919: Impact of introduction of NIPT on uptake of genetic testing in fetuses with CNS anomalies.

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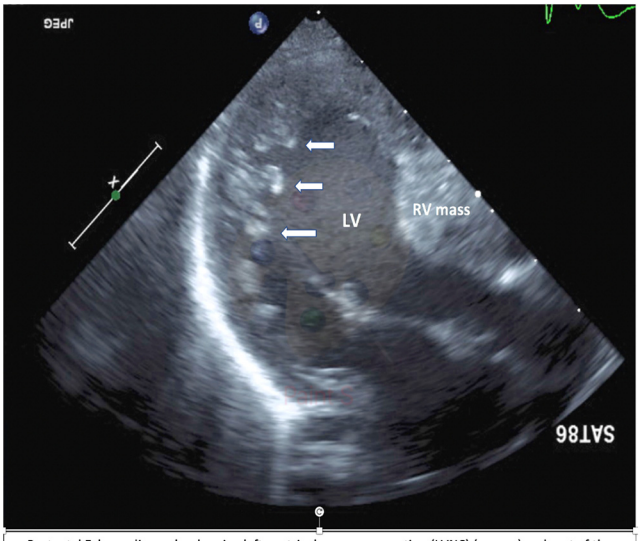
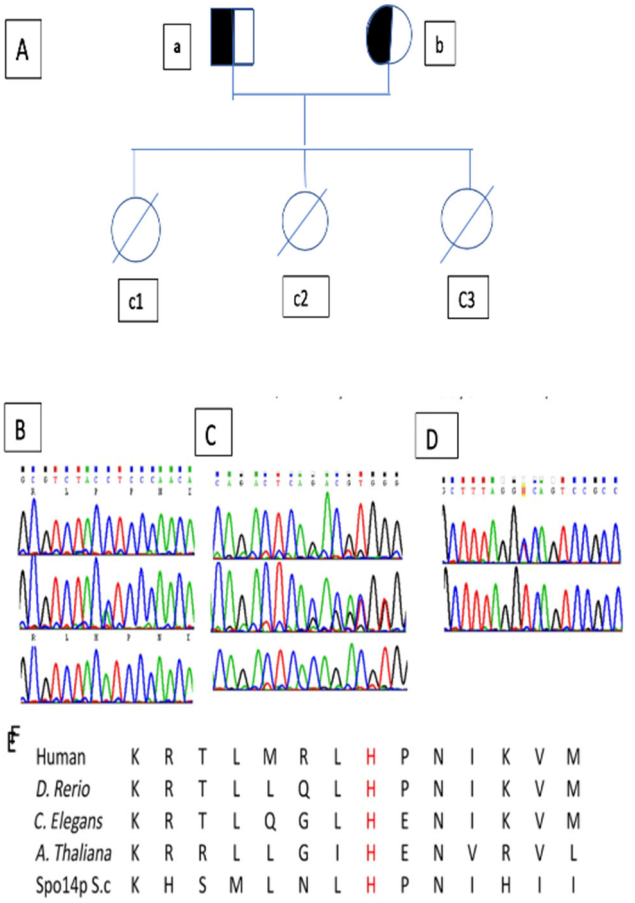
ventricular septal defect, atrial septal defect, and bilateral superior vena cava without evidence of bridge; infant C: functional single ventricle (tricuspid atresia, absent pulmonary valve, right ventricle hypoplasia due to right ventricular septal mass, left ventricle non compaction cardiomyopathy), dual atrioventricular node physiology, and multi-factorial pulmonary hypertension. Postnatal aCGH and NGS were performed on all family members. This allowed for the detection of compound heterozygous changes in the *PLD1* gene in all three of the infants. The mother was heterozygous for the missense mutation, c.3142C>G on chromosome 3 in the region of the *PLD1* gene. The father was heterozygous for a partial duplication of exon 12-19 in the *PLD1* gene. All three infants were found to have compound heterozygous mutations of *PLD1*, including a partial duplication and a missense mutation.

CONCLUSION: While *PLD1* pathogenic variants have been associated with cardiac changes mainly in the valves, this report shows that the same genetic changes in identical siblings can have a dramatic variation in phenotype. It also reveals a new association between left ventricular non-compaction and the *PLD1* gene.



Postnatal Echocardiography showing left ventricular non-compaction (LVNC) (arrows) and part of the right ventricular (RV) mass



(A) Family pedigree. a. Has heterozygous for partial duplication in chromosome 3 exon 12-19. b. Has heterozygous missense mutation in PLD1, variant c.314c>G. c1, c2, and c3: have compound heterozygous mutation (one allele has the duplication and other has the mutation) (B) Chromatogram of part of exon 13 of the *PLD1* gene around the c.A1325C (p.H442P) mutation site in the patient (upper panel), a carrier (middle panel) and a healthy control (lower panel). (C) Chromatogram of part of exon 14 of *PLD1* gene around the c.1484_1485del mutation site in the patient (upper panel), a carrier (middle panel) and a healthy control (lower panel). (D) Chromatogram of part of exon 25 of the *PLD1* gene around the c.2882+2T>C mutation site in the patient (upper panel) and a healthy control (lower panel). (E) Conservation of the human His442 (in red) throughout evolution.

919 Impact of introduction of NIPT on uptake of genetic testing in fetuses with CNS anomalies.

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OBJECTIVE: Fetal central nervous system (CNS) anomalies are often associated with genetic anomalies and further genetic testing is therefore recommended. Cell-free fetal DNA screening (NIPT) has decreased the uptake of invasive testing. NIPT is however not recommended in the presence of major fetal anomalies as it will fail to detect pathogenic microscopic and sub-microscopic chromosomal anomalies. The aim of our study was to assess whether introduction of NIPT has changed genetic testing strategies in pregnancies complicated by fetal CNS anomalies.

STUDY DESIGN: Retrospective review of all singleton pregnancies complicated by fetal CNS anomalies seen at a single tertiary center

between 2010 and 2017. Cases who had undergone invasive testing or NIPT prior to the diagnosis of the CNS anomaly were excluded. Cases were segregated according to whether they were seen prior to introduction of NIPT (Group A, 2010-2013) or thereafter (Group B, 2014-2017). We examined the rate of invasive and non-invasive genetic testing in each group.

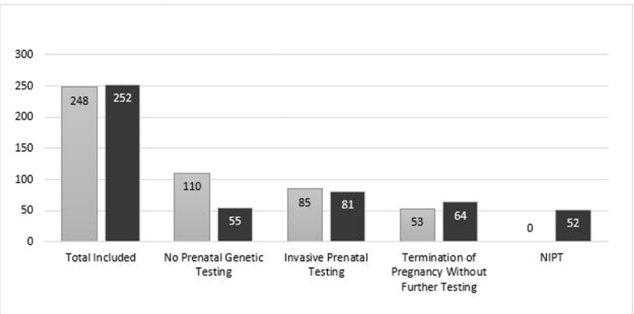
RESULTS: We retrieved 500 cases of fetal CNS anomalies (Fig1). Overall, 308 (62%) cases were isolated and 192 (38%) had additional structural anomalies ('complex'). In the total cohort, 165 women (33%) underwent expectant management with no further prenatal genetic testing, 166 (33%) had invasive testing, 52 (10%) had NIPT and 117 pregnancies (23%) were terminated without further genetic tests. In Group B, 21% underwent NIPT. The introduction of NIPT significantly decreased the number of pregnancies having no genetic testing (44% Group A vs 22% in group B, $p<0.0001$.) but did not change the uptake of invasive testing (34% vs 32% in group A and B, respectively; $p=0.61$).

In subgroup analysis, this decrease in patients choosing no testing was only significant in the subgroup of patients presenting with ventriculomegaly: where in group A 43 of 60 cases of fetal ventriculomegaly (72%) chose not to have any further testing, only 22 of 60 (37%) in group B chose not to have further testing in group B ($p=0.0002$).

Of 47 low-risk NIPTs, 17 had follow-up with microarray, 3 of which showed pathogenic copy number variants (18%) (Table 1).

CONCLUSION: Uptake of invasive prenatal testing in fetuses with brain anomalies was not affected by the introduction of NIPT. NIPT missed a significant number of CNVs.

Figure 1 – Prenatal management and genetic testing strategies used.



Legend: Gray bars: group A (prior to introduction of NIPT). Black bars: group B (after introduction of NIPT).

Table 1: Table representing result of genetic testing per subgroup.

	Number	Trisomy 13, 18 or 21	Microarray Abnormality
Invasive testing	**166**		
Isolated CNS anomaly	74 (44.6%)	-	3 (4.1%)
Complex CNS anomaly	92 (55.4%)	30 (32.6.1%)	5 (5.4%)
NIPT	**52**		
Low Risk NIPT result			
Isolated CNS anomaly*	29 (55.8%)	-	2(6.9%)
Complex CNS anomaly**	18 (34.6%)	-	4 (22.2%)
High Risk NIPT result			
Isolated CNS anomaly	-	-	-
Complex CNS anomaly***	5 (9.6%)	2 (40%)	-

Table 1 – Genetic Confirmation in IPT and NIPT groups

* *Only 9 cases underwent follow-up invasive microarray testing*
** *Only 9 cases underwent follow-up invasive microarray testing*
** *Only 3 cases underwent follow-up invasive microarray testing*

920 Microsoft Excel-based decision analysis to determine the cost effectiveness of fetal aneuploidy screening

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OBJECTIVE: Decision analysis is a powerful tool in determining the cost effectiveness of medical interventions. However, such analyses require access to expensive and unintuitive software. As a proof of concept, we attempt to use Microsoft Excel—a more widely used program—to analyze the cost effectiveness of aneuploidy screenings.

STUDY DESIGN: Though both sequential screening and cell free DNA (cfDNA) testing are widely offered in the clinic, various professional organizations disagree on which method is better suited for younger, low-risk populations. This issue is further complicated by inconsistent insurance coverage for cfDNA tests and low-risk patients' willingness to pay out- of-pocket. Thus, we designed an Excel algorithm that outputs the most cost-effective aneuploidy screening based on the patient's age and out-of-pocket costs for both types of screenings. The algorithm is fed up-to-date risks for common trisomy disorders (13, 18, 21), screening sensitivities, costs of diagnostic tests (CVS or amniocentesis), procedure related pregnancy loss in case of false positives, and the possibility of missing aneuploidy (Table 1). The program was simplified with macro functions that quickly recalculate costs after changing one or more inputs.

RESULTS: The program successfully calculates the three most cost-effective combinations of screenings/diagnostics based on the patient's age and ability to pay. In addition, the algorithm calculates the exact price point at which an initial cfDNA test becomes more cost effective than a sequential screening from ages 19-44 (Table 2). In other words, a patient could easily determine the maximum price of a cfDNA test at which it would be more cost-effective for the patient to pay for the test herself, rather than undergoing sequential screening.

CONCLUSION: Microsoft Excel can be used to carry out complex decision analysis and be useful in helping patients and physicians plan the most cost-effective screening/diagnostic regiment. Up-to-date risks statistics and more accurate assumptions on costs can further improve this algorithm, while such inexpensive and more intuitive Excel-based algorithms can be applied to other clinical settings beyond aneuploidy screening.