The presentation and Investigation of single gene causes of lymphatic-related fetal hydrops

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Objective
1) To provide a detailed description of the presenting phenotype of those lymphatic disorders which present with fetal hydrops. 2) To compare and contrast the fetal presentation of the RASopathy syndromes and PIEZO1-related generalised lymphatic dysplasia. 3) To discuss the pathways to diagnosis of suspected single gene causes of NIFH. 4) To discuss the importance of a molecular diagnosis in genetic NIFH.

Methods
Approximately 60 cases with a suspected RASopathy diagnosis have undergone deep fetal phenotyping. This included not only the presence/absence of hydrops and other significant congenital malformation but also detailed fetal biometry. Statistical analysis has been undertaken to identify significant differences in the phenotypes between those in whom a molecular RASopathy diagnosis was made from those who tested negative. An international case series of patients presenting with NIFH and found to PIEZO1 mutations on exome sequencing have been collected. Detailed phenotyping has been gathered as well as the outcomes of affected pregnancies.

Results
Statistically significant differences exist in the fetal biometry of cases with a RASopathy diagnosis when compared with those who do not. This includes, but is not limited to, the likelihood of finding abnormalities of the ductus venosus and polyhydramnios. The fetal abdomen also appears to be large in mutation positive cases and this is independent of the presence of fetal ascites. There are notable differences in the phenotype of the PIEZO1 affected fetuses from those with a RASopathy diagnosis. The PIEZO1 cases tend to have a normal (or near normal) nuchal translucency in the first trimester. Also, they do not have the range of congenital structural malformations or the risk of hypertrophic cardiomyopathy.

Conclusion
Genetic diagnoses for fetal hydrops are being made more frequently in the prenatal period given the increasing availability of prenatal exome sequencing (and soon whole genome sequencing). Detailed phenotyping is essential to the interpretation of the sequencing data. A diagnosis not only allows for more accurate counselling but can inform the management of the pregnancy including the potential for therapeutic options.