Nothing more controversial than PGS

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It has been estimated that in 2016 approximately 20% of IVF cycles in the U.S. were accompanies by preimplantation genetic screening (PGS). Assuming approximately 250,000 IVF cycles annually in the U.S., this would represent an added annual cost of ca. U.S. $200 million for a procedure that, even by PGS proponents no longer is claimed to improve pregnancy and live birth chances; but now is claimed to warrant effort and expense because it allegedly reduces miscarriage risks and time to conception. That, like prior claims by PGS proponents of improving pregnancy and live birth rates, these two new claims also are unsupported by validated evidence, should not surprise since the PGS industry, from its founding in the 1990s, based on the seemingly unassailable hypothesis that exclusion of aneuploid embryos prior to embryo transfer must improve IVF outcomes, never hesitated to make unsupported claims.

When an earlier form of PGS (PGS 1.0), performed on cleavage-stage embryos, was, finally, declared ineffective by professional societies like ASRM, the solution for the PGS industry was simple: The industry created PGS 2.0, with even bigger promises of IVF outcome improvements and, therefore, not surprisingly, with even bigger cost and wider utilization. But, like with PGS 1.0, there were no validation studies to confirm hypothetical claims before PGS 2.0 was brought to the market.

When more recently evidence became irrefutable that trophectoderm was much more mosaic than previously unanimously claimed by the PGS industry, once again without any “mea-culpa,” the industry, literally overnight, changed course, simply declaring all prior pronouncements void, and establishing brand-new diagnostic criteria for PGS: Suddenly, embryos were no longer either normal (euploid) or abnormal (aneuploid), but, low and behold, embryos (likely in a majority of cases) could fall into a third diagnostic category of being mosaic and, even more remarkably, such embryos could also, selectively, be transferred (PGS 3.0).

What makes the overnight appearance of PGS 3.0 so remarkable, is not only that publication of newly recommended guidelines for diagnostic laboratory criteria and clinical practice by the Preimplantation Genetic Diagnosis International Society (PGDIS) in late 2016 did not comment on why the PGDIS, so suddenly, radically changed how PGS was to be reported out (i.e., recognition that the high prevalence of trophectoderm mosaicism did not allow for only diagnostic criteria of euploid and aneuploid and, at minimum, mandated a third category of “mosaic-normal”) but that the PGDIS (in speaking for the PGS industry) did not have the courage to acknowledge that under the prior PGS 2.0 criteria, likely tens of thousands of potentially transferrable embryos had been erroneously discarded and, with it, pregnancy chances for thousands of women.

PGS 3.0, in a typical marketing ploy to separate this allegedly new PGS-product from earlier PGS failures, ha now by some in recent publications also been renamed as preimplantation genetic diagnosis for aneuploidy screening (PGS-A). It is, however, once again an only an unvalidated product with completely unsupported claims: According to new PGDIS guidelines, embryos with up to 19% aneuploid cells (per biopsy, meaning ca. 1.2 cells in an average 6-cell biopsy) are normal-euploid and should be the preferred embryos for transfer. Embryos with 20-80% aneuploid cells (1.2-4.8 cell in an average 6-cell biopsy) are euploid-mosaic, and are potential candidates for transfer, following a hierarchical selection process. Embryos with over 80% aneuploidy (4.8-6.0 embryos) are considered aneuploid and should not be transferred (i.e., discarded).

Where these cut offs come from has, however, remained unclear since no data in the literature support them. The 20% cut off between euploid and euploid-mosaic is obviously based on high-resolution next generation sequencing (hr-NGS) being the only diagnostic platform capable of detecting mosaicism with reasonable accuracy, though only above 20%. The PGS industry, thus, does not separate normal-euploid from normal-mosaic based on any clinical validation in differences of IVF outcomes but, solely, based on technical limitations of hr-NGS. An embryo with 19% aneuploid, therefore, under PGDIS criteria is automatically transferrable but an embryo with 20% or 21% aneuploidy should only be transferred with considerable caution and selectively. The same complete lack of clinical evidence also underlies the 80% cut off between euploid-mosaic and full aneuploidy, as defined by the PGDIS. An 80% aneuploid embryos, therefore, can selectively transferred but an 81% aneuploid embryos should be discarded.

We, therefore, do not see any rational in the new PGDIS guidelines, and categorically reject them as arbitrary and, still, leading to discarding of potentially healthy embryos. Increasing evidence supports that trophectoderm mosaicism at blastocyst stage is a completely normal physiological phenomenon. Its extent, lack of congruency between trophectoderm and inner cell mass and significant self-correction of embryos downstream from blastocyst stage make it biologically and technically impossible to correctly diagnose an embryo's ploidy at blastocyst stage. PGS in all forms, therefore, should be clinically abandoned.