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The Importance of Intermediate Risk Report

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Why Intermediate Risk is being reported?

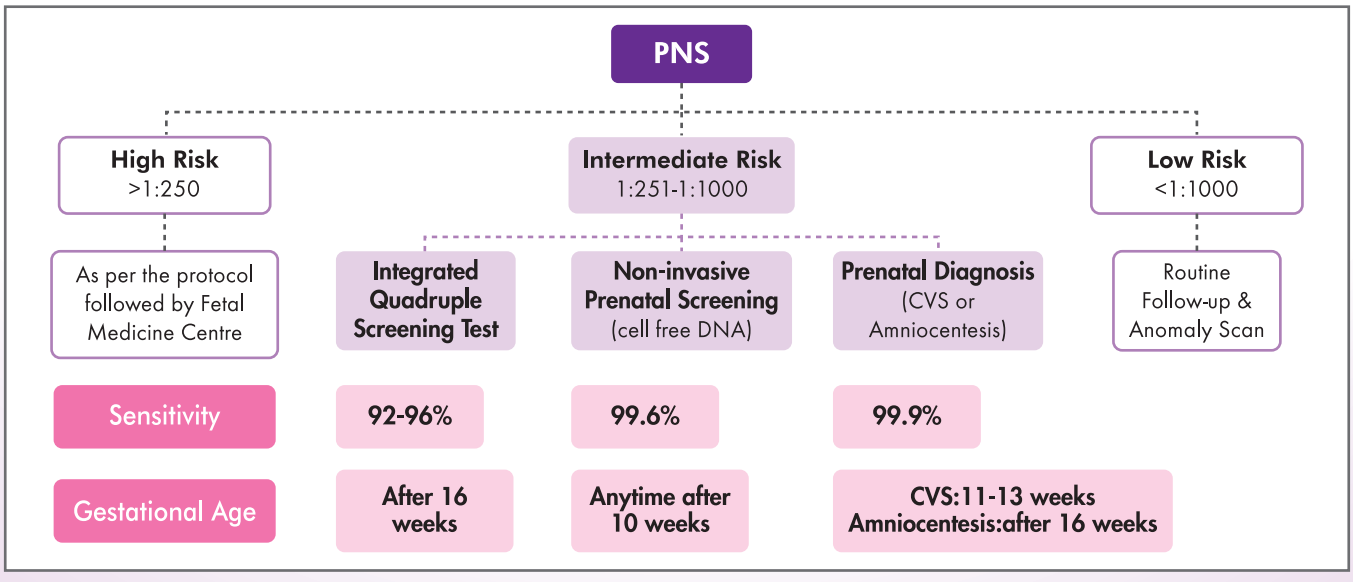
- In India, **23000-29000** children are born with Down Syndrome (DS) every year
- **Cost burden** of raising a child with Down Syndrome is approx. ₹60 lacs and intangible impact on quality of life of the family (varies with varying phenotypes)
- Currently, there are **Prenatal screening and diagnosis options available** to detect common aneuploidies in an ongoing pregnancy
- **Detection Rate (DR) of Combined First Trimester Screening (FTS)** is **90%-92% for common aneuploidies,** when the risk cut-off is considered to be **1:250**[1]
- **Increasing the risk cut-off** to **1:1000** (inclusion of Intermediate risk sub-group), **improves DR to 99%** for common aneuploidies[1]
- Therefore, the patients are divided into 3 categories depending on their personalised risk[1,2]
  - **High risk** >1:250
  - **Intermediate risk** 1:251 to 1:1000
  - **Low risk** <1:1000
- Aiming to **reduce the burden of common aneuploidies (genetic disorders)** in the Indian population

Intermediate Risk - beyond aneuploidies

- Important to **identify the reason** for intermediate risk assessment
- Is it because of - NT (Nuchal Translucency), free β-hCG (Beta Human Chorionic Gonadotrophin), PAPP-A (Pregnancy-Associated Plasma Protein A)
- Variability in the biochemical marker distribution could be **indicative of abnormalities** other than the common aneuploidies, **such as placental insufficiency, pre-eclampsia, threatened abortion and adverse obstetric outcomes**

Managing Intermediate Risk cases

- There are different options available for managing patients with intermediate risk assessment, depending on the screening program followed by the respective centres[1,2]



1. M. Sanatorium et. al, Accuracy of FTS, Ultrasound Obstet Gynecol 2017;49:714-720; 2. Sonek JD, et al., Inverted Pyramid of care, Clin Lab Med, 36, 2016, 305–317.

Case Studies

CASE I

- **Combined FTS was performed on a pregnant woman aged 30 years. Nuchal Translucency (NT) and biochemical values were incorporated to generate her personalised risk.**

First Trimester Screening (NT+Biochemistry) Summary

Date of birth:	08 April 1989
Examination date:	20 July 2019

Address: Patna Hospital no.:

Referring doctor:

Address: Patna

History

Ethnic origin: South Asian (Indian, Pakistani, Bangladeshi).
Parity: 0.
Maternal weight: 48.0 kg.
Smoking in this pregnancy: no; Diabetes Mellitus: no.
Conception: ICSI;
last period: 20 April 2019 EDD by dates: 25 January 2020

First Trimester Ultrasound

Gestational age: **12 weeks + 5 days** from CRL EDD by scan: 27 January 2020

Crown-rump length (CRL)	62.4 mm
Nuchal translucency (NT)	1.42 mm

Maternal Serum Biochemistry

Sample , taken on: 26 July 2019, analysed on: 29 July 2019. Equipment: Roche.

Free ß-hCG	635.30 IU/l	equivalent to 15.609 MoM
PAPP-A	9.428 IU/l	equivalent to 1.395 MoM

Condition	*Background risk*	*Adjusted risk*
Trisomy 21	1: 885	1: 385
Trisomy 18	1: 10450	<1: 20000
Trisomy 13	<1: 20000	<1: 20000

- **The patient opted for NIPS (InsighT) post counselling.**

FTS: First Trimester Screening; ICSI: Intra-cytoplasmic Sperm Injection; EDD: Estimated Due date

Test Results

CONDITIONS	PROBABILITY	RISK ASSESSMENT
Trisomy 21	**>1/20**	**High risk**
Trisomy 18	1/94408362	Low risk
Trisomy 13	1/16384363	Low risk

It is advised that high risk results should be followed by confirmatory diagnostic testing

CONDITIONS	RISK ASSESSMENT
Trisomy 9	Low risk
Trisomy 16	Low risk
Trisomy 22	Low risk

SEX CHROMOSOME ANEUPLOIDIES	RESULT	INTERPRETATION
XO	Not detected	None
XXY	Not detected	None
XXX	Not detected	None
XYY	Not detected	None

Sex of the Fetus cannot be revealed as per PCPNDT Act 2003.

- **The InsighT report revealed a "High Risk" for Trisomy 21. Following which, the patient underwent confirmatory diagnosis on the Amniotic fluid sample.**

Detection of Chromosomes 13, 18, 21, X and Y Aneuploidies by Quantitative Fluorescent PCR (QF-PCR)

Specimen Description: Specimen was optimum for the test.

Methodology:

- Fetal DNA is isolated using standard proto col and tested for Chromosomes 13, 18, 21, X and Y aneuploidies by Quantitative Fluroscent PCR.
- The assay involves amplification of markers using fluoroscence labeled primers, followed by size separation and allele peak measurement on a genetic analyzer.
- The fragments are analysed using Genemapper software.

Result: The results are consistent with Trisomy 21, indicative of Down Syndrome.

No abnormalities were detected in chromosomes 13, 18 and sex chromosomes.

PCPNDT: Pre-Conception and Pre-Natal Diagnostic Techniques; QF-PCR: Quantitative Fluorescent Polymerase Chain Reaction

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Case Studies

CASE II

- **First Trimester Screening was performed for this patient, since the NT image was not as per the standard imaging criteria, the NT value wasn't included.**

First Trimester Screening (Only Biochemistry) Summary

Patient Name: Patient DOB: 27/03/1993

Ethnicity: Asian City:

Sample Type: Serum
Method: Time-resolved Fluroimmunoassay
Risk Assessment by: Algorithm validated by SURUSS 2003, N.J Wald

Result:

Posterior Risk for Down Syndrome	1:742	Intermediate Risk
Posterior Risk for Edward's Syndrome	1:100000	Low Risk
Posterior Risk for Patau Syndrome	1:100000	Low Risk

Interpretation:

The First Trimester Screening for the given sample is found **Intermediate Risk for Down Syndrome.**

Suggestion:

In view of equivocal or intermediate risk i.e. Risk >1:1000, further testing through the following options should be considered:

a) Integrated screening with detailed Genetic Sonogram (Detection rate: 92-95%), ref: ISPD guidelines 2011.
b) Non-invasive pre-natal Testing/ Screening (NIPT) (Detection rate: >99%), ref: ISPD guidelines 2015.
c) Definitive testing through Fetal Karyotyping.

- **The risk assessment for Trisomy 21 revealed risk of 1:742; free β-hCG MoM was 2.70 and PAPP-A MoM was 1.43. If the non-standardised NT would have been included (which was 1.1mm at 75mm CRL), the risk was decreasing to 1:2100.**
- **Following which, the patient underwent confirmatory diagnosis on the Amniotic fluid sample.**

Detection of Chromosomes 13, 18, 21, X and Y Aneuploidies by Quantitative Fluorescent PCR (QF-PCR)

Specimen Description: Specimen received was optimum for the test.

Methodology:

- Fetal DNA is isolated using standard protocol and tested for Chromosomes 13, 18, 21, X and Y aneuploidies by Quantitative Fluorescent PCR.
- The assay involves amplification of markers using fluorescence labeled primers, followed by size separation and allele peak measurement on a genetic analyzer.
- The fragments are analyzed using Genemapper software.

NT: Nuchal Translucency; CRL: Crown Rump Length; QF-PCR: Polymerase Chain Reaction

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Result: The results are consistent with Trisomy 21, indicative of Down Syndrome.
No abnormalities were detected in chromosomes 13, 18 and sex chromosomes.

- **This shows that the NT was under measured and the inclusion would have resulted in a false negative report.**

Benefits of Intermediate Risk reporting

- Increases Detection Rate to 99% of prenatal screening
- Better insights about the pregnancy
- Helps identify abnormalities other than the common aneuploidies

Our Approach

Best-in-class processes

Expert interpretation

Clinical guidance wherever necessary

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