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Para: Rafael Bertoni <rafadelucabertoni@hotmail.com>

Dear Author,

Thank you for having saved an abstract for presentation at our 36th Annual Meeting that will be held in Copenhagen (Denmark) from 5 to 8 July 2020. Your abstract is temporarily saved in our database, but is NOT YET SUBMITTED.

Category	**Clinical science**
Topic	**Reproductive (epi)genetics (incl. (epi)genetic causes of infertility, PGD, PGS, prenatal diagnosis)**
Presentation preference	**Oral or poster presentation**
Abstract title	**Noninvasive preimplantation genetic test for aneuploidy (NIPGT-A) has a lower false positive rate than that of the invasive PGT-A**
Biography	**Laura Vagnini gain her specialization in the laboratories of the Centre for Reproductive Medicine and Centre for Medical Genetics of the University Hospital of the Dutch-speaking Brussels Free University in 2004. She has been working in Paulista Center for Diagnosis and Research, Brazil. Her research is focused on PGD, Molecular Biology and role of DNA integrity . Currently the research line is based on the search SNPs to identify women predisposed to implantation failure and low ovarian reserve at fertile age and also in the standardization of technologies for noninvasive diagnosis.**

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Study question:

Does NIPGT-A have lower false positive rates (FPR) than invasive PGT-A?

Summary answer:

When DNA sequencing from whole embryo cells was used as the gold-standard, the FPR of NIPGT-A was 3.32-times smaller than that obtained with invasive PGT-A.

What is known already:

After many years of using PGT-A, there are still have many concerns, such as risks of invasive action and difficulties in the correct interpretation of mosaicism, which cause problems in the interpretation of false positive and negative results. Recently, a new technology (NIPGT-A) has arisen that uses cell-free DNA on spent culture media of human blastocysts; the DNA reflects the ploidy status of both the trophoblastic cells and inner cell mass without biopsy, suggesting that NIPGT-A could be less prone to errors and could be more reliable than invasive tests.

Study design, size, duration:

This cohort study included a total of 37 blastocysts vitrified on day 5 that were previously biopsied for invasive PGT-A and presented a diagnosis of aneuploidy.The embryos were donated under informed consent by patients following the Brazilian Medicine Federal Council regulations. Blastocysts were thawed and cultured in 15µl drops of culture medium under oil. After their expansion(between 4-8hours), whole expanded blastocysts were transferred to NGS tubes and their corresponding spent media were collected for analysis.

Participants/materials, setting, methods:

The DNA of all samples (spent culture medium and whole embryo) was amplified by the MALBAC method (Yikon Genomics). The samples were subjected to next-generation sequencing (NGS) using Illumina MiSeq system. The results obtained from Chromgo software (Yikon Genomics) for the culture medium and whole embryo were compared to determine the accuracy of NIPGT-A for screening chromosomal abnormalities in each embryo.

Main results and the role of chance:

DNA from all 37 spent media samples was successfully amplified. Compared with the results from DNA sequencing of whole embryos, the negative predictive value of NIPGT-A was 100%. The false negative rate was 0%, and the positive predictive value (PPV) of NIPGT-A was 93.5%. Additionally, the FPR was 6.5% (Table 1). On the other hand, comparing the whole embryo and PGT-A biopsy results, the PPV was 78.4%, and the FPR was 21.6 (Table 1). In the eight cases of disagreement the results are presented in the Table 2.

Table 1. NIPGT-A results and Invasive PGT-A results

NIPGT-A	Whole Embryo		Invasive PGT-A	Whole Embryo	
	Aneuploidy	Normal		Aneuploidy	Normal
Aneuploidy	29	2	Aneuploidy	29	8
Normal	0	6	Normal	-	-
PPV: 93.5%	**FPR: 6.5%**		**PPV: 78.4%**	**FPR: 21.6%**	

Table 2. Disagreement results of whole embryo, NIPGT-A and invasive PGT-A

NIPGT-A	Whole embryo	Invasive PGT-A
46,XY	46,XY	XY,+1q(x3);+3q(x3)
46,XY	46,XY	XY,-2(x1)
XY,-1(x1);-9q(x1)	46,XY	XY,+9q(x3)
46,XX	46,XX	XX,+9q(x3)
46,XX	46,XX	XX,-4(x1)
46,XY	46,XY	X0, multiple abnormalities
46,XX	46,XX	XX,+13(x3)
XY,-1(x1);-9(x1),-19(x1);-21(x1)	46,XY	XY,-9(x1)

Limitations, reasons for caution:

The sample size was relatively small however comparative analysis between genetic results of invasive or noninvasive PGT-A with whole embryo DNA analysis are rare. All donated embryos were determined to be aneuploidy by invasive PGT-A. Additionally, the cut-off for aneuploidy in cases of invasive PGT-A could be variable (multicenter study).

Wider implications of the findings:

NIPGT-A has a smaller FP rate than invasive PGT-A, does not require micromanipulation skill, avoids trophectoderm biopsy trauma, and seems to provide more accurate genetic correspondence with the ploidy status of the whole embryo. Thereby NIPGT-A should be considered as the test of choice for genetic evaluation of the embryo.

COI **I have no potential conflict of interest to disclose**

Keywords **PGT-A**
NIPGT-A
NICS
Noninvasive PGT-A
DNA free culture media