

Diagnostic yield of prenatal exome sequencing across the three trimesters of pregnancy: A multicenter retrospective study

Alexandros Sotiriadis¹, Chrysa Efstathiadou⁴, Eleftheria Demertzidou^{1,2},
Elisavet Siomou⁴, Makarios Eleftheriades³, Themistoklis Dagklis¹, Apostolos
Athanasiadis¹, Spyridon Vasileiadis⁴, Emmanouil Manolakos⁴, Ioannis
Papoulidis⁴

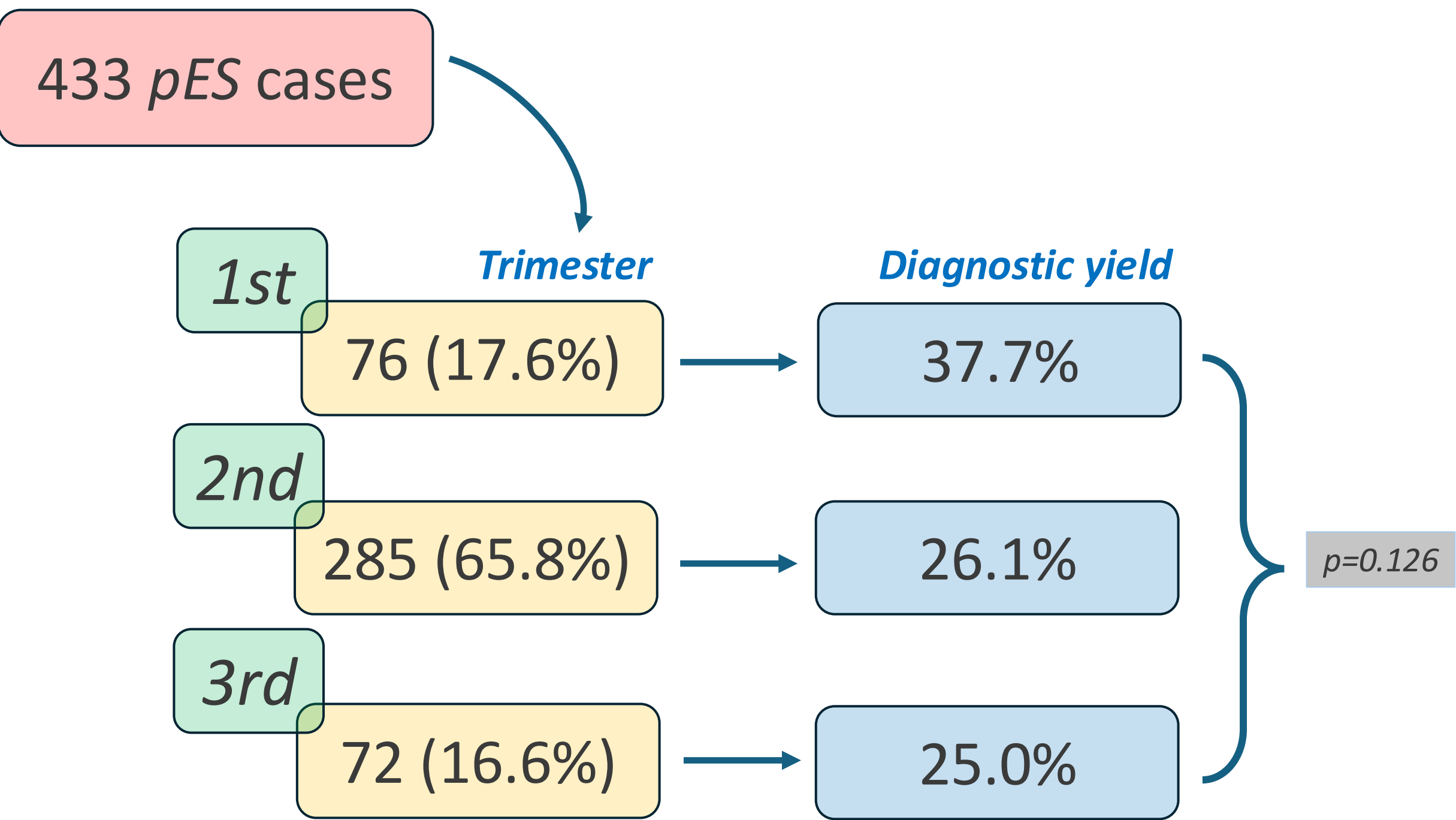
- OBJECTIVES
- Prenatal genetic diagnosis has progressed from standard karyotype to chromosomal microarray analysis (CMA), and recently to exome sequencing (ES)
 - Several national and international societies have established different phenotypic eligibility criteria for prenatal ES (pES)
 - While the second-trimester anomaly scan detects the majority of fetal structural defects, there is now strong evidence that approximately 25% of prenately diagnosed defects are detected in the third trimester, and a new major defect is diagnosed at the third-trimester scan in approximately 1 in 300 fetuses with a previously normal scan.

The aim is to characterize the incremental diagnostic yield of prenatal exome sequencing (pES) across the three trimesters of pregnancy, and analyze the evolution of referral indications.

- METHODOLOGY
- Retrospective analysis of **P/LP* results**
 - After invasive diagnostic testing [CVS/amniocentesis/other fetal specimens]
 - **10 centers in Greece; 2022-2026**
 - Trio-WES recommended in all cases
 - pES analyzed in an accredited central laboratory, after normal CMA results
 - Targeted panels without exome-wide coverage were excluded
 - **Trimester was defined by the GA at the time pES was initiated**, regardless of the time of original sampling

433 FETUSES

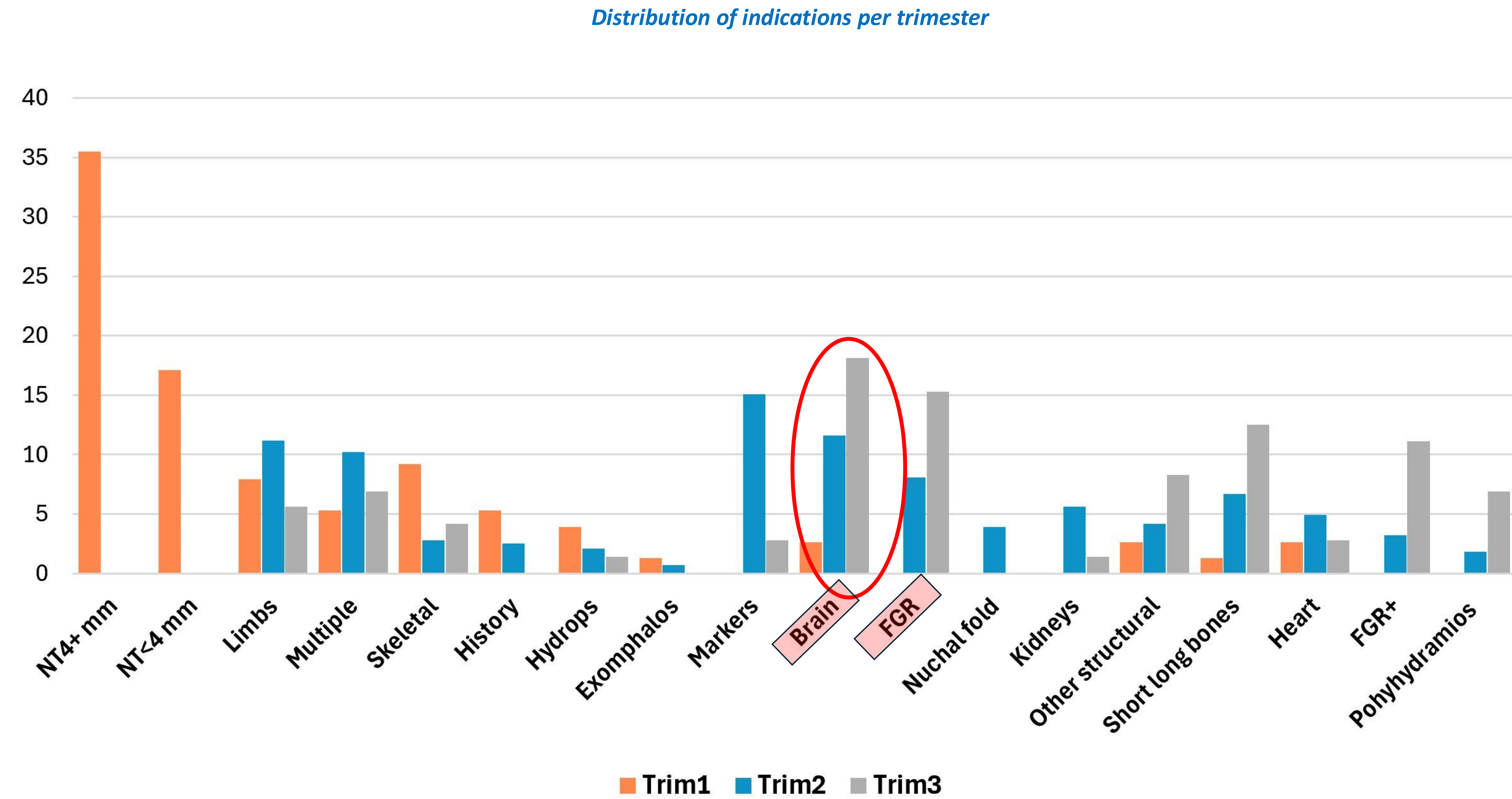
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Abnormal results	N	Yield (95% CI)
Skeletal	18	66.7 (43.7-83.7)
Genitalia	6	50.0 (18.8-81.2)
Limbs	42	40.5 (27.0-55.5)
Hydrops	10	40.0 (16.8-68.7)
Multiple	38	36.8 (23.4-52.7)
NT≥4 mm	27	33.3 (18.2-52.2)
Exomphalos	3	33.3 (6.1-79.2)
FGR (non-isolated)	17	29.4 (13.1-53.1)
Kidneys	17	29.4 (13.3-53.1)
Brain	48	29.2 (18.2-43.2)
Face	8	25.0 (7.2-59.1)
Short long bones	29	24.1 (12.2-42.1)
Markers	45	22.2 (12.5-36.3)
IUD	5	20.0 (3.6-62.4)
Heart defects	18	16.7 (5.8-39.2)
NT<4 mm	13	15.4 (4.3-42.2)
FGR (Isolated)	34	14.7 (6.5-30.1)
Other structural	18	11.1 (3.1-32.8)
Nuchal edema	11	9.1 (1.6-37.7)
Polyhydramnios (isolated)	10	0.0 (0.0-27.8)

pES yield according to indication for testing throughout pregnancy

RESULTS



- CONCLUSION
- pES yielded a P/LP variant in approximately one third of the fetuses analyzed across all three trimesters of pregnancy. Roughly one in six tests was performed in the third trimester, with structural defects, notably brain anomalies, carrying a yield of more than 38%
 - These findings support the clinical utility of pES in late pregnancy and reinforce the value of routine third-trimester anatomical scanning
 - Late-diagnosed isolated FGR may carry only a minimal risk, however more data would be needed to validate this finding.

