A Meta-narrative Review: Efficacy of Non-Invasive Prenatal Testing (NIPT) in the Detection of Sex Chromosomal Aneuploidy in Singleton Pregnancy

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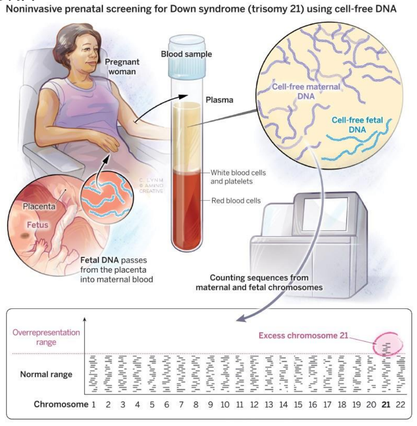
Introduction

Noninvasive Prenatal Testing (NIPT), also known as Cell-Free DNA (cfDNA) test, utilizes fetal DNA that is circulating in maternal blood to detect genetic anomalies within a fetus. Amniocentesis and chorionic villus sampling were the most common methods of assessing sex chromosome abnormalities before NIPT (Page-Christiaens, 2018). However, NIPT has been widely researched as a more convenient and safe screening method. cfDNA testing is limited due to being an adjunctive screening test thus a diagnostic test is required for confirmation, which are able to provide results with much greater accuracy and certainty than screening tests, but have greater risks. The diagnostic ability of cfDNA is still being researched and for this reason, it has not been widely adopted as a primary method of testing by many healthcare providers, along with having a higher cost than more traditional methods (Raj, 2022). Current research suggests that prenatal screening using cfDNA is not an optimal option for detecting sex chromosomal abnormalities (SCAs) due to its high rate of error in detecting SCAs (Guo, 2022). Current literature has demonstrated cfDNA is able to detect trisomies 13, 18, and 21 with great accuracy, though further research is needed on the topic of detecting other chromosomal abnormalities. This research utilizes a systematic review of the current literature regarding cfDNA screening in detecting SCAs to assess its function in clinical practice.

Figure 1

Image of Noninvasive Prenatal Screening using CffDNA



Research Question

How does detection rate of sex chromosomal abnormalities utilizing the Non-Invasive Prenatal Technique, Cell Fetal Free DNA (cfDNA) screening show its overall feasibility in clinical practice?

Methodology

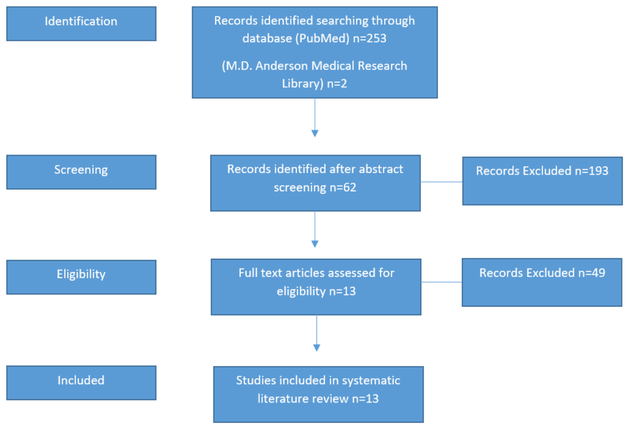
Literature utilized in this review needed to be recent (published within the last 5 years), a primary study (a clinical trial or other experimental work), and discuss the overall effectiveness of cfDNA in screening SCAs. Ideal studies included statistical analysis on the effectiveness of cfDNA in screening SCAs and discussed the limitations of widely adopting the cfDNA technique in clinical practice. Studies that assessed the effectiveness of cfDNA for other purposes were excluded.

The data collected for review included the specific screening information, methods being used, the PPV, NPV, FN, FP, the sample population, and any challenges, limitations, and bias reported in the study. All of which contribute to the feasibility of cell free fetal DNA as a primary screening method.

Article Selection

Figure 2

Flow diagram of selected and excluded literatures



Note. Literatures were obtained via Pubmed using specific key words. Literature were included or excluded based on specific criteria (as listed below) using abstract during the first screening and abstract/full body review during second screening. 13 studies were included in the final review.

Strengths

- Utilizes recent studies and primary research
- Focuses on statistical evidence to determine the effectiveness of NIPT
- Variation in sample (gestational age, cap off of ≥ 10 weeks, risk groups (low, intermediate, high)
- Provides background on cfDNA and NIPT, and compares and contrasts to traditional invasive methods
- Discusses future application and limitations

Limitations

- Insufficient time to review every clinical study that was within the search, narrowed to 13 articles
- First time through meta-review process
- Focused search through PubMed
- Inconsistent statistics of SCA

13 Studies' PPV

Table 1

Analysis of the PPV of various types of sex chromosome abnormalities across 13 studies

	45, X (%)	47, XXX (%)	47, XXY (%)	47, XYY (%)	46, XY (%)	SCAs (Combined) (%)
Baranova, E	-	-	-	-	-	57.14
Gou, N	21	42.2	46.9	52.9	N/A	36.9
Lai, Y	12.04	67.92	69.03	77.78	4	38
Liu, S	20	28.95	59.18	61.54	25	34.17
Page-Christiaens, L	-	-	-	-	-	-
Pang, Y	12.00	72.73	50.00	75.00	-	41.07
Raj, H	-	-	-	-	-	-
Wang, J	75.86	33.33	50.00	55.56	-	60.32
Wang, Y	21.4	-	-	-	-	57.6
Xu, L	-	-	-	-	-	42.66
Yang, J	30	70.58	81.13	81.13	-	50
Yuan, X	-	-	-	-	-	57.1
Zhao, G	16.13	42.86	45.45	100	10	31.97
Total	26.05	44.82	50.21	62.99	1.18	46.08

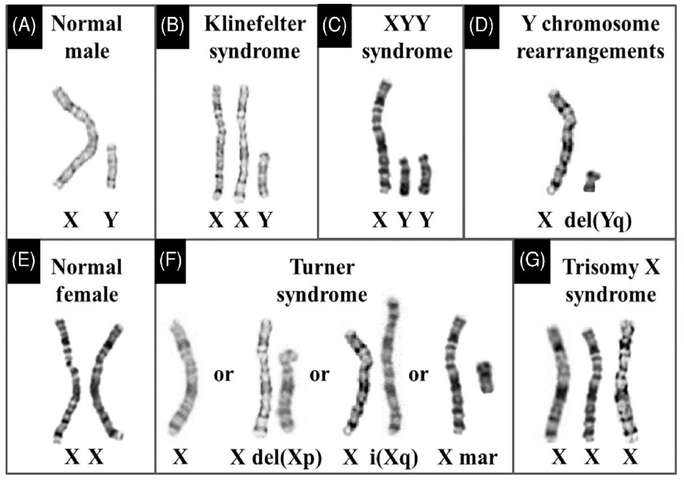
Note. Statistics show inconsistencies in PPV for different sex chromosomal aneuploidies across 13 studies. Lowest PPV seen in monosomy X and highest PPV seen in XYY. Not much statistical data provided for 46, XY. Overall, combined PPV for SCAs is low, thus low accuracy. Some studies do not provide statistics for specific sex chromosomal diseases; two being sources for background information on NIPT, cffDNA.

Key Findings

- NIPT for SCAs has varying but consistently low PPV, thus low accuracy
- NIPT is least accurate in detecting Monosomy X
- Lowest PPV for Monosomy X (Turner Syndrome) and highest for 47,XYY (Jacobs Syndrome)
- Inconsistency in the interpretation of PPV value

Figure 3

Cambridge Image depicting Sex Chromosome Aneuploidies



Note. Karyotypes of all SCA involved in studies analyzed.

Conclusion

Despite high specificity and sensitivity for SCAs, studies have inconsistent but low PPVs with a combined SCAs' PPV of 46.08%, thus demonstrating low accuracy. These PPVs range from being the lowest for monosomy X (average PPV of 26.05%) to highest for XXY (average PPV of 50.21%) and XYY (average PPV of 62.99%). Studies have shown PPVs for SCAs commonly ranging from 38-50% which is consistent with most of our sources (Gou, 2022). The data compiled from those sources has an average PPV of 46.08% across the 13 studies reviewed. The studies reviewed seemed to hold different minimum criteria to designate the effectiveness of NIPT for SCAs. Where one study may say the PPV range is moderately accurate, therefore the clinical use of NIPT is recommended, another study says that the PPV range accuracy is low and thus the clinical use of NIPT for SCA is not recommended. Although NIPT for SCAs has positive implications in clinical practice, more methodological improvement is needed to improve its detection accuracy. Genetic counseling is needed following a positive NIPT to ensure subsequent confirmatory tests are carried out, to ensure that prospective parents fully understand the diagnosis and make an informed decision.

Future Directions

- Establishing baseline of PPV for SCAs
- Evolving technology to increase detection accuracy of SCAs and utilization as a diagnostic tool
- To make cfDNA testing more cost effective and commercially available
- Looking into utilizing cfDNA as treatment of genetic diseases in the unborn

References

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