Preimplantation genetic screening: what is the clinical efficiency?

In the current practice of in vitro fertilization (IVF), preimplantation genetic screening (PGS) is increasingly used to select embryos for transfer. This strategy is designed to maximize the probability of embryo implantation by eliminating embryos with low implantation potential from the cohort. However, PGS is inherently imperfect. Errors may occur during the genetic analysis of the small amount of DNA collected. More importantly, mitotic mosaicism, whose precise incidence in the preimplantation embryo is not known, may lead to sampling errors due to the intentionally limited collection of cells in the trophectoderm biopsy. In this manner, abnormal cells may be collected in an otherwise euploid embryo and vice versa. Therefore, it is inevitable that some normal embryos will be discarded, leading to an overall decrease in the cumulative pregnancy rate achievable by the eventual transfer of all embryos in the cohort.

To accurately counsel patients about the use of PGS, it is important to understand its clinical efficiency: How reliable are the results, and how many losses of potential implantations occur as a result of the procedure? In the only study to date in which biopsied embryos were transferred and the results of PGS were available only after the outcomes of the transfers were known, 41% of the "normal" embryos and 4% of the "abnormal" embryos implanted, suggesting a 10% error rate (1), and a 96% negative predictive value of an "abnormal" test result.

However, this study does not present a complete picture of the clinical efficiency of PGS. The efficiency of PGS may be further limited by the very real possibility of damage to the blastocyst as result of the trophectoderm biopsy. Only one study so far has directly addressed this issue (2), and no deleterious effect of the trophectoderm biopsy on embryo implantation was found. However, all of the patients in that study were under the age of 35 years and transfers took place within 3 hours after the biopsy. No studies have addressed the impact of trophectoderm biopsy in embryos with less than ideal morphologic characteristics, in older patients, or after an intervening cryopreservation procedure.

If the efficiency of PGS were 100%, then all embryos judged to be "abnormal" would have a 0% chance of implantation and their exclusion from transfer would result in an increased implantation rate of the remaining "normal" embryos. This idealized embryo implantation rate, EI(idealized), would be higher than the implantation rate of unscreened embryos, EI(unscreened), by the proportion of embryos that were normal:

$$\mathrm{EI(idealized)} = \frac{\mathrm{EI(unscreened)}}{\%\ \text{normal}}$$

This is an idealized model, and because testing is unlikely to be perfect the actual embryo implantation rate of screened embryos, EI(screened), will likely be lower than the calculated EI(idealized). The efficiency of the screening process can then be expressed as:

$$\text{Efficiency} = \frac{\mathrm{EI(screened)}}{\mathrm{EI(idealized)}}$$

The percentage of embryos lost in the process can then be calculated as:

$$\%\ \text{embryos lost} = 1 - \text{Efficiency}$$

The depiction of this analysis is most easily demonstrated in a graphic fashion. For this example, let us consider a hypothetical cohort of embryos from "good-prognosis" patients (2), under the age of 35 years, with multiple blastocysts in the 4AA or 4BB category, an unscreened implantation rate of 50%, and an "aneuploidy" rate of 40%. In the parlance of this calculation:

$$\mathrm{EI(unscreened)} = 0.50$$

$$\%\ \text{normal} = 60\% = 0.60$$

Figure 1 shows a hypothetical cohort of 100 embryos, 50 of which would implant if transferred. If these embryos are screened with the use of PGS and 40% are found to be "aneuploid," the screening test would eliminate 40 presumably low–implantation potential embryos from the cohort (Fig. 2). In this idealized setting, only nonimplanting embryos are eliminated, and of the remaining 60 embryos, all 50 of the original implanting embryos would be expected to implant (Fig. 3).

$$\mathrm{EI(idealized)} = \frac{\mathrm{EI(unscreened)}}{\%\ \text{normal}}$$

$$= \frac{0.50}{0.60} = 0.833$$

Because implantation rates this high have not been reported, let us consider a hypothetical implantation rate of 66.7%, which would clearly be a major improvement over the baseline rate of 50%. In this theoretical example:

$$\mathrm{EI(screened)} = 0.677$$

$$\text{Efficiency} = \frac{\mathrm{EI(screened)}}{\mathrm{EI(idealized)}}$$

$$= \frac{0.667}{0.833}$$

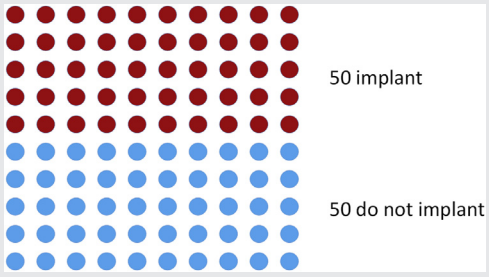
$$= 0.80$$

The embryo loss rate would be:

$$\%\ \text{embryos lost} = 1 - 0.80 = 0.20$$

This is depicted graphically in Figure 4. With a post-PGS implantation rate of 66.7%, 40 of the remaining 60 embryos would implant, representing a loss of 10 of the original 50

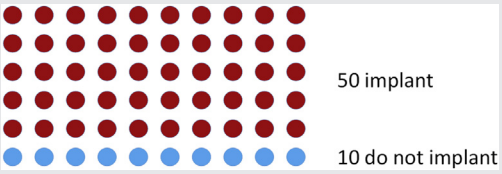
FIGURE 1



Hypothetical cohort of 100 "good-prognosis" embryos. The embryo impantation rate is 50%, therefore, 50 are expected to implant and 50 are expected not to implant. *Red dots* represent normal embryos, which have the potential to implant. *Blue dots* represent embryos that do not have the potential to implant.

Paulson. Inklings. Fertil Steril 2017.

FIGURE 3



Forty percent of the original cohort of 100 embryos has been eliminated, leaving 60 embryos. Because all of the "abnormal" embryos came from the "do not implant" group, only 10 of those remain, whereas all 50 of the "implant" group are still present. *Red dots* represent normal embryos, which have the potential to implant. *Blue dots* represent embryos that do not have the potential to implant.

Paulson. Inklings. Fertil Steril 2017.

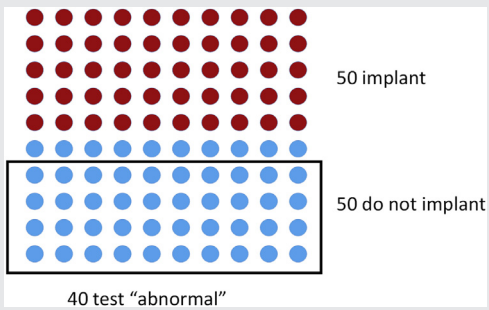
implantations, or 20% loss of normal embryos that would otherwise have implanted. This example illustrates that a very good, statistically significant, improvement in implantation rate from 50% to 66.7% is associated with a 20% loss rate of potential implantations.

However, most centers do not experience post-PGS implantation rates above 60%. The Society for Assisted Reproductive Technology (SART) registry report for 2014 for the first time includes data on embryo implantation rates with and without PGS (3). In women under the age of 35 years with elective single-embryo transfer (eSET), similar implantation rates are observed with and without PGS: Applying the filter "include only eSET and PGS" demonstrates a 50.9% live birth rate for this group; applying the filter "include only eSET and exclude PGS" reveals a similar 50.6% live birth rate for this same age group. These data are similar to those of Kang et al. (4), who performed an analogous retrospective analysis of eSET in PGS and control cycles. The authors found implantation rates to be similar, with a 54% implantation rate in both groups and live birth rates of 50% and 47%, respectively.

To estimate the efficacy of PGS in these real-world examples, let us consider an approximate implantation rate of 50% in both PGS and control groups. Aneuploidy rates are not reported in the SART registry, but the previously reported aneuploidy rate of 40% (2) has been confirmed by a large multicenter retrospective series (5) and seems to be a good approximation. Applying the calculations presented here, we arrive at Figure 5, with 40% of embryos removed from the original cohort by PGS testing and 50% of the remaining cohort of embryos achieving implantation. The percentage of embryos lost due to PGS is 40% (Fig. 5).

The application of this type of mathematical reasoning to clinical data is limited by the way that implantation rates are reported, because typically only results of the first embryo transfer are reported. We do not know what happens during the next (frozen) embryo transfer. Therefore, the calculation presented here is only one approximation. Calculating the true clinical efficiency of the entire cohort of embryos would require the transfer of all of the embryos in the cohort and an

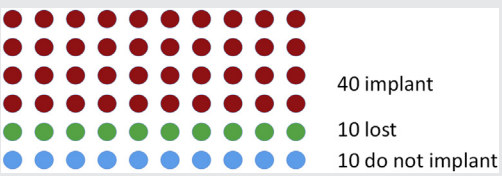
FIGURE 2



Embryo screening reveals that 40% of the original cohort are abnormal. All of these are expected to be in the "do not implant" group and are eliminated from the subsequent embryo transfer procedures. *Red dots* represent normal embryos, which have the potential to implant. *Blue dots* represent embryos that do not have the potential to implant.

Paulson. Inklings. Fertil Steril 2017.

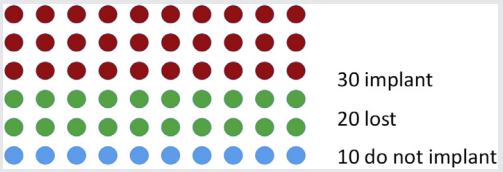
FIGURE 4



Hypothetical example of a 66.7% post–preimplantation genetic screening implantation rate: 40 embryos of the remaining 60 embryos implant. This represents a significant increase in implantation rates, but also a loss of 10 embryos from the original "implant" group. Because 10 of the original 50 implantations were lost, this is a loss of 20% of the potential implantations. *Red dots* represent normal embryos, which have the potential to implant. *Blue dots* represent embryos that do not have the potential to implant. *Green dots* represent embryos that are lost owing to the inefficiency of the embryo screening process.

Paulson. Inklings. Fertil Steril 2017.

FIGURE 5



A "real-world" example of an actual 50% post–preimplantation genetic screening implantation implantation rate: 40 embryos are eliminated by the screening test, and 30 of the remaining 60 embryos implant. Because 20 of the original 50 normal embryos have been lost, this is a loss of 40% of potential implantations. *Red dots* represent normal embryos, which have the potential to implant. *Blue dots* represent embryos that do not have the potential to implant. *Green dots* represent embryos that are lost owing to the inefficiency of the embryo screening process.

Paulson. Inklings. Fertil Steril 2017.

assessment of the cumulative pregnancy rate after all of the embryos are transferred. Nevertheless, the calculation presented here is an important part of the overall picture of the risk and benefit of PGS, especially if PGS is applied as a screening test to every IVF cycle performed in a given center.

Genetic analysis of the preimplantation human embryo is a novel technique that promises to rid humanity of hundreds of inherited genetic diseases by testing for them before embryo transfer. Information about the ploidy of these embryos likewise promises to significantly decrease the probability of Down syndrome or other trisomic pregnancies that lead to abnormal births or miscarriages. However, we must be cognizant of the reality that this type of screening is inherently inefficient and that many normal embryos are discarded. The proportion of normal embryos that are discarded likely varies among clinical settings, but it may be as high as 40% in the current practice of PGS. Individual programs may need to examine their own rates of embryo implantation with and without PGS and calculate their embryo loss rate. We owe it to our patients to understand the clinical efficiency of PGS in order to provide a true picture of the risks and benefits of this procedure and to attain true informed consent.

Richard J. Paulson, M.D.
Department of Obstetrics and Gynecology, University of Southern California Keck School of Medicine, Los Angeles, California

http://dx.doi.org/10.1016/j.fertnstert.2017.06.023

You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/17988-24506

REFERENCES

1. Scott RT Jr, Ferry K, Su J, Tao X, Scott K, Treff NR. Comprehensive chromosome screening is highly predictive of the reproductive potential of human embryos: a prospective, blinded, nonselection study. Fertil Steril 2012;97:870–5.
2. Scott RT Jr, Upham KM, Forman EJ, Zhao T, Treff NR. Cleavage-stage biopsy significantly impairs human embryonic implantation potential while blastocyst biopsy does not: a randomized and paired clinical trial. Fertil Steril 2013;100:624–30.
3. Society for Assisted Reproductive Technology. Final CSR for 2014. Available at: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2014. Accessed June 7, 2017.
4. Kang H-J, Melnick AP, Stewart JD, Xu K, Rosenwaks Z. Preimplantation genetic screening: who benefits? Fertil Steril 2016;106:597–602.
5. Ata B, Kaplan B, Danzer H, Glassner M, Opsahl M, Tan SL, et al. Array CGH analysis shows that aneuploidy is not related to the number of embryos generated. Reprod Biomed Online 2012;24:614–20.