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The interim analysis of the PAGE study (Lancet. 2019) noted that in this prospective cohort study, two groups in Birmingham and London recruited patients (fetuses with structural anomaly on USS) from 34 fetal medicine units in England and Scotland. We used whole-exome sequencing (WES) to evaluate the presence of genetic variants in developmental disorder genes (diagnostic genetic variants) in a cohort of fetuses with structural anomalies and samples from their parents, after exclusion of aneuploidy and large CNVs. Women were eligible for inclusion if they were undergoing invasive testing for identified nuchal translucency or structural anomalies in their fetus, as detected by ultrasound after 11 weeks of gestation. The partners of these women also had to consent to participate. Sequencing results were interpreted with a targeted virtual gene panel for developmental disorders that comprised 1628 genes. Genetic results related to fetal structural anomaly phenotypes were then validated and reported postnatally. The primary endpoint, which was assessed in all fetuses, was the detection of diagnostic genetic variants considered to have caused the fetal developmental anomaly.

Over a three year period, the clinical data were collected until end of March, 2018. After exclusion of fetuses with aneuploidy and CNVs, 610 fetuses with structural anomalies and 1202 matched parental samples (analysed as 596 fetus-parental trios, including two sets of twins, and 14 fetus-parent dyads) were analysed by WES. After bioinformatic filtering and prioritisation according to allele frequency and effect on protein and inheritance pattern, 321 genetic variants (representing 255 potential diagnoses) were selected as potentially pathogenic genetic variants (diagnostic genetic variants), and these variants were reviewed by a multidisciplinary clinical review panel. A diagnostic genetic variant was identified in 52 (**8·5%; 95% CI 6·4-11·0**) of 610 fetuses assessed and an additional 24 (3·9%) fetuses had a variant of uncertain significance that had potential clinical usefulness. Detection of diagnostic genetic variants enabled us to distinguish between syndromic and non-syndromic fetal anomalies (eg, congenital heart disease only vs a syndrome with congenital heart disease and learning disability). Diagnostic genetic variants were present in 22 (15·4%) of 143 fetuses with multisystem anomalies (ie, more than one fetal structural anomaly), nine (11·1%) of 81 fetuses with cardiac anomalies, and ten (15·4%) of 65 fetuses with skeletal anomalies; these phenotypes were most commonly associated with diagnostic variants. However, diagnostic genetic variants were least common in fetuses with isolated increased nuchal translucency (≥4·0 mm) in the first trimester (in three [3·2%] of 93 fetuses).

These data and the potential use of prenatal WES will be discussed and how it has informed the development of the routine clinical Fetal Medicine / Genetics Clinic within National Health England.