State-wide performance of traditional and cell-free DNA based prenatal testing pathways: the Victorian Perinatal Record Linkage (PeRL) study

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Introduction

- Women's choices of prenatal screening and diagnostic pathways have increased in complexity since the introduction of cell-free DNA (cfDNA) screening and chromosomal microarrays.
- We performed individual record-linkage of women residing in Victoria, Australia, undergoing screening with cfDNA, combined first trimester screening (CFTS), second trimester serum screening (STSS), and/or prenatal and postnatal cytogenetic testing in 2015 to:
  1. Obtain population-based estimates on women's utilization of screening and diagnosis
  2. Analyse the performance of different screening strategies.
  3. Report the residual risks of any major chromosome abnormality following a low risk aneuploidy screen.

Methods

- Patient-funded cfDNA referrals from multiple providers were merged with state-wide results for government-subsidized CFTS, STSS and invasive diagnostic procedures.
- Postnatal cytogenetic results from products of conception and infants up to 12 months of age were obtained to ascertain cases of false negative screening results and atypical chromosome abnormalities.
- Individual record-linkage was performed with LinkageWiz™ and statistical analyses with STATA v14.0.

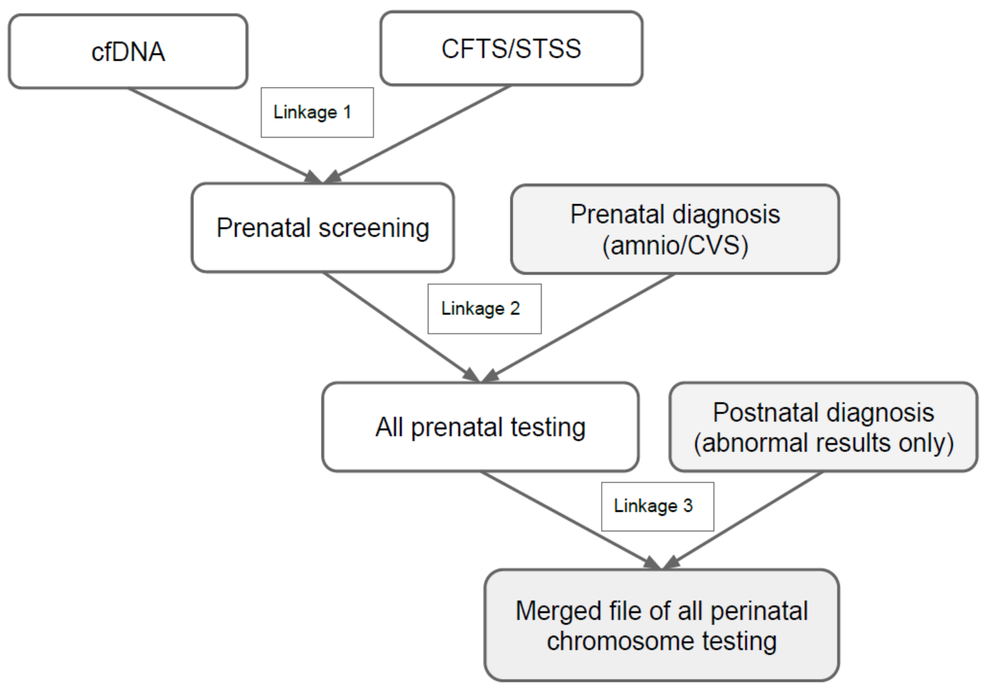

Figure 1. Overview of linkage process.
Amnio, amniocentesis; cfDNA, cell-free DNA; CFTS, combined first trimester screening; CVS, chorionic villus sampling; STSS, second trimester serum screening

Results

- There were 79,140 births during the study period; 66,166 women (83.4%) underwent at least one form of aneuploidy screening.
- Linkage data were complete for 92.4% of women undergoing screening (n=61,911)
- The risk of any major chromosome abnormality (including atypical abnormalities) detected on prenatal or postnatal diagnostic testing after a low risk screening result was 1 in 1188 for CFTS (n=37) and 1 in 717 for cfDNA (n=16) (p= 0.13).

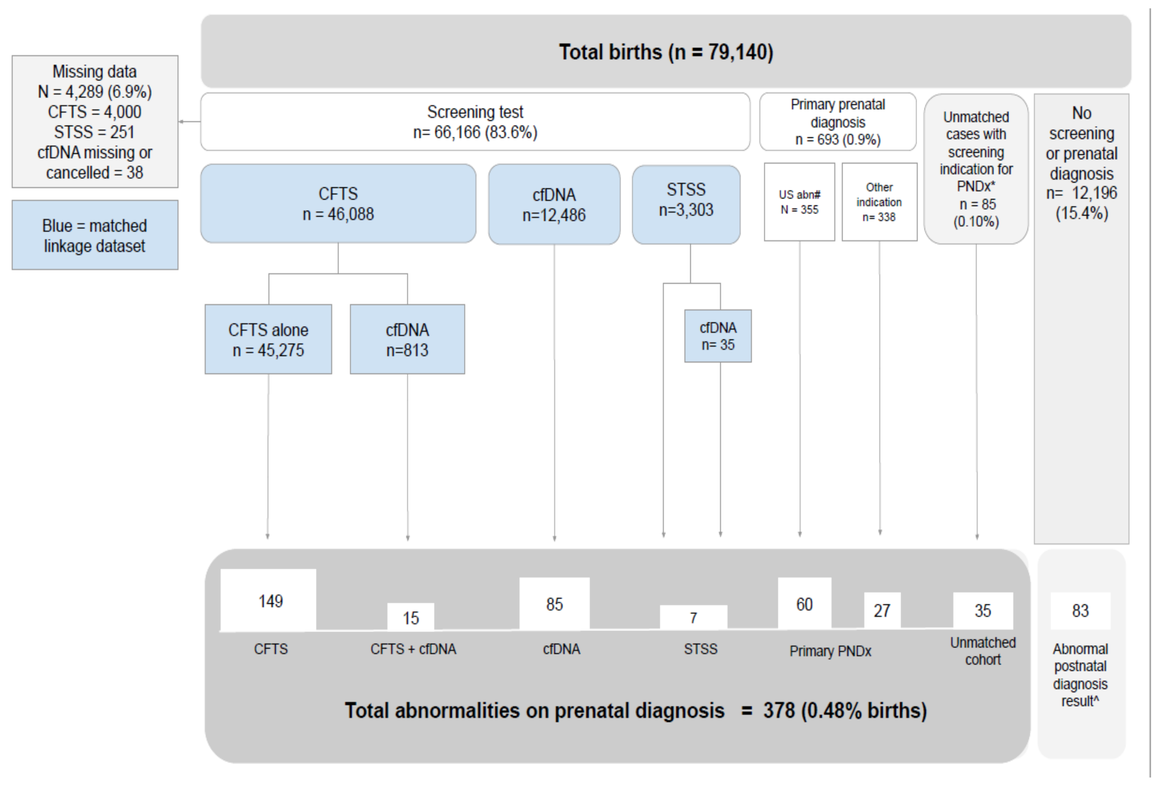

Figure 2. Utilization of prenatal testing pathways and detection of major chromosome abnormalities in Victoria 2015

Prenatal testing pathway	T21 Sensitivity %	95%CI	T21/13/18 Sensitivity %	95% CI	Specificity for 21/13/18	95% CI	Screen positive rate %	95% CI
1. CFTS alone N = 45,275	87.95 (73/83)	79.22-93.32	89.57 (103/115)	82.64-93.93	97.25 (43,934/45,176)	97.10-97.40	2.94 (1329/45,275)	2.78-3.09
2. cfDNA alone N = 12,486	100 (57/57)	93.69-100.00	100 (73/73)	95.00-100.00	99.93^ (12,184/12,193)	99.86-99.96	1.21^ (151/12486) 2.42$ (302/12486)	1.03-1.42 2.16-2.70
3. STSS alone N=3268	50 (1/2)	9.45-90.55	60 (3/5)	23.07-88.24	93.17 (3040/3263)	92.25-93.98	6.92% (226/3268)	6.10-7.84

Table 1. Performance of prenatal testing pathways 1, 2 and 3.
^Only high risk results for T21/18/13 included
$Including all high risk results (including sex chromosome aneuploidies) and failed cfDNA results

Conclusion

- Our state-wide linkage analysis delineated the utilization and clinical performance of the multitude of screening pathways available to pregnant women.
- The sensitivity of cfDNA for trisomies 21, 13 and 18 was clearly superior to CFTS (100% vs 89.6%).
- While there was no statistically significant difference in the residual risk of any major chromosome abnormality after low risk CFTS or cfDNA result, there were fewer live infants diagnosed with a major chromosome abnormality in the cfDNA cohort.
- These data provide valuable population-based evidence to inform practice recommendations and health policy.

Acknowledgments

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