria from MedGenome offers the complete range of Reproductive Testing solutions



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