The use of preimplantation genetic testing for aneuploidy: a committee opinion

Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

American Society for Reproductive Medicine, Washington, DC

The use of preimplantation genetic testing for aneuploidy (PGT-A) in the United States has been increasing steadily. Moreover, the underlying technology used for 24-chromosome analysis continues to evolve rapidly. The value of PGT-A as a routine screening test for all patients undergoing in vitro fertilization has not been demonstrated. Although some earlier single-center studies reported higher live-birth rates after PGT-A in favorable-prognosis patients, recent multicenter, randomized control trials in women with available blastocysts concluded that the overall pregnancy outcomes via frozen embryo transfer were similar between PGT-A and conventional in vitro fertilization. The value of PGT-A to lower the risk of clinical miscarriage is also unclear, although these studies have important limitations. This document replaces the document of the same name, last published in 2018. (Fertil Steril® 2024;122: 421–34. ©2024 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

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Traditionally, morphology-based grading had been the primary technique used in in vitro fertilization (IVF) to evaluate and select the most competent embryo for transfer. Technologies have been developed in the fields of genomics, transcriptomics, proteomics, metabolomics, time-lapse imaging, and artificial intelligence to try to assist in the selection of the best embryos. However, the primary focus has been on analysis of 24-chromosome copy number for evaluation and transfer of only euploid embryos, also known as preimplantation genetic testing for aneuploidy (PGT-A). Several molecular techniques have been used during IVF cycles to determine ploidy including fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), array CGH (aCGH), digital polymerase chain reaction, single-nucleotide polymorphism (SNP) array, real-time quantitative PCR (qPCR), and next-generation sequencing (NGS). These technologies vary in terms of methodology, the number of chromosomes analyzed, algorithms used, cost, and time to completion.

The earliest iterations of PGT-A evaluated a subset of the chromosomes primarily using FISH to examine 5–10 unique chromosomes. Despite the hypothesis that exclusion of aneuploid embryos from transfer should improve IVF outcomes, all but one randomized controlled trial (RCT) of this initial approach failed to demonstrate a benefit (1, 2). Since 24-chromosome techniques have become available, there have been few well-designed studies providing high-quality evidence regarding IVF pregnancy outcomes in select populations with these techniques (3, 4).

The use of PGT among patients undergoing IVF in the United States has been increasing steadily. On the basis of national data from the Society for Assisted Reproductive Technology (SART), the proportion of IVF cycles using PGT has increased from 14% in 2014 to 44% in 2019 (5, 6). The aim of this communication is to review the current evidence and provide guidance for the continued use of PGT-A in IVF.

CLINICAL OUTCOMES IN FAVORABLE-PROGNOSIS PATIENTS

Literature search revealed 5 RCTs, several retrospective cohort studies, meta-analyses, and a systematic review. A 2012 pilot study randomized 112 favorable-prognosis patients (age <35 years, tubal or male factor infertility, and no prior IVF treatment) to either day-5 aCGH after trophectoderm biopsy plus morphology assessment or traditional morphology assessment alone for selection of the single best embryo on day 6 (7). Ongoing per transfer pregnancy rates after fresh D6 single-embryo transfer (SET) were significantly higher in the aCGH group compared with the traditional

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Correspondence: Practice Committee, American Society for Reproductive Medicine, Washington, DC (E-mail: asrm@asrm.org).

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morphology group (69.1% vs. 41.7%, $P=.009$). Of note, time to pregnancy was not reported, nor was the total reproductive potential of the cycle. There was no statistically significant difference in miscarriages or multiples between the groups, although the study was not powered to address these outcomes. Biopsy for aCGH could not be completed in 32 blastocysts in the study group because of embryo degeneration or poor morphology and failure of amplification resulting in ''no signal'' after biopsy was performed in 8 blastocysts. Interestingly, for these favorable-prognosis patients, the investigators found a blastocyst aneuploidy rate of 44.9% (191/425 biopsied blastocysts). The investigators acknowledged their small numbers and limited study population but concluded that outcomes with elective single-embryo transfer (eSET) are substantially improved with the addition of aCGH testing to the traditional screening methodology.

Another group of investigators from a single center performed 2 RCTs, comparing pregnancy rates after transfer of morphologically graded embryos (controls) vs. euploid embryos, using rapid qPCR-based PGT-A (8). First, they hypothesized that SET with a euploid embryo would result in an equivalent pregnancy rate compared with double-embryo transfer (DET) of morphologically graded embryos. There were 175 patients (mean age 35.1 and 34.5 years for the study and control groups, respectively) who were eligible for randomization on the basis of having at least 2 expanded blastocysts (most were randomized on day 5, but some did not have adequate blastocysts until day 6 of embryo development). The overall rate of aneuploidy was 31% (162/521) in the study group (mean maternal age 35.1 $\pm$ 3.9 years). The primary outcome of ongoing pregnancy beyond 20 weeks per transfer was similar between the study and control groups (60.7% [54/89] vs. 65.1% [56/86]). The secondary outcome of clinical miscarriage was similar also between the study and control groups, although the study was not powered to address this outcome. The multiple pregnancy rate for patients in the study group was significantly lower than that in the control group (0% [0/54] vs. 53.4% [31/56]). The investigators concluded that transfer of a single euploid blastocyst was noninferior in terms of ongoing pregnancy rates (OPRs) compared with transfer of 2 blastocysts with an unknown chromosome status.

A second study by the same group randomized women with 2 or more blastocysts on day 5 to biopsy with rapid qPCR-based PGT-A on day 5 and transfer on day 6 ($n = 72$) or the control group with morphologic grading and embryo transfer on day 5 ($n = 83$) (9). There was no significant difference in the mean maternal age or the number of high-quality blastocysts between the subjects and controls (7.1 and 6.2 blastocysts for the study and control groups, respectively). Patients in the control group had significantly more embryos transferred than the PGT-A group (2.0 vs. 1.86, $P<.001$), and the investigators explain that this was due to 10 patients in the study group having only 1 euploid embryo for transfer whereas all patients in the control group underwent DET. They report that clinical implantation rates were significantly higher in the PGT-A vs. control group (79.8% [107/134] vs. 63.2% [103/163], $P=.002$). In addition, the proportion of PGT-A screened embryos that progressed to delivery was significantly higher than the control group embryos (66.4% [89/134] vs. 47.9% [78/163], $P=.001$). Analysis of secondary outcomes demonstrated a higher delivery rate per cycle in the PGT-A vs. control group (84.7% [61/72] vs. 67.5% [56/83], $P=.01$). On the basis of the reported data, the calculated spontaneous abortion rates for the PGT-A and control groups were 8.9% and 21.1%, respectively, and twin rates were approximately 59.7% and 45.1%. The investigators concluded that trophectoderm biopsy with rapid qPCR-based PGT-A improves the chance of sustained implantation and delivery rates over traditional embryo selection.

It is worth noting that there are significant limitations to these RCTs. Specifically, randomization occurred only for patients who had a number of good-quality blastocyst embryos, which likely means that these are favorable-prognosis patients. If randomization occurred at the start of the cycle, some percentage of those in the PGT-A group would not have had embryos to biopsy or transfer, thus likely altering the success rates in that cohort, on the basis of intent-to-treat analysis. In addition, 2 of these studies were performed at a high-volume PGT-A clinic, which may limit generalizability to smaller programs. Another limitation is that these studies may not be reflective of current clinical practice, as most clinics biopsy embryos on day 5 and 6 vitrify and thaw in a later cycle. Although vitrified and thawed cycles have been postulated to have some benefits, there are likely to be some embryos that do not survive the thaw. In addition, instead of qPCR or aCGH that was used in these RCTs, many clinics now use the NGS technology owing to its potential increased efficiency and precision along with a lower cost (10).

A 2019 multicenter, RCT (STAR) evaluated the impact of PGT-A with NGS on frozen embryo transfers (FETs) (3). The study was conducted at 34 clinics in 9 laboratories for PGT-A testing. The genetic laboratories followed their own internally validated criteria for identification of PGT-A results. The trial excluded patients over 40 years of age, those who had multiple miscarriages, and those who had multiple IVF failures. The trial randomized 661 patients aged 25–40 years (average age: 33.7) with at least 2 blastocysts that could be biopsied, to either PGT-A ($n = 330$) or morphology alone ($n = 331$). The OPR at 20 weeks' gestation was similar between the PGT-A and the control arms, with no significant difference per embryo transfer (50% [137/274] vs. 46% [143/313], PGT-A vs. control, respectively) or per intention to treat (ITT) at randomization (41.8% [138/330] vs. 43.5% [144/331], PGT-A vs. control, respectively). Post hoc analysis of women aged 35–40 years showed a significant increase in OPR per embryo transfer (51% [62/122] vs. 37% [54/145]) but not per ITT. For women <35 years of age, 52.0% of embryos were aneuploid whereas for women of 35–40 years, 64.5% of embryos were aneuploid. Of the abnormal embryos, 31.0% were found to have a whole or partial chromosome mosaic aneuploidy for 1 or more chromosomes. Mosaic embryos were excluded from embryo transfer in this study which resulted in exclusion of 25 patients with 1 or more mosaic embryo results. There was a wide range in the percentage of euploid embryos on the basis of the laboratory involved. The small number of patients enrolled per laboratory prevented statistical comparison.

The investigators concluded that PGT-A did not improve pregnancy outcomes in all women, as analyzed per embryo transfer or per ITT.

Another multicenter randomized controlled noninferiority trial from 2021 randomized women in China between age 20 and 37 with 3 or more good-quality blastocysts to undergo PGT-A with NGS (n = 606) vs. conventional IVF (n = 606) (4). Patients underwent up to 3 sequential embryo transfers up to 1 year after randomization. A total of 1,212 patients underwent randomization. Live births occurred in 468 women (77.2%) in the PGT-A group and in 496 (81.8%) in the conventional IVF group (absolute difference, −4.6 percentage points; 95% confidence interval [CI], −9.2 to −0.0; $P<.001$). The cumulative frequency of clinical pregnancy loss was 8.7% and 12.6%, respectively (absolute difference, −3.9 percentage points; 95% CI, −7.5 to −0.2). The average age of patients undergoing PGT-A was 29.1. Of the embryos analyzed, 69.8% were euploid, 17.2% were aneuploid, 11.7% were mosaic, and 1.4% did not yield an interpretable result. Mosaic embryos were not transferred in the study protocol. The investigators concluded that conventional IVF resulted in a cumulative live-birth rate that was noninferior to that with PGT-A. Although the frequency of pregnancy loss among clinical pregnancies appeared to be lower in the PGT-A group, this differential did not translate into a higher cumulative live-birth rate or shorter mean time until a live birth. Unlike typical clinical practice where all good-quality blastocysts undergo biopsy for PGT-A, the study group only had 3 blastocysts biopsied, even if more were available. Therefore, some patients in the study group had fewer than 3 embryo transfers performed. Thus, rather than a true noninferiority trial, the study was more of a safety study and there was no decrease in the cumulative pregnancy rate with PGT-A.

Analysis of data from the SART from 2019 has found that the use of PGT-A is associated with higher implantation rates and lower miscarriage rates, particularly in older age groups. Implantation rates with and without PGT-A, respectively, in the SART age groups are as follows: <35: 62.7% vs. 54%; 35–37: 60.7% vs. 44.9%, 38–40: 59.5% vs. 30.0%; 41–42: 56.1% vs. 17.9%; and 43+: 53.7% vs. 7.4%. The miscarriage rates with and without PGT-A, respectively, are as follows: <35: 11.2% vs. 15.4%; 35–36: 13.0% vs. 20.3%; 38–40: 13.6% vs. 27.7%; 41–42: 13.9% vs. 37.9%; and 43: 18.3% vs. 51.5% (11). PGT-A of embryos appeared to improve the likelihood of having a live birth among women >37 years, with 1 study showing that 21 cycles (or 35 embryo transfers) as the number needed to treat with PGT-A to have 1 additional live birth (12). In this study, cycles that were intending PGT-A were more likely to reach embryo transfer in all age groups, but more significantly in women aged >37. This likely indicates that these women are from a patient cohort with a better prognosis and makes it difficult to isolate the benefit of PGT-A vs. the intrinsic likelihood for success in these patients. A retrospective study from a large US clinic from 2010 to 14 found similar results with autologous fresh non-PGT-A cycles vs. frozen cycles with PGT-A tested euploid embryos (13). When looking at clinical pregnancy, miscarriage, or live-birth rates, there was no difference between PGT-A and non-PGT-A cycles for women aged ≤37 years, and for women aged >37 years, there was no difference when comparing on a per cycle basis.

A Cochrane Database systematic review was performed and it included 13 trials involving 2,794 patients. The quality of evidence was low to moderate. Only 1 trial was included utilizing blastocyst stage biopsy analyzing 24 chromosomes with NGS. The remainder looked at polar body biopsy or cleavage-stage biopsy utilizing FISH or 24-chromosome testing or blastocyst biopsy utilizing FISH. It was concluded that there was insufficient good-quality evidence of a difference in cumulative live-birth rate, live-birth rate after the first embryo transfer, or miscarriage rate with and without PGT-A (14).

OTHER SUBSETS OF PATIENTS

Advanced maternal age

The aforementioned studies were performed in either young or overall favorable-prognosis patients without stratified analysis for age in most cases. However, post hoc analysis of the STAR trial showed increased OPR per embryo transfer in patients 35–40 years old (3). Given the increased aneuploidy rates in older women, pragmatic trials with ITT analysis specifically addressing this patient population are needed. There was 1 RCT that focused on women with advanced maternal age (38–41 years old), randomizing before cycle start to routine blastocyst transfer vs. a PGT-A group that had a biopsy of a single blastomere on day 3 with transfer on day 5 (15). The live-birth rate was significantly higher in the PGT-A group when analyzed per transfer (52.9% vs. 24.2%, $P=.0002$) and per cycle (36% vs. 21.9%, $P=.031$). Of note, only 68% of the PGT-A patients had a transfer vs. 95% in the control group ($P=.001$). The miscarriage rate was significantly lower in the PGT-A group (2.7% vs. 39%, $P=.0007$). Of all cleavage embryos that were biopsied, they got results for 97.2%, and 78.6% of embryos were aneuploid. There was no statistically significant difference in live-birth rates when they included outcomes for FET cycles for the 6 months after the study (37% vs. 33.3% in controls) and the time to pregnancy was 4.5 weeks with PGT-A and 5.8 weeks with controls (P is not significant). Time to pregnancy resulting in live birth was estimated at 7.7 weeks for the PGT-A group vs. 14.9 weeks for controls.

Retrospective studies suggest a benefit of PGT-A testing in older patient cohorts, particularly in women up to age 43 years (improved live-birth rate per cycle start seen in women aged 38–40 years with PGT-A) (16) and improved implantation rates in women of 40–43 years (implantation rate was 50.9% in euploid embryos compared with unscreened fresh [23.8%] and FET [25.4%] cycles) (17). The retrospective nature, inclusion criteria, and small numbers limit these studies; in particular, 1 study stratified groups by age, thus comparing only 8 cycles per group in the oldest age cohort (12), whereas another only included women with euploid embryos to transfer (only 76 of 145 patients had euploid blastocysts to transfer [52.4%]) (13). Furthermore, there is potential bias because only good-prognosis patients who were able to have a biopsy would have been included in the PGT-A group. The investigators in both groups believe that the improved

pregnancy success demonstrates a benefit of PGT-A; however, the study methodologies leave questions regarding these conclusions. An observational prospective cohort study of patients aged 38–44 years from a single center demonstrated that PGT-A use is associated with a higher per transfer but not cumulative live-birth rates and lower multiple pregnancy and miscarriage rates compared with controls. However, a significant number of patients (106/414) withdrew consent to PGT-A after fertilization results became available (most having less than 5 normally fertilized oocytes), which introduces a selection bias in the PGT-A group toward more favorable prognosis (18). Given these data, PGT-A may have a beneficial role in patients of advanced maternal age, especially those with good ovarian reserve.

Use of donor oocytes

Regarding donor oocyte IVF cycles, the benefit of PGT-A was considered in a cohort study of 31 PGT-A cycles compared with 39 control cycles. PGT-A cycles showed no statistically significant difference in ongoing/live-birth rates (64.4% vs. 54%) or in miscarriage rates (19.2% vs. 9.5%) (19). The small numbers likely explain the heterogeneity of the study, thus limiting statistical power. Another group demonstrated a 15% aneuploidy rate in PGT-A tested embryos from donor oocyte cycles; yet clinical pregnancy rates decreased when PGT-A tested embryos were used (20). Studies demonstrate that the euploidy rates of donor oocyte-derived embryos vary by the fertility center, embryology and genetic testing laboratory (21–23). A retrospective cohort study on the basis of the SART database (2005–2013) suggested that the use of PGT-A is associated with reduced live-birth rates in donor oocyte cycles (odds ratio [OR], 0.65, 95% CI, 0.53–0.80; $P<.001$) (24). However, this study did not account for embryos derived from frozen vs. fresh oocytes, slow freeze or vitrification, or cleavage vs. blastocyst biopsies. Another retrospective cohort study analyzed the outcomes of fresh donor oocyte-derived embryos and compared euploid SET to fresh and frozen untested embryo transfers, and no difference was found in pregnancy and live-birth rates (25). Fresh embryo transfers showed higher implantation rates in this study, which is consistent with the evidence that fresh embryo transfers from fresh donor eggs are associated with higher live-birth rates compared with frozen and thawed embryos (26). Given that most PGT-A cycles require cryopreservation, the potential impact of freezing and thawing on embryos derived from donor oocytes needs to be considered in decision-making. Similar to the previous study, an additional retrospective cohort study showed no benefit of PGT-A in donor oocyte cycles (27). A retrospective paired cohort study of vitrified donor oocytes from an egg bank allowed the comparison of outcomes between PGT-A tested and untested embryos from the same donor (i.e., a single donor served as her own control because of the use of multiple egg lots from the same patient) and did not show a difference in live-birth rates after first embryo transfer (53.8% in the PGT-A group vs. 55.8% in the no PGT-A group, $P=.44$) and live-birth rate per transfer when all transfers from the same egg lot were analyzed (48.4% in the PGT-A group and 47.2% in the non-PGT-A group, $P=.700$). The median euploidy rate per recipient was 75% (22). Given the high probability of multiple pregnancy if more than 1 embryo (with or without PGT-A testing) derived from donor oocytes is transferred, SET should be the approach in most (if not all) cases, especially when the gestational carrier is used (28, 29). In addition, the use of PGT-A in fresh donor oocyte cycles does not appear to be cost-effective (30). Overall, the totality of evidence argues against the routine use of PGT-A in donor egg cycles.

Advanced paternal age

The impact of advanced age on semen parameters is well established and the mean paternal age is increasing (31). Advanced paternal age (APA) has been associated with stillbirth, congenital anomalies, single gene defects, and adverse neurodevelopmental outcomes (32). Approximately 10% of Down syndrome cases are paternal in origin; however, the impact of APA on the incidence of trisomy 21 and other aneuploidies is controversial because of lack of controls for maternal age in most cases (32). The use of donor oocytes accounts for this confounder. One multicenter retrospective case series with 1,202 oocyte donor intracytoplasmic sperm injection (ICSI) cycles, blastocyst biopsy, and PGT-A with NGS failed to demonstrate any association between embryo aneuploidy and paternal age (33). These data were corroborated by a similar study which assessed the aneuploidy rates in 3,118 embryos derived from oocyte donors and showed no association between paternal age and the embryo chromosomal status (34). However, age $\geq$50 years was associated with increased segmental aneuploidy rate according to this study. Similarly, meta-analysis of 3 retrospective studies did not demonstrate an association between the paternal age and embryo aneuploidy when oocyte donors were used (35). It is not clear whether adverse effects of APA on embryo ploidy manifest itself when superimposed on advanced maternal age (i.e., higher quality donor oocytes may have compensatory mechanisms that counteract genetic and epigenetic defects in sperm). However, the available evidence suggests that routine PGT-A testing should not be performed for APA.

Elective single-embryo transfer

Live-birth rates after eSET of a euploid embryo from women across the reproductive aging spectrum are similar or only slightly decreased (but still >50%) with advancing age (36, 37). ASRM recommends the transfer of a single euploid embryo regardless of age in effort to promote singleton and reduce multiple gestations (38). Therefore, use of PGT-A may increase the utilization of eSET. In a retrospective analysis of 382 embryo transfers, similar live-birth rates were observed in good-prognosis patients (<38 years old, at least 2 frozen blastocysts) with eSET of a euploid embryo compared with the transfer of 2 euploid embryos (56% vs. 57%). However, multiple pregnancy rates were significantly higher with DET (0% vs. 65%). Live-birth rates following DET of untested blastocysts were not significantly different from eSET of a euploid embryo (66% vs. 56%, respectively); however, the multiple pregnancy rate was significantly higher in the

DET group (45% vs. 0%) (39). A 2015 study compared IVF success before and after a change in the clinical protocol designed to decrease the number of embryos transferred in patients older than 35 years. eSET was offered in patients with fewer than 2 implantation failures if favorable embryo morphology and/or PGT-A screening occurred. There were no significant differences in clinical pregnancy rates per transfer before and after the change in protocol, but there was a significant increase in live-birth rates per embryo transfer cycle for the eSET/PGT-A recipients. However, only 43.6% of PGT-A cycles had at least 1 euploid embryo to transfer. When comparing live-birth rates per cycle, there was no significant difference between groups (20.9% without PGT-A vs. 24.4% with PGT-A) (40).

RECURRENT PREGNANCY LOSS

The mechanism of first-trimester pregnancy loss is largely due to aneuploidy, providing biologic plausibility for PGT-A. An analysis of a retrospective cohort study (118 PGT-A vs. 188 expectant management) demonstrated similar clinical pregnancy rates and miscarriage rates between the 2 groups (41), although the time to successful pregnancy was statistically shorter in the expectant management group (3.0 vs. 6.5 months, respectively). Of the PGT-A cohort, 77% were able to create embryos that were tested and, of those, 74% had at least 1 euploid embryo to transfer.

A retrospective analysis of the SART-CORS database compared couples with recurrent pregnancy loss (RPL) undergoing FET with or without PGT-A and found a significantly higher live-birth rate with PGT-A with an adjusted OR of 1.31 (95% CI 1.12, 1.52) for age <35, 1.45 (95% CI 1.21, 1.75) for ages 35–37, 1.89 (95% CI 1.56, 2.29) for ages 38–40, 2.62 (95% CI 1.94–3.53) for ages 41–42, and 3.8 (95% CI 2.52, 5.72) for ages >42 (42). After adjusting for covariates, no difference in rates of spontaneous abortions were seen. This study was restricted to couples already undergoing FET, limiting generalizability to couples pursuing IVF with PGT-A as a primary treatment of RPL. These studies are limited by their retrospective design, which makes it difficult to interpret potentially different clinical prognoses for those who did or did not pursue PGT-A.

A prospective study explored the relationship between ovarian reserves in patients with RPL and found that in women younger than 38 years, decreased ovarian reserve (defined as a cycle day-3 follicle-stimulating hormone level >10 mIU/mL and/or anti-mullerian hormone <1 ng/mL) resulted in a significantly lower likelihood of having a euploid embryo to transfer compared with women with normal ovarian reserve testing (43). These studies can assist in personalizing the counseling for patients considering PGT-A, regarding one's likelihood of successfully obtaining a euploid embryo from the technology. It is worth noting that the increased rate of aneuploidy with decreased ovarian reserve is likely not unique to the RPL population (44). However, to date, definitive evidence of the benefit of PGT-A in this patient population is lacking.

FROZEN EMBRYO TRANSFER CYCLES

Because of logistical, technical, and cost requirements, currently, most clinics performing PGT-A do not process cells for ploidy assessment in-house. In addition, blastocysts can be biopsied on day 5, 6, or 7, and therefore, most euploid blastocysts are transferred in cryopreservation (vs. fresh) cycles. Data from 1 retrospective cohort study support equal or superior reproductive potential for frozen euploid blastocyst transfers (vs. fresh euploid blastocyst transfers) with higher implantation and live-birth rates, and lower miscarriage rates (45). Additional plausible benefits may include a lower incidence of both ovarian hyperstimulation syndrome and multiple gestation if eSET is used. Limitations include the retrospective nature of the study and potential limited generalizability because of the need for good-quality blastocysts for inclusion in this study. One prospective single-center RCT randomized 179 patients planning PGT-A with NGS at the time of hCG to either "freeze-all" or fresh day 6 embryo transfer (46). ITT analysis demonstrated a significantly higher ongoing pregnancy rate (PR) (50.9% vs. 62.2%; $p < 0.1$) and live birth rate (LBR) (39.8 vs. 61.5%; $p < 0.1$) for the freeze-all group. A per protocol analysis included 46 patients who underwent a fresh euploid blastocyst transfer and 61 patients who underwent a frozen and thawed euploid blastocyst transfer. Ongoing PR and LBR were significantly higher for the FET group (ongoing PR 80% vs. 61%; $P=.03$; LBR 77% vs. 59%; $P=.04$). Logistic regression analysis of LBR adjusting for female age and number of MII oocytes did not show a statistically significant difference between fresh and frozen strategies (OR 2.1, 95% CI 0.95–4.68; $P=.68$). The investigators concluded that the strategy was reasonable for patients, with a trend toward favoring the freeze-all option (46). Potential risks of a "freeze-all" strategy include increased risk of maternal hypertensive disorders of pregnancy and having a large-for-gestational-age infant (47).

DAY OF EMBRYO BIOPSY

When comparing the outcomes for blastocysts biopsied on day 5 (n = 730) vs. day 6 (n = 441), the aneuploidy rate was not significantly different in the day-6 group (69.9% vs. 61.9%) (48). The age of the women in the 2 groups was not significantly different (mean age 38.5 years). Embryos biopsied on day 5 could be transferred fresh on day 6 or frozen, but all day-6 embryos were frozen for future FET. The implantation rate, clinical pregnancy rate, and live-birth rates were not significantly different. This study suggests that the developmental rate of euploid blastocysts that form on day 6 may be approximately as likely to result in live birth as those that form on day 5, although day-6 blastocysts may require cryopreservation for future transfer in an FET cycle.

The relatively recent application of culture through day 7 in some centers increases the pool of transferable embryos for patients who may otherwise have no usable embryos if culture was terminated on day 6. However, embryos that reach blastocyst stage on day 7 may have a higher risk of aneuploidy and lower implantation potential if euploid. A

retrospective study by Tiegs et al. (49) of 229 NGS-tested euploid day 7 blastocysts found that pregnancy rates were slightly but not significantly reduced compared with day 5 and day 6 blastocysts. The sustained implantation rate for day 7 euploid blastocysts was 52.6% compared with 68.9% and 66.8% in day 5 and day 6 blastocysts with $P=.29$ and $P=.14$, respectively. A separate retrospective study by Hernandez-Nieto et al. (50) found a significant reduction in euploidy and implantation rates for day 7 blastocysts compared with day 5 and day 6 blastocysts. The euploidy rate was 40.5% in day 7 blastocysts compared with 54.7% in day 5 blastocysts and 52.9% in day 6 blastocysts ($P<.0001$). In this study, 116 day 7 euploid blastocysts (by PGT-A) were transferred, resulting in a significant decrease in implantation (OR, 0.32; $P<.001$), clinical pregnancy (OR, 0.28; $P<.001$), and live birth (OR, 0.28; $P<.001$). These data support the selection of day 5 and day 6 blastocysts over day 7 blastocysts when available.

PGT-A WITH PREIMPLANTATION GENETIC TESTING FOR MONOGENETIC DISORDERS

Preimplantation genetic testing for monogenic disorders (PGT-M) predates PGT-A for embryo aneuploidy. With improvements in embryo biopsy and deoxyribonucleic acid (DNA) amplification techniques, it became possible to perform simultaneous PGT-M/PGT-A in the same biopsy sample. One study compared outcomes of PGT-M/PGT-A vs. PGT-M alone and found that 50% of PGT-M-unaffected embryos were aneuploid (mean maternal age 32.4 years) (51). Accordingly, the investigators reported an implantation rate of 75% vs. 53% ($P=.19$) and live-birth rates of 59.4% vs. 37.5% in the PGT-M/PGT-A group, with miscarriage rates of 20% vs. 40% ($P=.56$). Patients undergoing PGT-M/PGT-A ultimately will have fewer embryos remaining for transfer after testing, but potentially will have a better assessment of their overall reproductive potential. It is possible that some potentially viable embryos will be discarded because of mosaicism and false-positive aneuploidy after PGT-A. In one study, retrospective NGS-based PGT-A testing of stored genetic material from PGT-M cases that resulted in unremarkable live birth of 76 infants revealed that 1 in 6 embryos (17.1%) with reproductive potential would have been discarded because of mosaicism or false aneuploidy if PGT-A was used before transfer (52). However, the whole-genome amplification method used and relatively long time (~2 to 3 years) from the time of TE biopsy and PGT-A may have affected these results. Therefore, further studies on the use of PGT-A in the setting of PGT-M are needed in this population, and the counseling needs to be individualized.

THAWING AND WARMING, BIOPSY, AND RE-CRYOPRESERVATION FOR PGT-A

Patients with previously cryopreserved unbiopsied embryos may wish to thaw or warm their embryos for biopsy and testing followed by use or repeat cryopreservation. Reasons for this include previous miscarriage, disease discovery, family balancing, or desire to use new technology. Although fresh biopsy is preferable, reproductive outcomes did not seem significantly compromised with respect to the implantation rate, clinical pregnancy rate, or biochemical loss in 1 study on surviving euploid embryos after a sequence of warming and thawing, biopsy, (re)vitrification, and (re)warming (53). There was no comparison of live-birth rates in this group. One study found that the survival rate was lower for the second warming (87.5% vs. 98.3% in first thawing and warming, P .035), but some of the embryos had been slowly frozen on the first freeze. In contrast to embryos that were warmed for an initial biopsy, embryos warmed for a second biopsy (i.e., after initial "no read," n = 3) did not perform well; in fact, none implanted in this study. Another study with a small sample size (under- powered) reported that for blastocysts that were warmed, biopsied, and transferred within 2 days (day 6 or day 7 of progesterone), the OPRs were 35.3% for age ≤35 (n = 17), 40% for age 36–44 (n = 16), and 100% for donor egg (n = 2) (54). Some patients may benefit from warming embryos for preimplantation screening, although, again, they may expect a reduction in the number of embryos available for transfer.

An inconclusive result is reported to occur after biopsy for PGT-A in 0.86% to 3.8% of cases (55). The option to re-biopsy a no-result blastocyst requires warming, followed by a second round of biopsy and vitrification. There are mixed data on the impact of multiple vitrification and biopsy cycles on clinical outcomes. One retrospective cohort study analyzed the impact of 2 rounds of vitrification with 1 or more rounds of biopsy (56). This study found comparable clinical pregnancy rates in embryos that underwent double vitrification with a single biopsy (44%) to controls that underwent single vitrification and single biopsy (46%). However, there was a trend toward lower clinical pregnancy rates in the double vitrification and double biopsy group (35%), which was not statistically significant. These findings were corroborated by another group (57), who did see a detrimental effect of double vitrification and double biopsy. A third group found that embryos that underwent 2 vitrifications and 1 biopsy (n = 3,452) had an ongoing pregnancy and clinical loss rate of 63.2% and 9.8%, respectively, compared with 50% and 21.7% in embryos that underwent double vitrification and double biopsy (n = 36) ($P=.08$) (58). This was further corroborated by another group that found that double vitrified and double biopsied embryos had a significantly reduced clinical pregnancy rate (31% vs. 54.3%) compared with single vitrification single biopsy embryos ($P=.13$) (59). On the other hand, 2 studies found that blastocysts can tolerate a second round of biopsy without compromising clinical pregnancy and live-birth rates (55, 60). Although the data are mixed, it appears that at least multiple rounds of vitrification and biopsy may impact the implantation of euploid blastocysts, and this should be balanced against the necessity of obtaining a PGT-A result.

MALE FACTOR INFERTILITY

One study compared rates of blastocyst aneuploidy for men with normal semen analyses to men with oligozoospermia and reported a threefold increase in sex chromosome abnormalities in the oligozoospermia group, regardless of oocyte age (61). The investigators hypothesized that ICSI, which is

used traditionally for PGT-A and PGT-M cycles, could increase aneuploidy by affecting sperm nuclear decondensation or by destabilizing the oocyte spindle apparatus, but reported no difference in blastocyst aneuploidy rates for men with normal semen analyses who underwent IVF or PGT-A using conventional vs. ICSI fertilization. In oligozoospermic men, ICSI did not increase the overall aneuploidy (vs. conventional) but did increase aneuploidy in chromosomes 1, 2, 11, and 18. Similarly, comparison of aneuploidy rates in predominantly non-male factor infertility population in conventional IVF and ICSI split insemination cycles showed no differences in overall aneuploidy, sex chromosome aneuploidy, and embryo mosaicism between these insemination groups (62). Two retrospective cohort studies did not demonstrate an improved pregnancy and/or live-birth rates with the use of PGT-A for severe male factor infertility (63, 64), and additional studies show that the euploidy rates also do not appear to be affected in these cases (65, 66). Very limited evidence suggests that embryo chromosomal abnormality rate maybe increased when testicular sperm from azoospermic patients is used; however, the patients in these studies either had high rate of karyotypic abnormalities or FISH was used for aneuploidy analysis (65–68). In summary, male factor infertility does not appear to be associated with increased embryo aneuploidy according to the available studies, and PGT-A should not be used for this purpose only. The evidence is insufficient to make recommendation for cases when testicular sperm is used, and more studies are needed on this subject.

USE OF ICSI

There is theoretical concern that conventional insemination of oocytes may produce a higher risk of genetic contamination during PGT because of the presence of lysed DNA from granulosa cells and excess sperm being adherent to the zona pellucida. The risk of such contamination has not been demonstrated and recent studies suggest that genetic material from sperm may not amplify using PGT methods (69, 70). Although ICSI may be preferred by some laboratories offering PGT-A and mandatory when PGT-M is being used, there is insufficient evidence to support this recommendation. Data reassure that the use of ICSI for non-male factor infertility in PGT-M does not increase the risk of birth defects (71). Given the importance of obtaining a reliable PGT-M result, it is reasonable to recommend ICSI in these cases, but it is not needed routinely for PGT-A.

ETHNICITY

Although IVF outcomes have been reported to vary by ethnicity (72), a 2016 study found no difference in aneuploidy rates on the basis of maternal ethnicity as defined by ancestry informative markers (AIMs) (73). Limitations include the lack of data around paternal AIMs and the current AIMs' inability to identify ethnicity subgroups, and most of the study population was of European descent. A wider group is needed for future study, but aneuploidy risk stratification by ethnicity is not indicated currently.

NEONATAL AND CHILDHOOD OUTCOMES

Obstetric, neonatal, and early childhood outcome data seem reassuring thus far, although much has focused on PGT-M (single gene) rather than PGT-A (aneuploidy). The PGT-M vs. PGT-A parental groups are often inherently different in that most patients undergoing PGT-M do not have concomitant infertility. Nonetheless, kindergarten-aged PGT-M offspring perform as well as their IVF and ICSI and naturally conceived peers on measures of cognition (Wechsler Preschool and Primary Scale of Intelligence), motor skills (Movement ABC), psychosocial development (Child Behavior Checklist and Caregiver-Teacher Report Form) (74, 75), and body composition and blood pressure measurements (76). A prospective, assessor blinded, multicenter follow-up evaluation of a RCT of cleavage-stage PGT-A evaluated the neurodevelopment of children born after randomization to PGT-A or no PGT-A at age 9. The investigators found no difference in neurological optimality score (Touwen test), global cognition (Wechsler Abbreviated Scale of Intelligence, Dutch version of the Neuro Psychological Assessment-II), behavior (Child Behavior Checklist and Teacher Report Form), blood pressure, and anthropometrics (total body fat, BMI, and head circumference) between PGT-A and non-PGT-A offspring, although prevalence of minor neurological dysfunction was judged as high across both groups (PGT-A group 17/43 [40%], control group 19/56 [34%]) (77). A cohort study from Denmark noted that adverse obstetric and neonatal outcomes seemed more related to the parental condition than the technology used to treat the condition, although PGT-M pregnancies had more placenta previa than spontaneously conceived pregnancies. PGT-M pregnancies tested for monogenic disorders demonstrated more low birth weight, preterm premature rupture of membranes, placenta previa, cesarean delivery, and neonatal intensive care unit stays than both IVF or ICSI and spontaneously conceived pregnancies; however, the PGT-M offspring did not differ in these variables when compared with their unaffected siblings who were not from PGT-M cycles, suggesting an underlying familial or parental risk milieu (78). A retrospective cohort study linking Massachusetts maternal and neonatal hospitalization discharge diagnoses to SART-CORS data for singleton births after frozen and thawed single-embryo transfers compared outcomes for 585 cycles having embryo biopsy vs. 2,191 cycles having no embryo biopsy. There were no differences in preeclampsia, pregnancy-induced hypertension, placental disorders, preterm birth, low birthweight, cesarian delivery, gestational diabetes mellitus, or prolonged hospitalization for mothers or infants (79). In contrast, an observational cohort study compared pregnancy and neonatal outcomes of trophectoderm biopsy for PGT pregnancies and IVF without PGT pregnancies and found threefold higher odds of preeclampsia with trophectoderm biopsy while controlling for mode of conception (fresh vs. frozen ET, NC FET vs. programmed FET) (10.5% vs. 4.1%, aOR 3.02; 95% CI 1.1, 8.29). Other measured outcomes of placenta previa, gestational diabetes mellitus, preterm premature rupture of membranes, and post-partum hemorrhage were not statistically significantly different. Neonatal

outcomes of gestational age at delivery, rate of preterm birth, low birth weight, NICU admission, neonatal morbidities, or birth defects were also not found to be different between the 2 groups (80). A prospective RCT studying PGT-A vs. conventional IVF included obstetric and neonatal outcomes as secondary outcomes. No differences in pregnancy or newborn complications were found between the 2 groups (4). In summary, most studies do not show a negative impact of PGT on obstetric, neonatal, and childhood outcomes.

COST-EFFECTIVENESS

Cost-effectiveness for PGT-A is difficult to quantify, because cycle costs and insurance coverage vary considerably. It is difficult to quantify the intangible costs of miscarriage and failed implantation, and many studies do not consider all obstetric, neonatal, and ongoing costs of disease or aneuploidy. One study using a theoretical model found that applying PGT-A to patients with unexplained RPL (n = 232) was not cost-effective when compared with expectant management (n = 302); although PGT-A decreased miscarriage rates (7% vs. 24%), the live-birth rate was not improved (40% vs. 55%) (81). Another study used a decision analytic model utilizing actual clinical data and assumptions about PGT-A from the literature applied to 8,998 patients from 74 IVF centers. As expected, once all embryos were exhausted, the cumulative live-birth rate was equivalent. However, PGT-A reduced time in treatment by 4 months and patients experienced fewer failed embryo transfers and clinical miscarriages (82). A third study applied a theoretical cost-effectiveness model utilizing costs from the regional public health system provider. They found that cost-effectiveness improves with female age and number of available blastocysts. They determined that, in theory, PGT-A can be cost-effective in specific clinical settings and population groups (83). Another theoretical cost-effectiveness study looked at the use of PGT-A with fresh oocyte donors and did not find it to be cost-effective (84). More research is needed, particularly as costs for PGT-A decrease, and clinicians should tailor their recommendations to the preference and situation of the individual patient (30).

CONCERNS WITH INTERMEDIATE COPY NUMBER (MOSAICISM), TESTING PLATFORMS, AND ACCURACY

Mosaicism refers to 2 or more cell populations with different chromosomal complements being present within the same embryo. Mosaicism was first identified as a common phenomenon in cleavage-stage embryos, although the exact prevalence of mosaicism in embryos is unknown. Mosaicism is diagnosed with PGT-A on the basis of intermediate copy number results. It is important to recognize that, aside from mosaicism, other proposed explanations for intermediate copy number results include statistical variation, amplification bias, contamination, mitotic state, variation in embryo biopsy technique, and embryology laboratory conditions (85, 86). With more recent and sensitive assays such as NGS, it has become increasingly common to report identification and quantification of mosaicism within a trophectoderm biopsy sample. The rate of mosaic diagnoses in clinical testing of trophectoderm can vary depending on the specific NGS platform used, the cutoffs used to classify results as mosaic, technician and software interpretation, and individual PGT-A testing laboratory classification schemes.

Mosaic embryos can implant and generate apparently euploid offspring; however, they may implant at a lower success rate (85, 87–89). These data suggest a need for additional investigation of the validity and accuracy of a mosaic diagnosis. The fact embryos with a mosaic diagnosis can result in apparently euploid offspring is due to either inaccurate classification or from a correction process such as post-zygotic chromosome loss, chromosome gain, mitotic nondisjunction, or trisomic rescue (90–92). Further details surrounding the clinical management of mosaicism are provided in the ASRM committee opinion (86).

Testing platforms

Originally limited to subsets of chromosomes with FISH analysis, more recent platforms evaluate all 24 chromosomes. Early platforms for comprehensive chromosome screening included aCGH and qPCR. qPCR had the advantages of low cost and quick turnaround time; however, it is not able to detect segmental aneuploidies or mosaicism. At present, NGS and SNP microarray are the primarily used platforms. SNP microarray has the ability to indicate if the source of aneuploidy is from the sperm or egg and reliably detect triploidy and tetraploidy. Recently, NGS has become increasingly used in PGT-A because of its high throughput, ability to detect mosaicism and segmental mutation, and capability of concomitant PGT-A and PGT-M. PGT-A platforms are evolving rapidly and it is important that providers understand them in appropriate detail to counsel patients and select suitable platforms to meet the specific needs. Because of differences in laboratory protocols and quality controls, current data do not exist to conclusively determine the superiority of any platform.

Accuracy

One of the items which requires clarification with PGT-A is how likely the portion of the embryo which is biopsied represents the entire embryo and accurately predicts the clinical outcomes. Although most published studies report the negative predictive value – the chance that a euploid embryo will produce a euploid pregnancy – very limited studies report the positive predictive value – the chance that an aneuploid embryo will not produce a pregnancy. The only study design that can do this adequately is a prospective nonselection study. One study analyzed cleavage-stage and blastocyst embryos utilizing SNP-microarray PGT-A (93). The investigators found the positive predictive value of PGT-A utilizing SNP microarray to be 96%. Positive predictive values were never established for qPCR or aCGH. A multicenter nonselection study utilizing NGS has also been published and of the 102 aneuploid embryos ultimately transferred, there were no ongoing pregnancies. The binomial proportion 95% CI of aneuploid diagnosis clinical error rate was calculated between 0% and 2.43%

(94). In a recently published case series, 50 patients (average age at retrieval 41.4 years) underwent 57 FET cycles of 141 PGT-A abnormal (including mosaic) embryos, resulting in 11 miscarriages and 8 live births (95). Among the 141 abnormal embryos, 76 were aneuploid resulting in 4 first-trimester miscarriages and 1 live birth. Of 30 embryos transferred with complex (>2 chromosomal abnormalities), 28 had no evidence of implantation and 2 resulted in a first-trimester loss. Because new technology evolves which allows for diagnoses such as mosaicism, segmental duplications, and deletions, it will be important to understand the reproductive potential of embryos assigned these results before wide-spread utilization.

EMBRYO DAMAGE

There are few data on embryo biopsy techniques used in PGT-A; however, it is generally accepted that trophectoderm biopsy has less impact on embryo viability than cleavage-stage biopsy. This is because although more cells are removed during trophectoderm biopsy, it represents a smaller percentage of embryo mass and, by definition, trophectoderm biopsy removes only trophectoderm cells and not cells that have any fetal fate. Conversely, cleavage-stage biopsy occurs at a time when cell lineage has not yet been established and the cell removed could potentially impact viability of the embryo and the fate of the fetus. Available data evaluating the impact of cleavage-stage embryo biopsy show a significant developmental insult that is associated with the biopsy process itself, thereby inflicting trauma to the developing embryo and relative reduction in embryo implantation and progression to delivery (96, 97). There was potential selection bias in this study, given that only poorly developing embryos were biopsied on day 3, whereas normally developing embryos were allowed to grow until day 5 or 6 before biopsy. In a multicenter nonselection study, trophectoderm biopsy had no detectable impact on sustained implantation after embryo transfer (97). The impact of biopsy of the trophectoderm is not well understood and given the importance of the trophectoderm for implantation, damage to the trophectoderm may impact this critical event (98).

Pretest counseling of patients or informed consent regarding clinical policy for abnormal test results

Informed consent before use of genetic testing, to include PGT-A, should include a thorough discussion of risks, benefits, and limitations of the technology used. In the case of PGT-A, possible outcomes including no result, embryos with results consistent with mosaicism or segmental aneuploidy, and misdiagnosis are important to discuss before testing. The counseling ought to include the alternate option of not performing PGT-A. In addition, clinics should strive to implement a written policy on disposition of abnormal embryos, including those with mosaic results and segmental aneuploidy. This policy should be disclosed to the patient before testing. Ready access to genetic counseling at any point in patients' decision-making process is also consistent with best practice regarding the use of PGT-A. Comprehensive post-test counseling is also warranted in many cases, and referral to a genetic counselor can aid patient decision-making regarding the use of PGT-A tested embryos (99).

SEX SELECTION

The use of PGT-A may give patients the choice to select the sex of their embryo, which may in effect allow for elective sex selection. In the United States, such potential choices and decisions are left between individual patients and their providers. With increasing use of PGT, there is potential for such elective sex selection leading to gender bias and skewing of the sex ratio. Two recent analyses of national SART data from 2014 to 2016 found that IVF cycles with PGT for any indication were much more likely to have a male offspring (5, 100). Between 2014 and 2016, the overall sex ratio (male/female) from all IVF live births was 107. In context, the overall sex ratio in the US population is estimated to be 105 (101). The sex ratio was however significantly higher (favoring male) among IVF live births from any PGT use compared with IVF live births without PGT use (115 vs. 105, respectively, $P<.001$). Among IVF live births using PGT specifically for sex selection, the sex ratio was 164. Such findings are concerning, and further research to monitor such utilization patterns is recommended.

GAPS IN KNOWLEDGE

Other potential advantages and disadvantages exist with PGT-A, although there are limited data to support or refute these. For example, PGT-A testing may lower the risk of aneuploidy detected during pregnancy or after birth. In addition, identifying euploid embryos may decrease the time to pregnancy by focusing embryo transfer cycles only using euploid embryos to select populations; this may be helpful in older women, those who want large families or those using gestational carriers to conceive. Another consideration is that identification and discarding of aneuploid embryos could potentially lessen the burden of excess embryos cryopreserved. On the other hand, patients using PGT-A may be left with the potential dilemma of how to handle excess mosaic embryos. In addition, the time to pregnancy may be faster in patients who conceive after a fresh transfer without PGT-A, because only those who did not conceive would pursue subsequent FETs with tested euploid embryos. Ideally, more RCTs that randomize patients at cycle start and evaluate cumulative live-birth rates are needed to elucidate some of these answers.

There are potential disadvantages to using PGT-A, such as the need for increased resources and up to 8 cumulative hours of labor for the embryology team for each biopsy case (102). Furthermore, not all embryos will survive in culture to the blastocyst stage for biopsy, although hypothetically they may have resulted in a healthy live birth if they had been transferred in the cleavage or early blastocyst stage. Given the uncertainty about self-correction, false-positive PGT-A results, and/or accuracy of a mosaic diagnosis, there is concern that one may be discarding embryos that may have resulted in healthy neonates (98). Potential variations

in aneuploidy rates in same age groups between laboratories also need further investigation. In addition, more data are needed about cumulative pregnancy rates from 1 retrieval cycle, effects of PGT-A on miscarriage rates, and defining which patient groups could benefit from this technology.

PATIENT PRIORITIES AND INDIVIDUAL CONSIDERATION

Despite the lack of evidence in support of universal use of PGT-A, uptake of this technology continues to grow. Factors that may contribute to patients and clinicians selecting this option include but are not limited to: insurance coverage (5) that mandates use of all embryos before additional retrievals or that limits the number of covered transfers such that knowledge that transferrable embryos are euploid may outweigh the risk of having fewer transferrable embryos or even losing some viable embryos in the process; consideration of banking extra embryos with a high likelihood of success to achieve ideal family size in older women, RPL with proven aneuploid conceptions, and the desire to limit recurrences. Older patients at a higher risk for aneuploid pregnancy may also be motivated to request PGT-A, especially in cases in which anticipated embryo yield is high, to reduce the likelihood of miscarriage or an ongoing aneuploid pregnancy. It is important to counsel patients on the published success and outcomes of PGT-A and discuss any social and financial concerns so that patients can make informed decisions around care.

CONCLUSIONS

Adoption and use of PGT-A as part of IVF treatment has been increasing in the United States. The underlying technology used for 24-chromosome analysis also continues to evolve rapidly. The value of PGT-A as a universal screening test for all patients undergoing IVF has not been demonstrated. Some earlier single-center studies reported higher birth rates after PGT-A and eSET in the primary embryo transfer of favorable-prognosis patients, suggesting the potential for this testing to increase eSET utilization and minimize the incidence of multiple gestations. However, 2 recent, multicenter, randomized control trials in women with available blastocysts concluded that overall pregnancy outcomes via FET were similar between conventional IVF vs. PGT-A. The value of PGT-A to lower the risk of clinical miscarriage is also unclear. However, these studies have important limitations and there remain questions about appropriate patient selection and testing platforms.

Subjects participating in these RCTs are generally favorable-prognosis patients who have produced blastocysts for biopsy and analysis. A broader selection of patients with randomization at cycle start rather than blastulation would more appropriately address the applicability of wider use of this technology. Furthermore, the randomized trials were performed in centers with broad and deep experience in embryo biopsy and specimen preparation. The ability to expand reliably these techniques to centers with less experience has yet to be established.

Other important considerations about PGT-A that must be addressed by further research include cost-effectiveness, use of mosaic embryos, false-positive results, risk of embryo damage, the role and effect of cryopreservation, time to pregnancy, utility in specific subgroups (such as RPL, prior implantation failure, advanced maternal age, and so on), use of sex selection, and total reproductive potential per intervention.

Large, prospective, well-controlled studies evaluating the combination of multiple approaches (genomics, time-lapse imaging, transcriptomics, proteomics, metabolomics, artificial intelligence, and so on) for enhanced embryo selection applicable in a more inclusive patient population are needed to determine not only the effectiveness, but also the safety and potential risks of these technologies. PGT-A will likely remain part of a multidimensional approach to embryo screening and selection. At present, however, the routine use of blastocyst biopsy with aneuploidy testing in all infertile patients undergoing IVF treatment cannot be recommended.

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El uso de pruebas genéticas preimplantacionales para la aneuploidía: opinión de un comité

El uso de la prueba genética preimplantacional para aneuploidías (PGT-A) en los Estados Unidos ha estado aumentando de manera constante. Además, la tecnología subyacente utilizada para el análisis de 24 cromosomas continúa evolucionando rápidamente. El valor del PGT-A como prueba de detección rutinaria para todos los pacientes sometidos a fertilización in vitro no ha sido demostrado. Aunque algunos estudios previos de un solo centro informaron tasas de nacimientos vivos más altas después de PGT-A en pacientes con pronóstico favorable, ensayos clínicos multicéntricos, randomizados control en mujeres con blastocistos disponibles concluyeron que los resultados generales del embarazo a través de la transferencia de embriones congelados fueron similares entre PGT-A y la fertilización in vitro convencional. El valor de PGT-A para reducir el riesgo de aborto clínico también es incierto, aunque estos estudios presentan limitaciones importantes. Este documento reemplaza el documento con el mismo nombre, publicado por última vez en 2018.