Editorial

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Doubts about Preimplantation Genetic Screening for Aneuploidies: Will Liquid Biopsy Solve the Problem?

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ABSTRACT

Preimplantation genetic screening (PGS) for aneuploidies is currently performed by analyzing samples of 5-6 cells obtained by trophectoderm biopsy at the blastocyst stage. With the use of available molecular biology techniques, the chromosomal constitution of the cells sampled by the biopsy can be determined with a very high reliability. However, doubts are currently increasing as to the possibility of considering the results obtained with these small samples of trophectoderm cells as representative of the whole trophectoderm and, in a broader sense, of the inner cell mass which is the ultimate diagnosis target. Both empirical data and mathematical models converge to suggest that PGS, as performed nowadays, is prone to interpretation errors due to which normal embryos can actually be discarded and abnormal ones transferred. Here we suggest that using soluble DNA obtained by liquid biopsy (spent medium after blastocyst culture) merits further investigation as a viable solution to this problem.

Keywords
Preimplantation genetic screening, DNA, PGS, Aneuploidy, Trophectoderm biopsy, Liquid biopsy, Soluble.

There is growing concern about the current state of preimplantation genetic screening (PGS) for the detection of aneuploidies [1-3]. The opinions about the current place of PGS in this indication vary from the postulation of less rigid scoring systems for the evaluation of the risk associated with the transfer of embryos diagnosed with different types of aneuploidy [1] to a radical recommendation to discontinue the use of this technique until sufficient knowledge on genetic mosaicism in preimplantation embryos and on the phenotypical relevance of mosaic aneuploidies is available [3]. Rather than the molecular biology techniques employed, the current criticism of the use of PGS concerns the ability of the cells sampled for analysis (5-6 trophectoderm cells removed from a day-5 blastocyst) to represent a reliable source of information about ploidy of the whole embryo, and especially about that of its inner cell mass, the precursor of the future fetus [4]. Consequently, unless this basic problem is resolved, any further refinement of the methods used for genetic screening cannot change this situation.

There are three main points that put into question the use of trophectoderm biopsy as a source of information about the future fetus: a high probability of non-random distribution of aneuploid cells in the trophectoderm, a high probability of differences in the incidence of aneuploid cells in the trophectoderm and the inner cell mass, and the possibility that the embryos can self-correct eventual inner cell mass aneuploidies downstream from blastocyst stage [4]. Interestingly, the first two concerns may be resolved by sampling DNA for ploidy analysis from the spent blastocyst culture medium [5]. In fact, both the trophectoderm and the inner cell mass are likely to release soluble DNA to culture medium, although the exact mechanism of this phenomenon remains to be determined. Even in case that the relative contribution of each of the two cell lineages is not equal, on the per-cell basis, the eventual differences are likely to be similar among different embryos. If this is confirmed, the probable relative contribution of the trophectoderm and the inner cell mass to aneuploidies detected in the soluble DNA isolated from the culture medium can be assessed by using appropriate mathematical formulas.

Though originally designed merely as a more “embryo-friendly” method for chromosome screening as compared to trophectoderm biopsy, the sequencing of soluble DNA from embryo culture medium has also been shown to have a high sensitivity (0.882)

and specificity (0.840) for identification of embryo aneuploidies [5]. In fact, this method represents a new application of liquid biopsy technology which is currently replacing conventional "solid" biopsy methods in different medical specialties, ranging from cancer management [6] to the detection of fetal single-gene disorders by analyzing circulating cell-free DNA in maternal plasma [7]. Hopefully, sampling of soluble embryonic DNA by liquid biopsy from embryo culture medium will help resolve the current problems of PGS for aneuploidies.

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