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Should second trimester hypoplastic nasal bone be a sole indication for diagnostic testing with chromosomal microarray?

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Running Head: Prenatal diagnosis for hypoplastic nasal bone

Keywords: Nasal Bone, Prenatal ultrasound, Trisomy 21, soft markers, cell free DNA

Prior use of prenatal screening lowers the residual risk of trisomy 21 for women undergoing a midtrimester morphology scan. The International Society for Ultrasound in Obstetrics and Gynecology (ISUOG) issued a consensus statement stating that the 'genetic sonogram', which includes soft markers of trisomy 21, should not be performed in women with a low risk cfDNA screen due to poor positive predictive value.[1] However, the use of chromosomal microarrays (CMA) in the presence of ultrasound abnormality is standard practice due to the additional yield of pathogenic copy number variants (CNVs).[2] Data on the yield of CMA for isolated hypoplastic nasal bone (NB) in midtrimester is scarce. It is possible that pathogenic CNVs or atypical chromosome abnormalities might be increased in fetuses with hypoplastic NB[3], and that these will remain undetected if diagnostic testing is forgone due to a prior low risk screening result. We therefore performed a secondary analysis of a state-wide prenatal diagnosis dataset to determine the rate of atypical chromosome abnormalities and pathogenic CNVs in fetuses with a hypoplastic NB in midtrimester.[4] Our population has a high uptake of prenatal screening (approximately 90%), with the vast majority having either first trimester combined screening (69%), or cfDNA (24%) screening as their first-tier test.[5]

All ultrasound-indicated prenatal diagnostic procedures performed $\geq$ 18 weeks gestation from 2012-2016 for an indication of hypoplastic NB (as defined by the clinical referrer) were extracted from the Victorian Prenatal Diagnosis Collection. This state-wide dataset contains the results of all amniocenteses

and chorionic villus sampling performed in the Australian state of Victoria, which has over 70,000 births annually. The midtrimester morphology scan is routinely performed at 18-22 weeks.

During the 5-year study period, 3,258 diagnostic procedures were performed for the primary indication of ultrasound abnormality. Of these, 75.5% were analysed by CMA.

There were 127 diagnostic amniocentesis performed at ≥ 18 weeks for an ultrasound indication including hypoplastic NB. Overall, 22 (17%) had a major chromosome abnormality detected, including 16 cases of trisomy 21 (Figure 1).

There were 80 cases of isolated NB (sole indication), of which 8 (10%) had trisomy 21. There were no cases of pathogenic CNVs or atypical chromosome abnormalities detected in the remaining 72 cases with isolated hypoplastic nasal bone (0%, 95%CI 0-5.0%), including the 47 cases analysed by CMA (0%, 95%CI 0-7.1%).

Of the 47 cases of non-isolated NB (hypoplastic NB in combination with another soft marker or a structural abnormality), chromosome abnormalities were detected in 14 (30%). Of these, 3 were pathogenic CNVs that would have been missed on cfDNA screening.

This population-based study of midtrimester fetuses undergoing prenatal diagnosis for hypoplastic NB confirms the strong association with trisomy 21 and demonstrates that the risk of an atypical

chromosome abnormality is raised when additional ultrasound abnormalities are present. There were no non-trisomy 21 abnormalities in those with isolated NB in our cohort, though the upper limit of the confidence interval was 5%. This provides new data with which to inform the role of diagnostic testing following low risk cfDNA screening.

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Ethics approval

Human Research Ethics Committee (HREC) approval for the prenatal diagnosis data collection and related research was received from the Royal Children's Hospital HREC (Ref. No. 31135A) and Monash Health HREC (Ref. No. 12063B).

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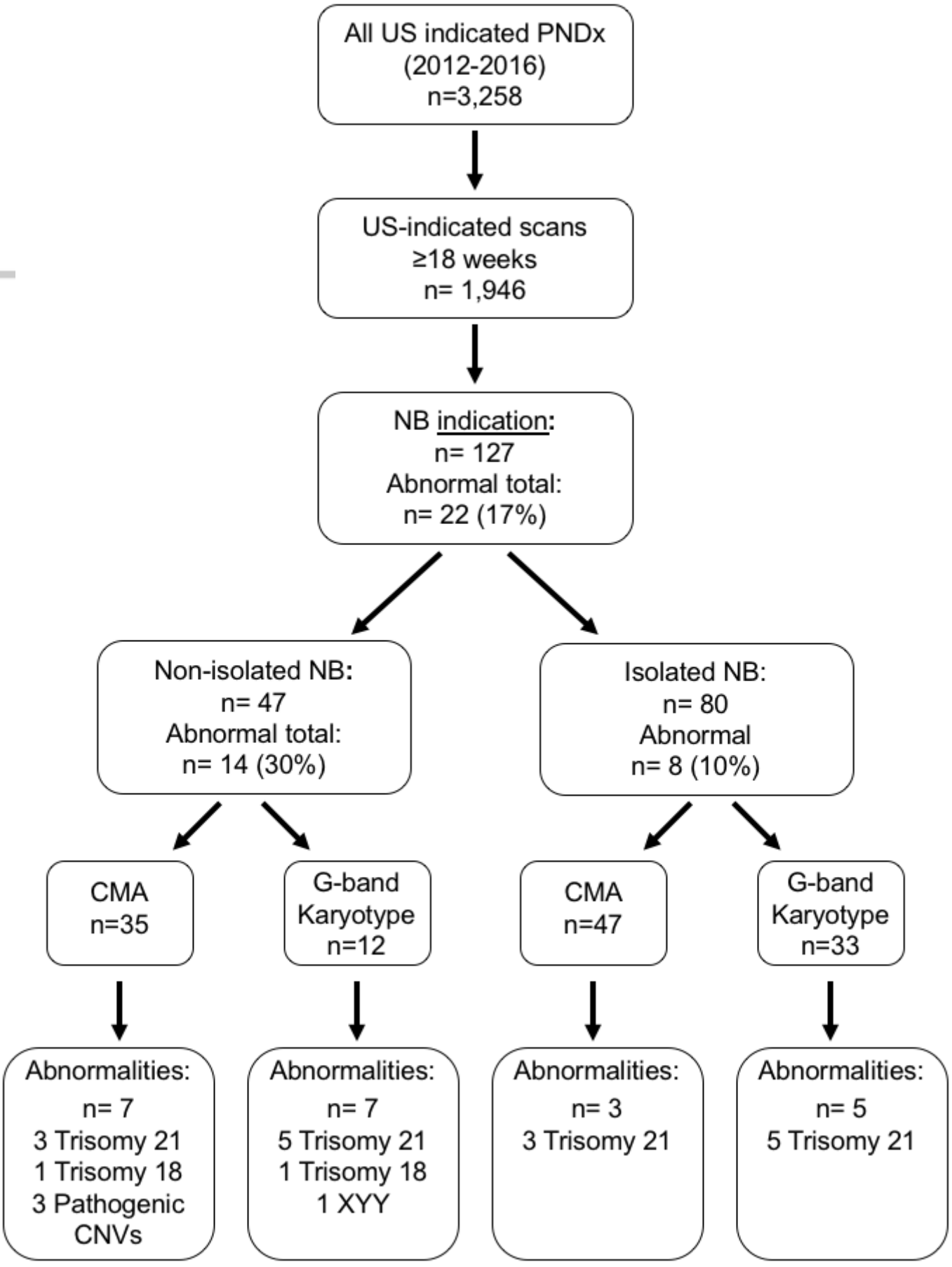
Figure Legends:

Figure 1: Prenatal diagnosis for isolated and non-isolated hypoplastic nasal bone in Victoria, Australia (2012-2016)

NB: Hypoplastic nasal bone, CMA: Chromosomal microarray, CNV (copy number variation)

Variants of unknown or uncertain significance on CMA not included in the figure (3 in the non-isolated NB group and 2 in the isolated NB group).



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