Preimplantation genetic testing for aneuploidies screening is not diagnostic

The report from Lin et al. (1) in this issue of *F&S Reports* describes the successful delivery of a healthy infant after the transfer of a single embryo that was reported by next-generation sequencing–based preimplantation genetic testing for aneuploidies (PGT-A) screening to have chaotic aneuploidy. Henry Adams said, "Chaos always breeds life when order breeds habit." As clinicians, we have developed a habit of giving too much credence to technology when a healthy dose of skepticism would bring us closer to the truth.

Screening tests are intended to help us identify patients at risk of a disease. The PGT-A testing provides an estimate of the potential viability of a preimplantation embryo based on the ploidy of a few trophectoderm (TE) cells in a biopsy. That PGT-A is not intended to be diagnostic is clear from the universal recommendation that patients should undergo age-appropriate diagnostic prenatal testing when PGT-A is performed on their embryos. Most couples undergoing prenatal screening, after establishing a pregnancy with a PGT-A tested embryo, choose to screen their pregnancies using noninvasive prenatal testing (NIPT) (2).

Klimczak et al (3) have pointed out that NIPT testing for PGT-A-screened pregnancies has a significantly lower positive predictive value than when NIPT is used for non–PGT-A screened pregnancies. This is because patients who have had PGT-A screened embryo transfers have an understandably lower risk of having an aneuploid pregnancy; hence, false-positive results with NIPT are significantly more common for this lower-risk group. Klimczak et al. (3) goes on to say the results of such testing should never be treated as diagnostic; a chorionic villus biopsy or amniocentesis must be performed to find if the screening test can be confirmed.

Klimczak et al.'s logic should also be applied to the PGT-A screening results. True, an embryo found to have a PGT-A euploid TE biopsy will have a greater chance of becoming an ongoing euploid pregnancy than an untested embryo or an embryo reported to be mosaic or aneuploid. However, as evidenced by Lin et al. (1), even embryos with a fully aneuploid biopsy retain a possibility of ongoing pregnancy and, with appropriate counseling, could be transferred if more favorable embryos are not available. Although one could perform a second biopsy, repeated biopsy has the potential to damage the fragile blastocyst. The only way to fully evaluate the viability of an embryo is to complete the embryo transfer.

The indications for PGT-A keep changing. The PGT-A was introduced as a means of screening among a group of morphologically similar favorable embryos to find the ones most likely to succeed. Screening of this kind was anticipated to decrease the number of transfers a patient would have to undergo and to allow the transfer of a single embryo, reducing the chance of multiple pregnancies. The PGT-A is associated with a greater number of single embryo transfers and, thus, reduces the chance of multiple pregnancy. However, it is becoming increasingly clear that PGT-A does not shorten the time to establish an ongoing pregnancy compared with fresh morphologically selected embryo transfers (4).

The STAR trial was a large randomized controlled trial of PGT-A. Participants in the STAR trial had a normal ovarian reserve and were required to have at least 2 blastocysts eligible for biopsy by day 6 of development. Even in this favorably selected group, the STAR trial failed to find any advantage of PGT-A when evaluated on an intention-to-treat basis (5). When the STAR investigators mapped Gardner scores to good, fair, or poor quality, the PGT-A randomized group had more poor-quality embryos transferred than controls, from which we can infer that the PGT-A result led to the transfer of morphologically poorer embryos.

Some observational studies of PGT-A have found improved ongoing pregnancy rates when PGT-A is performed in older patients compared with patients of the same age who did not have PGT-A. However, improved pregnancy outcomes among older patients undergoing PGT-A may just reflect that their better ovarian reserve provided enough embryos to make them eligible for PGT-A screening.

The STAR trial was unable to show a reduction in miscarriage risk associated with the transfer of PGT-A screened embryos (5). Even if PGT-A were to reduce the chance of miscarriage, then the cost of having fewer miscarriages might well be an overall reduction in cumulative pregnancy rates because embryos that could have resulted in ongoing pregnancy would be deselected by the PGT-A process and never transferred. Our patients come to us to establish an ongoing pregnancy. Embryos that are never transferred cannot establish a pregnancy. Miscarriage is an accepted risk of older women trying to establish a pregnancy naturally. Shall we now recommend all women should have PGT-A as a means of reducing the risk of miscarriage?

The case reported by Lin et al. (1) is the exception that proves the rule. Others have argued that any pregnancy resulting after the transfer of embryos with fully aneuploid TE biopsy will have resulted from sample mix-up, analytic error, or the establishment of a natural pregnancy. Although we must acknowledge that there is still the possibility of a sample mix-up or analytic error, establishing a natural pregnancy seems unlikely for this female same-sex couple. Lin et al (1) tell us that Igenomix found approximately 40% of embryos reported to have ≥ 6 aneuploidies were euploid on rebiopsy. Thus, an analytic error is a very real possibility. However, whether because of error, mix-up, or self-correction of the embryo: transfer of this embryo with a fully aneuploid chaotic biopsy report has resulted in the birth of a healthy viable infant. If the investigators and patients had accepted the results of the biopsy, this infant would not be here. One must wonder about the many other couples who have been advised not to transfer such embryos and the children who might have been.

David H. Barad, M.D
Director Assisted Reproductive Technology, Center For Human Reproduction, New York, New York.

https://doi.org/10.1016/j.xfre.2022.11.004

REFERENCES

1. Lin J, Vitek WS, Scott EL. Order from chaos: case report of a healthy live birth from a genetically "chaotic" embryo. F&S Reports 2022;3:301–4.
2. Kimelman D, Confino R, Confino E, Shulman LP, Zhang JX, Pavone ME. Do patients who achieve pregnancy using IVF-PGS do the recommended genetic diagnostic testing in pregnancy? J Assist Reprod Genet 2018;35:1881–5.
3. Klimczak AM, Seli E, Scott RT Jr. Noninvasive prenatal testing in women undergoing in vitro fertilization with preimplantation genetic testing. Curr Opin Obstet Gynecol 2021;33:184–7.
4. Yan J, Qin Y, Zhao H, Sun Y, Gong F, Li R, et al. Live birth with or without preimplantation genetic testing for aneuploidy. N Engl J Med 2021;385:2047–58.
5. Munné S, Kaplan B, Frattarelli JL, Child T, Nakhuda G, Shamma FN, et al. Preimplantation genetic testing for aneuploidy versus morphology as selection criteria for single frozen-thawed embryo transfer in good-prognosis patients: a multicenter randomized clinical trial. Fertil Steril 2019;112:1071–9.e7.