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Current Practices And Perspectives Of Genetic Counselors And Reproductive Endocrinologists Regarding Transfer Of Mosaic Embryos

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CURRENT PRACTICES AND PERSPECTIVES OF GENETIC COUNSELORS AND REPRODUCTIVE ENDOCRINOLOGISTS REGARDING TRANSFER OF MOSAIC EMBRYOS

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CURRENT PRACTICES AND PERSPECTIVES OF GENETIC COUNSELORS AND REPRODUCTIVE ENDOCRINOLOGISTS REGARDING TRANSFER OF MOSAIC EMBRYOS

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With the recent transition in testing methodology used for preimplantation genetic testing for aneuploidy (PGT-A) from array comparative genomic hybridization to next generation sequencing, mosaic embryos are being identified more readily. Given the limited clinical guidance and information regarding outcomes after the transfer of mosaic embryos (TME), a mosaic test result can present challenging scenarios for providers and patients. The current landscape of this area of reproductive medicine must be described before a consensus can be determined and areas for improvement can be identified. This cross-sectional descriptive study aimed to define the current practices regarding TME as reported by prenatal and/or infertility genetic counselors (GCs) and reproductive endocrinologists (REs). In addition, it aimed to determine GCs' and REs' perspectives on patient education, informed consent, decision making and clinical guidance with regard to the TME. An invitation to participate in the electronic survey was distributed to GCs through the National Society of Genetic Counselors listserv and to REs via an email from the principal investigator. A total of 223 responses were analyzed consisting of 194 GCs and 29 REs. Data analysis showed that infertility GCs practices and perspectives were more consistent with REs than non-infertility GCs. However, regardless of specialty, responses showed little to no consensus among providers regarding their perspectives on this topic. Overall, respondents reported feeling more comfortable with pre-test PGT-A counseling compared to counseling about TME. Furthermore, a majority of respondents indicated that additional consensus and/or guidance is needed for several topics related to TME, such as when to discuss the possibility of mosaic embryos with patients, when the decision should be made whether or not to transfer mosaic embryos and prioritization when multiple

mosaic embryos are available. These results support the urgent need for additional consensus and guidance regarding best practices when mosaic embryos are identified.

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Introduction

In vitro fertilization (IVF) with preimplantation genetic testing for aneuploidy (PGT-A) of embryos is a rapidly evolving area of reproductive medicine that has become progressively accessible and advanced in the last several years. With the transition in testing methodology from array comparative genomic hybridization (CGH) to next generation sequencing (NGS), mosaic embryos are being more readily identified prior to transfer. One important limitation of PGT-A is that the results are only representative of the genetic makeup of the cells biopsied from the embryo and may not always be reflective of the genetic makeup of the entire embryo. Given the limitations of embryo sampling, embryos that yield mosaic test results are thought to be at risk for fetal mosaicism, but it cannot be definitively determined that the transfer would result in a mosaic fetus. Furthermore, PGT-A results cannot determine the level of mosaicism in the entire embryo or whether the mosaicism is isolated to the trophoectoderm or is also present in the inner cell mass. For those patients who are left with only mosaic test results after PGT-A, the decision must be made to either transfer a potentially mosaic embryo, accepting the associated risks and uncertain outcome, begin another cycle, or discontinue their IVF experience without a transfer.

In 2015, a letter to the editor of The New England Journal of Medicine titled, *Healthy Babies after Intrauterine Transfer of Mosaic Aneuploid Blastocysts* outlined 18 pregnancies with a normal karyotype on chorionic villus testing after transfer of one or more mosaic embryos that resulted in the birth of full-term [apparently] healthy infants (Greco et al. 2015). This letter started a discussion amongst health care providers about whether they should be offering the option to transfer a mosaic embryo(s) to patients who may have no euploid embryos following PGT-A. Although some clinical practices have elected to consider transfer of mosaic embryos, others remain hesitant. This hesitation is presumably due to the potential risks of transferring mosaic embryos. In addition, the limited and sometimes conflicting data that has been published regarding transfer of mosaic embryos and the expected pregnancy outcomes has added to this hesitation (Kushnir et al., 2018; Harton et al., 2017). There has been research analyzing

how various factors of the mosaic finding may affect ongoing pregnancy rates. One study found no significant difference in the ongoing pregnancy rates between embryos with a single mosaic monosomy versus a single mosaic trisomy (Munne et al. 2017). Additionally, some studies have presented data suggesting that embryos with a lower percentage of the abnormal cell line in the biopsied sample have a higher ongoing pregnancy rate than embryos with biopsies comprised of a higher percentage of the abnormal cell line (Munne, 2017; Spinella et al., 2018). Contrary to this finding, other studies have shown that the percentage of abnormal cells in the trophectoderm biopsy does not necessarily correlate with the percentage of abnormal cells in the inner cell mass, which eventually becomes the fetus (Taylor, 2015). In addition, Victor et al. (2019) reported on the transfer of 100 mosaic embryos and did not find any correlation between percentage of mosaicism in the biopsy and ongoing pregnancy rates. When evaluating live birth rates following the transfer of a mosaic embryo(s), Fragouli et al. (2017) showed that the live birth rate was significantly lower (27.3%) when compared with transfer of an embryo with normal PGT-A testing (47%). Furthermore, when separated by the type of mosaic PGT-A result, the same study showed that embryos with segmental or partial mosaicism had a live birth rate that was slightly lower or comparable to transfer of euploid embryos, whereas whole chromosome mosaicism and complex mosaicism resulted in a live birth less frequently.

In addition to several publications addressing the advancing technology of PGT-A, the Preimplantation Genetic Diagnosis International Society (PGDIS, 2016) and the Congress for Controversies in Preconception, Preimplantation and Prenatal Diagnosis (CoGEN, 2016) have put forth position statements on this topic. These position statements are similar to one another in their recommendations. Specifically, they recommend providers should consider transfer when there are no euploid embryos and no option for undergoing another IVF cycle. They suggest prioritizing mosaic embryos based on the percentage of the aneuploid cell line (lower levels preferable), whether they are mosaic for trisomy vs. monosomy (monosomy preferable) and then based on which chromosome is aneuploid. They also provide some brief guidance for laboratories performing the testing and clinicians providing counseling. Of note, these position statements are not evidence-based or peer-reviewed, but

rather a product of discussion amongst these organizations' membership. Sachdev et al. (2017) and Munne et al. (2017) cited these position papers and agreed with several recommendations put forth but also acknowledged that the guidance should be reviewed in light of recent studies providing contradictory information. Munne suggests that these guidelines may be overly cautious, but a conservative approach is understandable given the scarcity of data available. In contrast to these position papers, Grati et al. published *An Evidence-based Scoring System for Prioritizing Mosaic Embryos Following Preimplantation Genetic Screening* in April of 2018. This put forth a different prioritization scheme with a specific risk for each chromosome. This was a retrospective study that included cytogenetic and molecular testing results from over 72,000 chorionic villi samples and over 3,000 products of conception. Currently, there have been no studies to determine how much and in what manner these publications are being utilized by providers to counsel patients and guide decision making.

Given the small amount of data and guidance in this emerging area, there are unique challenges for patients trying to make reproductive decisions as well as their providers who are charged with providing recommendations and counseling. Some examples of the potential dilemmas faced by patients include added difficulty in deciding whether or not to pursue PGT-A (Gebhart et al., 2016), using complex and often uncertain testing information to make reproductive decisions in a high pressure or sometimes time-sensitive manner, feelings of regret about pursuing testing after receiving uncertain results (Bernhardt et al., 2012) and/or additional decision-making burden regarding transfer or storage of mosaic embryos (Besser et., 2017).

Providers also face several challenges both before and after a patient's decision to pursue testing and to transfer mosaic embryos. Some of these challenges are due to the absence of negative or positive predictive values for PGT-A results, contradictory data regarding best practice for prioritization when multiple mosaic embryos are available, and limited outcome data to provide anticipatory guidance. Variability amongst labs regarding the thresholds for reporting mosaicism and what information is reported/excluded, and/or challenges collecting outcome data also create complexities for providers. Providers may also have difficulty determining what time point is most appropriate for counseling and/or

consenting the patient about the risks and limitations of transferring a mosaic embryo(s), obtaining informed consent to transfer and determining recommendations for the most appropriate prenatal testing plan following established viability.

There is currently no consensus between healthcare providers regarding the best practices with respect to the transfer of mosaic embryos. Outside of the position statements put forth by PGDIS and CoGEN, there is limited guidance for providers who are faced with these cases. Two such groups of health care providers that are currently navigating this new era are genetic counselors (GCs) and reproductive endocrinologists (REs). There is limited literature discussing the clinical experience of transferring mosaic embryos and the role of GCs and REs in the education and consent process. While Besser et al. (2017) outlined the genetic counseling considerations, there is little known about the current practices and perspectives of healthcare providers regarding the transfer of mosaic embryos. The current landscape of this field must be described before a consensus can be determined and areas for improvement can be identified. In an effort to address this gap in knowledge, this study aimed to descirbe current practices regarding transfer of mosaic embryos, as reported by GCs and REs. In addition, it aimed to determine GC and RE perspectives on patient education, informed consent, decision making and clinical guidance with regard to the transfer of mosaic embryos.

Methods

Study Design

This cross-sectional descriptive study surveyed two populations of health care providers involved in the IVF and PGT-A process: GCs and reproductive endocrinologists REs. More specifically, eligible participants consisted of practicing prenatal, preconception and/or infertility GCs, along with practicing REs and fellows enrolled in RE fellowship programs in the United States. This research project was approved by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston (HSC-MS-18-0566). Responses were collected from September 25th, 2018 to March 15th, 2019. GCs were accessed through the National Society of Genetic Counselors (NSGC). An invitation to participate in the online survey was sent out to the NSGC membership listserv three times over the course of the data collection period. GCs were allowed to forward the survey to other GCs who may not have received the survey invitation email from NSGC. In addition, GCs were allowed to forward the email survey invitation to REs that they work with or provide their email address(es). An email invitation to participate was then sent to any RE's email address provided by a participating GC. Additionally, a recruitment email to participate in the survey was sent out twice to 104 RE fellowship program directors and faculty within the United States. REs were also allowed to forward the survey to other REs or RE fellows. Initially, an attempt to distribute the study invitation to REs through the Society of Reproductive Endocrinology and Infertility listserv was made; however, this recruitment method was unsuccessful.

In order to encourage participation and promote awareness for the study, an announcement was made at the assisted reproductive technologies and infertility special interest group meeting at the Annual Education Conference held by the National Society of Genetic Counselors on November 14th, 2018. At this meeting, attendees were alerted to the survey and provided a paper handout with basic information about the study and instructions on how to participate. All participants who completed the survey, regardless of recruitment method, were given the opportunity to provide their email address to be entered into a drawing for one of three $25 Amazon gift cards.

Instrumentation

The online survey tool, Qualtrics, was used to create and administer the survey (Qualtrics 2015). The survey was an investigator-designed, non-validated questionnaire consisting of various question formats that included free response, Likert scale, multiple-select and multiple-choice. Although the survey was not validated, it was piloted by 4 genetic counseling students for timing and readability. The number of questions a participant was given varied and was dependent on their area of practice (prenatal and/or infertility GC or RE) and their answers to particular gateway questions. On average, the survey should have taken no more than 15 minutes to complete. The survey questions were split up into 5 main sections: introduction to the study and consent, demographics, GC experience (GCs only), RE experience (REs only), confidence/decision-making/consenting, and resources/guidance. The GC and RE experience sections focused on determining providers' current practices in cases involving transfer of mosaic embryos. The remainder of the questions aimed to determine providers' perspectives regarding their confidence level counseling patients on this topic, the patient decision-making process, consenting of patients, utilization of existing resources/guidance and need for additional resources/guidance.

Data Analysis

Survey responses were collected electronically (Qualtrics, Provo, UT) and were anonymous. The responses were then coded into a Microsoft Excel file and stored on a secure server. Any respondents who only completed demographic information were excluded from data analysis. Data analysis was conducted with STATA (v.130, College Station, TX). Comparisons within and between clinical groups were conducted using rank sum, chi-square, Spearman's correlation or Fisher exact tests for categorical data and Kruskal-Wallis test with a post-hoc Dunn's test for interval data. Statistical significance was assumed at a Type 1 error rate of 5%.

Results

Respondent Demographics

Of the 273 respondents that accessed the survey, 223 met the inclusion criteria and answered at least one question. One hundred and ninety-four of these respondents identified as GCs while 29 identified as REs. (Figure 1). Since answers were not required for every question, the number of respondents can vary between questions. Refer to tables for the number of respondents who provided an answer for each question.

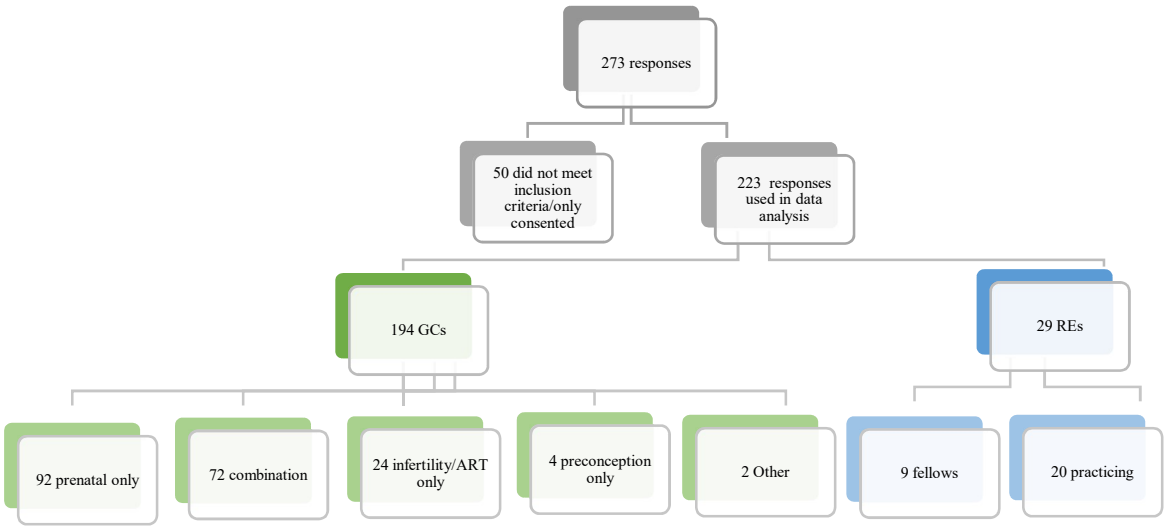

Figure 1: Respondent flowchart describing GC and RE cohorts

Using the most recent professional status survey (PSS) published by National Society of Genetic Counselors in 2018 as an estimate, there were approximately 1,800 GCs who received the survey and were eligible to participate (currently practicing prenatal, preconception and/or infertility GC). Our responses reflect an 11% response rate from GCs. The active RE recruitment email was sent to 110 practicing REs. Prior to this email being sent out, we had collected 18 RE responses. These 18 individuals presumably received the survey invitation from a GC colleague. After sending out the recruitment email twice, we collected an additional 11 RE responses. This reflects an estimated 10% response rate amongst invited practicing REs. Of the 29 RE responses, 20 identified as practicing and 9

identified as fellows. It is difficult to determine the response rate for RE fellows because the total number of RE fellows in the United States can fluctuate from year to year. Also, the recruitment email was not sent directly to fellows but to program directors and faculty members. Although we invited them to forward the survey invitation to fellows, we do not know how many fellows received an invitation to participate. Approximately half (48%) of GCs selected prenatal as their only specialty while 13% selected infertility/ART as their only specialty. Thirty-eight percent of GCs reported more than one specialty. The proportion of preconception counselors in our cohort (39%), whether it was the only specialty reported or reported in combination with another specialty, was comparable with the estimate of preconception GCs reported in the 2018 NSGC PSS (36%). However, the proportion of prenatal GCs included in our study (81%) was overly representative of the proportion of prenatal GCs reported in the PSS (64%). The PSS did not provide information regarding the proportion of GCs who identify as infertility counselors.

GCs from 34 states participated with most practicing in California (24), New York (22) or Texas (21). The majority of responding REs practice in Texas (14). We collected one response from an RE who practices outside of the United States. The GC cohort predominantly reported less than five years of experience (60%) with a decrease in number of respondents as years of experience increased. The RE cohort consisted of nine fellows and 20 practicing REs with practicing REs most commonly reporting less than five years of experience (24%) and being one of five to nine REs in their practice (48%). GCs most commonly reported working in a group of two to four counselors (38%), followed by 22% reporting a total of five to nine GCs and 20% indicating they are the only GC at their institution within their specialty (Table 1).

	GCs n (%), n = 194	**REs** n (%), n = 29
Years working in specialty		
Fellow	0	9 (31)
<5	116 (59.8)	7 (24.1)
5-9	34 (17.5)	3 (10.3)
10-14	20 (10.3)	1 (3.4)
15-19	14 (7.2)	1 (3.4)
20-24	7 (3.6)	2 (6.9)
25-29	0	3 (10.3)
≥30	0	3 (10.3)
No response/blank	3 (1.5)	0
Total GCs/REs in clinic within specialty		
1	39 (20.3)	0
2-4	72 (37.5)	6 (20.6)
5-9	43 (22.4)	14 (48.3)
10-14	21 (10.9)	5 (17.2)
15-19	12 (6.3)	0
20-29	1 (0.5)	1(3.4)
30-39	1 (0.5)	0
40-49	1 (0.5)	0
≥50	2 (1)	0
No response/blank	2 (1)	3 (10.3)
GC work setting (check all that apply)		
Academic institution	89	-
Nonacademic institution	61	-
Private clinic	33	-
IVF clinic	15	-
Other	16	-
No response/blank	2	-

Table 1: Practice information of respondents

Current practices and experience regarding PGT-A and transfer of mosaic embryos

All but one RE reported that their clinic offers PGT-A to their patients. The one RE who does not offer PGT-A was a fellow who does not practice in the United States, and this participant specified that the reason for this is due to clinic policy. Among those who offer PGT-A, just over half (54%) offer it to all their patients, while the remaining were split between those that offer testing only if the patient meets specific criteria (25%) or if the patient is of a certain age (21%) (Table 2). Nearly all of these REs (93%) offer this test to patients at least once a week. Most GCs (80%) report that they do see patients to discuss PGT-A (Table 3). There was variability with regard to the frequency that PGT-A is offered based

on the GC specialty. GCs who identify with infertility as their only specialty or one of multiple specialties they practice (Infertility GCs) offered PGT-A significantly more frequently with 67% offering PGT-A at least once per week compared to six percent of prenatal only GCs and 19% of GCs who identify as prenatal/preconception counselors ($p<0.001$). Of the 156 GCs who reported counseling about PGT-A, 153 provided a response regarding whether they see these patients before testing, after testing or both before and after testing. Of those 153 GCs, they typically see patients either before testing only (37%) or both before and after testing (37%) to discuss the option of PGT-A. REs most commonly report (89%) that they conduct pre-test counseling themselves while 18% utilize a lab GC. Only one RE reports referring to an outside/contracted clinical GC. This was significantly different when compared to who conducts the post-test/pre-transfer counseling ($p<0.001$) with REs providing this less frequently (29%) than pre-test counseling and instead, utilize contracted outside clinical GCs (27%) and lab GC (24%) more often post-test/pre-transfer. REs most commonly report (43%) that about 51-75% of their patients elect PGT-A. Eighty-two percent of REs who offer PGT-A have received a report with no normal embryos but one or more mosaic embryos. Most of these REs (65%) estimated that 1-10% of their patients who pursue PGT-A end up with no normal but one or more mosaic embryos.

	REs n (%)
Circumstance under which PGT-A is offered	n = 28
Offer to all	15 (54)
Offer to all of certain age	6 (21)
Only offer to patients who meet specific criteria	7 (25)
Never offer	0
Frequency PGT-A offered	n = 28
Never	0
At least 1/year	0
At least 2/year	0
At least 1/ month	2 (7)
At least 1/week	26 (93)
Unsure	0
Percentage of patients that elect PGT-A	n = 28
None	0
1-10%	0
11-25%	2 (7)
26-50%	6 (21)
51-75%	12 (43)
76-100%	7 (25)
Other	1 (4)
Who conducts pre-test counseling for PGT-A (select all that apply)	n = 28
I do	25
In house GC	3
Contracted/ outside clinical GC	1
PGS lab GC	5
Other	2
Percentage of those who elect PGT-A who are left with no euploid embryos but one or more mosaic embryos	n = 23
None	0
1-10%	15 (65)
11-25%	2 (9)
26-50%	0
51-75%	1 (4)
76-100%	0
Unknown	5 (22)

Table 2: RE practices and experience regarding PGT-A

	Non-infertility GCs n (%)	Infertility GCs n (%)	Total GCs n (%)
Frequency of PGT-A counseling	n = 148	n = 46	n = 194
Never	38 (25)	1 (2)	38 (20)
At least 1/yr	20 (14)	4 (9)	24 (12)
At least 2/yr	44 (30)	5 (11)	50 (26)
At least 1/month	34 (23)	7 (15)	41(21)
At least 1/week	12 (8)	29 (63)	41 (21)
Timing of PGT-A counseling	n = 109	n = 44	n = 153
Before testing	47 (43)	10 (23)	57 (37)
After testing	22 (20)	7 (16)	29 (19)
Both before and after testing	34 (31)	23 (52)	57 (37)
It depends	5 (5)	4 (9)	9 (6)
Other	1 (1)	0	1 (1)

Table 3: GC experience regarding PGT-A

Eighty-two percent of REs who offer PGT-A indicated that their clinic also offers transfer of mosaic embryos. When asked if they had ever discussed the option of transferring a mosaic embryo with a patient, the majority of REs (87%) and infertility GCs (67%) said yes, while only 20% of non-infertility GCs indicated that they had counseled on this topic ($p<0.001$). Of the 143 GCs who said they had not discussed this option, 31% specified it was because the situation had not presented itself. Non-infertility GCs were more likely to say the opportunity had not presented itself (58%) than other GCs and infertility GCs were more likely to say transfer of mosaic embryos is against their/their referring clinic's policy (40%; $p=0.012$) than other GCs as the reason for why they have not seen a patient to discuss transfer of mosaic embryos. For the 59 GCs who had discussed the option to transfer a mosaic embryo, 55 provided a response about the number of cases they had seen to discuss mosaic embryos and 53 provided a response about the percentage of the patients that elected to transfer a mosaic embryos(s). Of the GCs who provided a response, the majority (41%) reported discussing mosaic embryos in a total of 1-2 cases while infertility GCs most commonly indicated that they had seen greater than 20 cases (39%) ($p<0.001$) (Table 4). The majority of REs (40%) had seen 3-5 cases in which the option to transfer a mosaic embryo was discussed. Of the 53 GCs who provided a response about the percentage of the patients that elected to transfer a mosaic embryos(s), 43% indicated that they did not know what percentage of their patients elected to proceed with the transfer of mosaic embryo(s) or reported that information was unavailable while only 15% of REs indicated that information was unknown ($p=0.02$).

There was no significant difference between GCs who worked in an IVF clinic and those not working in an IVF clinic with regard to the percentage of patients who elected to transfer a mosaic embryo(s). REs most commonly (30%) selected 1-10% as the percentage of patients who decided to proceed with transfer of mosaic embryo(s) after discussing the option. There was no significant difference found between REs and infertility GCs responses on this question. When asked whether any of the patients who elected transfer of a mosaic embryo had a documented viable pregnancy (defined as a heartbeat noted on ultrasound), approximately one third (33%) of GCs were able to respond with an affirmative while the majority (55%) were unsure. When further divided by specialty, infertility GCs were more likely (41%) to be aware of a documented heartbeat on follow up ultrasound compared to non-infertility GCs (24%). Conversely, 70% of REs were able to confirm viability of pregnancies following transfer of a mosaic embryo with only one RE being unsure about viability following transfer.

	REs n (%)	**Infertility GCs** n (%)	**Non-infertility GCs** n (%)	**Total GCs** n (%)
Who counsels post-test/pre-transfer (select all that apply)	n = 23	n/a	n/a	n/a
I do	12	-	-	-
In house GC	7	-	-	-
Contracted/ outside clinical GC	11	-	-	-
PGS lab GC	10	-	-	-
Other	1	-	-	-
Number of cases to discuss TME	n = 20	n = 28	n = 27	n = 55
1-2	6 (30)	7 (25)	16 (59)	23 (42)
3-5	8 (40)	4 (14)	7 (26)	11 (20)
6-10	1 (5)	5 (18)	1 (4)	6 (11)
11-20	4 (20)	1 (4)	3 (11)	4 (7)
>20	1 (5)	11 (39)	0	11 (20)
Percentage of patients that elect to TME	n = 20	n = 27	n = 26	n = 53
none or 0%	0	5 (19)	5 (19.2)	10 (19)
<10%	6 (30)	3 (11)	2 (7.7)	5 (9)
10-25%	3 (15)	4 (15)	3 (11.5)	7 (13)
26-50%	1 (5)	2 (7)	0	2 (4)
51-75%	4 (20)	0	1 (3.9)	1 (2)
76-100%	3 (15)	0	1 (3.9)	1 (2)
other	0	3 (11)	1 (3.9)	4 (8)
unknown/information unavailable	3 (15)	10 (37)	13 (50.0)	23 (43)

Table 4: Practices and experiences regarding transfer of mosaic embryos

Figure 2 illustrates the identified factors and ranking of selected factors that are considered when prioritizing multiple mosaic embryos for transfer. The specific chromosome involved was the factor that was selected the greatest number of times within both groups (n=34, 62% of GCs and n=17, 94% of REs). The chromosome involved was also most frequently ranked as the most important factor by GCs (22%) while the level of mosaicism was most frequently ranked as the most important factor by REs (50%). When comparing factors selected between GCs, infertility only GCs are more likely to use which chromosome is involved (33%) and a published scoring system (25%) as factors than prenatal only GCs (9% and 3%, respectively) (p=0.01).

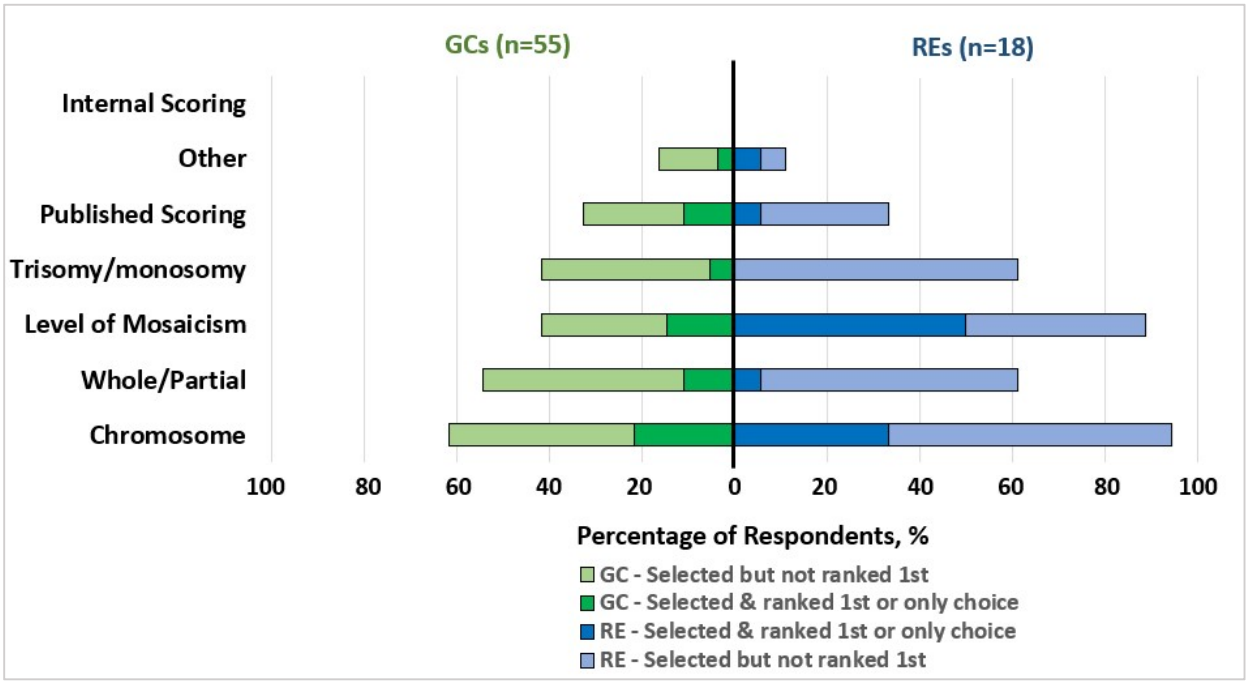

Figure 2: Factors used to prioritize multiple mosaic embryos and rank

Respondents were asked what prenatal testing and/or monitoring they recommend following transfer of mosaic embryos and were given a free text box to type in their answer. Figure 3 provides a summary of these free text responses.

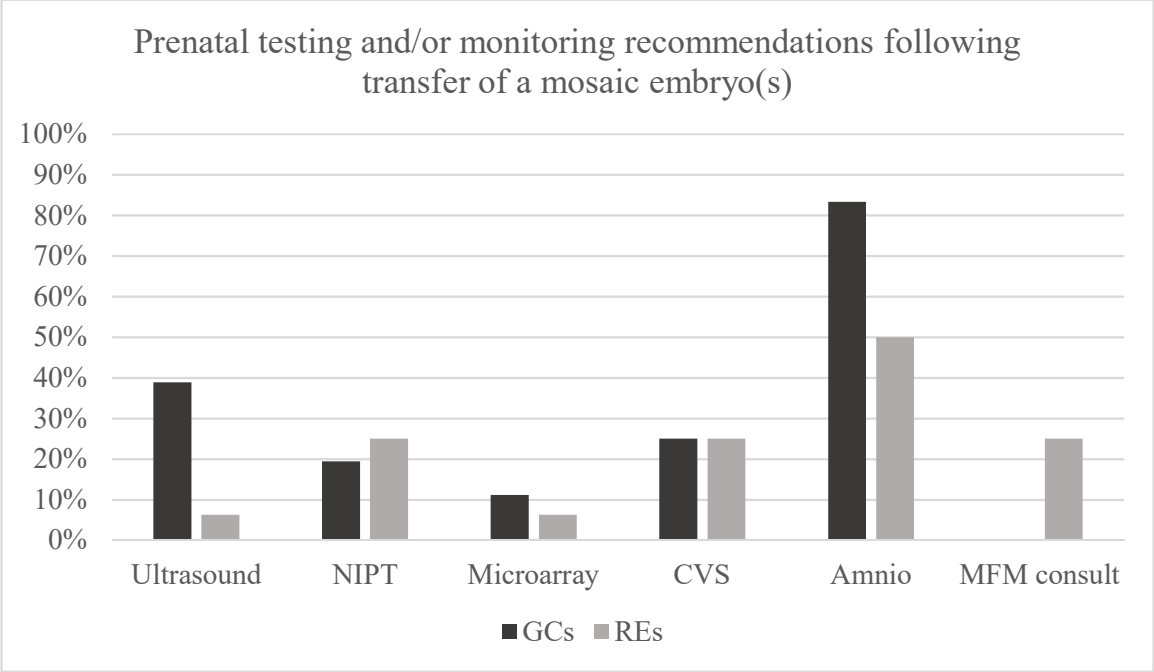

Figure 3: Prenatal testing and/or monitoring recommendations following transfer of a mosaic embryo(s)

Perspectives regarding education, consent, decision-making and clinical guidance

Most respondents, regardless of whether they had personally discussed the option with a patient, felt as though transfer of mosaic embryos should be an option (60% of GCs and 81% of REs). Although the difference in GCs and REs was not significant, prenatal only GCs were significantly more likely to answer, "it depends" (32%) than to say "yes" when compared to infertility only GCs (15%) or preconception only GCs (25%) ($p<0.001$). The most common theme identified in these free text responses for those that selected "it depends" was that it depends on which chromosome is involved (36%). The second most common theme was that it depends on if there are any normal embryos available (26%). Some other free text themes identified included: only if they had genetic counseling, patient's/family's understanding of the risks and limitations, case by case/circumstantial and patient's/family's threshold for risk.

All respondents were asked to indicate their comfort level discussing PGT-A and transfer of mosaic embryos. Eighty-six out of 92 prenatal only GCs, 20 out of 24 infertility only GCs, 63 out of 72 combination GCs and 27 out of 29 REs provided answers regarding their comfort level with these topics.

The following data is based on those who provided an answer for these questions. GCs who identified infertility as their only specialty (85%), followed by REs (74%) and then GCs reporting multiple specialties (49%) reported the highest comfort level when discussing PGT-A with those reporting the lowest amount of comfort being prenatal only GCs (31%) (p=0.002) as shown in Table 5. Similarly, infertility only GCs (55%), followed by REs (33%) and then GCs reporting multiple specialties (17%) reported the highest comfort level when discussing transfer of mosaic embryos with those reporting the lowest amount of comfort being prenatal only GCs (5%) (p<0.001). Overall, all respondents are more likely to report discomfort discussing transfer of mosaic embryos than discussing PGT-A itself (p=<0.001). Those who had seen more cases involving mosaic embryos reported more comfort discussing PGT-A than those with few cases (p=0.01).

	Infertility only GCs n (%) N = 20	**Combination GCs** n (%) N = 63	**Prenatal only GCs** n (%) N = 86	**Total GCs** n (%) N = 174	**REs** n (%) N = 27
Comfort discussing PGT-A					
Extremely comfortable	17 (85)	31 (49)	27 (31)	78 (45)	20 (74)
Somewhat comfortable	2 (10)	30 (48)	48 (56)	82 (47)	6 (22)
Neither uncomfortable or comfortable	0	1 (1.5)	6 (7)	7 (4)	0
Somewhat uncomfortable	0	1 (1.5)	4 (5)	5 (3)	1 (4)
Extremely uncomfortable	1 (5)	0	1 (1)	2 (1)	0
Comfort discussing TME					
Extremely comfortable	11 (55)	11 (17)	4 (5)	26 (15)	9 (33.3)
Somewhat comfortable	5 (25)	31 (49)	38 (44)	78 (45)	11 (40.7)
Neither uncomfortable or comfortable	1 (5)	6 (10)	15 (17)	22 (13)	1 (3.7)
Somewhat uncomfortable	2 (10)	14 (22)	24 (28)	40 (23)	5 (18.5)
Extremely uncomfortable	1 (5)	1 (2)	5 (6)	8 (4)	1 (3.7)

Table 5: Comfort level discussing PGT-A and transfer of mosaic embryos

Table 6 contains the results of a series of vignette questions that were posed to respondents where they were asked to provide their opinion. Following each vignette, they were asked whether their opinion about that situation was consistent with their clinic's policy. On average, there was a 90% response rate for GCs and 93% response rate for REs for all questions listed in Table 6. Approximately two thirds of all respondents (62%) agreed that the best time to discuss the possibility of having a mosaic embryo(s)

following PGT-A with a patient/couple is before the IVF cycle. Alternatively, 20% of GCs thought it should be discussed after IVF has started but before PGT-A is performed while zero REs selected the same option. Twenty-two percent of REs indicated "after IVF and PGT-A has identified mosaic embryos" as the most ideal time while 14% of GCs indicated the same feeling. GCs and REs responses had a similar distribution among answer choices when asked about the most ideal time for patients to decide whether or not to transfer a mosaic embryo and obtain informed consent with about half of all respondents (46%) selecting "after IVF and PGT-A and only mosaic embryos remain" as the most appropriate time. The second most commonly selected answer was "after IVF and PGT-A identified mosaic embryos" (31%) followed by "before the IVF cycle" as the third most common response (12%). For the scenario where a euploid embryo does not survive thawing and only mosaic embryos remain, there was no statistical difference between all GCs and REs responses. Almost half of all respondents (49%) thought the most appropriate next step would be to stop the cycle and discuss the possibility of transferring a mosaic embryo for a future transfer date. A smaller group indicated that they think obtaining consent to thaw a mosaic embryo and proceed with transfer as planned would be the most appropriate next step (17%). Fifteen percent of respondents selected "unsure" while 19% selected "other". Those who selected "other" were allowed to submit a free text response to elaborate. Five themes were identified from the free text responses which included: this decision should have already been made in previous conversations with the patient, discuss the possibility of another egg retrieval vs. transferring mosaic embryo(s), present both options (stopping the cycle or transferring mosaic embryo(s) right away) to the patient and let them decide, I don't think mosaics should be transferred/my clinic does not allow transfer of mosaic embryos, and no one correct answer in this scenario/decisions should be made on a case by case basis. One quarter of prenatal only GCs selected the option to obtain consent for transfer of a mosaic embryo(s) while none of the infertility only GCs thought obtaining consent and proceeding with transfer of mosaic embryos would be the most appropriate next step in this scenario. Instead, the majority of infertility only GCs (65%) selected to stop the cycle. This option was only selected by 40% of prenatal only GCs ($p=0.007$). In addition, GCs who see patients before and after PGT-A were more likely to "select stop the cycle" than GCs who see patients for PGT-A only before

testing or only after testing (p=0.04). There was no correlation found between when respondents thought was the ideal time to discuss the possibility of mosaic embryos and the most appropriate next step when a euploid embryo does not survive thawing and only mosaic embryos remain.

REs were significantly more likely to report that their opinions were consistent with their clinic's policy than GCs with regard to the ideal time to discuss the possibility of mosaic embryos with patients and the most appropriate next step after a euploid embryo does not survive thawing and only mosaic embryos remain ($p<0.001$). When looking at the topic of the ideal time for the patient to decide whether or not to transfer a mosaic embryo(s) and to obtain informed consent, there was no statistically significant difference between REs and infertility GCs regarding whether their opinion was consistent with their clinic's policy. Additionally, GCs were more likely to report that their referring clinic does not have a policy or that they are unsure if their opinion was consistent with the clinic policy than REs ($p=<0.001$). GCs who work in IVF clinics were more likely report that their opinions were consistent with their clinic's policy than GCs who do not work in an IVF clinic ($p<0.001$).

	GCs n (%)	REs n (%)
Best time to discuss possibility of mosaic embryos	n = 174	n = 27
Never	0	0
Before an IVF cycle begins	105 (60.3)	20 (74)
After IVF but before PGT-A	35 (20.1)	0
After IVF, PGT-A & mosaic embryos identified	25 (14.4)	6 (22)
Other	4 (2.3)	1 (4)
Unsure	5 (2.9)	0
Answer to above consistency with clinic policy	n = 174	n = 27
Yes	39 (22.4)	17 (63)
No	6 (3.4)	1 (4)
We/they do not have a policy	85 (48.9)	9 (33)
Unsure	44 (25.3)	0
When decision should be made & informed consent obtained to TME	n = 175	n = 27
Never	0	0
Before an IVF cycle begins	21 (12)	5 (18.5)
After IVF but before PGT-A	10 (6)	0
After IVF, PGT-A & mosaic embryos identified	52 (30)	10 (37)
After IVF, PGT-A & only mosaic embryos	81 (46)	11 (40.7)
Other	6 (3)	1 (3.7)
Unsure	5 (3)	0
Answer to above consistency with clinic policy	n = 174	n = 27
Yes	27 (16)	15 (56)
No	5 (3)	2 (7)
We/they do not have a policy	96 (55)	9 (33)
Unsure	46 (26)	1 (4)
Next step after euploid embryo does not survive thawing and only mosaic remain	n = 174	n = 27
Stop the cycle and discuss the possibility of mosaic transfer for a future transfer date	84 (48)	15 (55.6)
Obtain consent to thaw a mosaic embryo and proceed with transfer as planned	30 (17)	4 (14.8)
Other	31 (18)	7 (25.9)
Unsure	29 (17)	1 (3.7)
Answer to above consistency with clinic policy	n = 173	n = 26
Yes	12 (7)	12 (46)
No	5 (3)	0
We/they do not have a policy	96 (55)	12 (46)
Unsure	60 (35)	2 (8)

Table 6: Perspectives on decision-making and consent

All respondents were asked to report how much difficulty they perceive their patients encounter when trying to understand and make decisions regarding PGT-A and transfer of mosaic embryos (Table 7). On average, we received a 90% response rate for GCs and 93% response rate for REs for all questions regarding patients' perceived difficulty. About half of GCs (47%) and REs (56%) perceive that their patients find it somewhat difficult to understand the benefits and limitations of PGT-A (Table 7). However, 29% of GCs indicated they think it is either somewhat easy or very easy for their patients while 19% of REs selected somewhat easy or very easy. Those who reported more comfort discussing PGT-A were more likely to report that they perceived their patients had less difficulty understanding PGT-A ($p=0.02$). Regarding patients' perceived difficulty deciding whether to pursue PGT-A, 41% of both GCs and REs reported it appears somewhat easy for their patients while about one third (33%) of all respondents selected somewhat difficult.

Providers perceive more difficulty for their patients to understand the benefits and limitations of transferring a mosaic embryo with 80% of both groups selecting either somewhat difficult or very difficult. Similar to PGT-A, those who reported more comfort discussing transfer of mosaic embryos were more likely to perceive that patients have less difficulty understanding this option ($p=0.02$). Interestingly, a provider's comfort discussing transfer of mosaic embryos was not correlated with how much difficulty they perceived patients had deciding whether or not to elect transfer of mosaic embryos. Two percent of GCs and 11% of REs thought it was somewhat easy or very easy for their patients to decide whether to pursue transfer of a mosaic embryo(s) while 87% of GCs and 81% of REs indicated they think it is somewhat difficult or very difficult for their patients to make this decision. A moderate positive correlation was found between how much difficulty respondents perceived their patients encounter understanding benefits/limitations of PGT-A and perceived difficulty understanding benefits/limitations of transfer of mosaic embryos ($rho=0.44$, $p<0.001$). There was a weak correlation between perceived patient difficulty deciding whether to pursue PGT-A and difficulty deciding whether to transfer mosaic embryos ($rho=0.23$, $p<0.001$). The majority of respondents (77%) reported more patient difficulty with the decision whether or not to transfer mosaic embryos than the decision whether

or not to undergo testing initially. Lastly, a moderate positive correlation existed between how much difficulty respondents perceived their patients encounter understanding benefits/limitations of transferring mosaic embryos and perceived difficulty deciding whether to elect that transfer (rho=0.45, $p<0.001$).

	GCs n (%)	**REs** n (%)
Understanding benefits/limitation of PGT-A	n = 174	n = 27
Very easy	1 (0.6)	3 (11.1)
Somewhat easy	50 (28.7)	5 (18.5)
Neither easy nor difficult	27 (15.5)	1 (3.7)
Somewhat difficult	81 (47.8)	15 (55.6)
Very difficult	10 (6.5)	3 (11.1)
Unsure	5 (2.5)	0
Deciding whether to pursue PGT-A	n = 174	n = 27
Very easy	4 (2)	2 (7.4)
Somewhat easy	72 (41)	11 (40.7)
Neither easy nor difficult	19 (11)	2 (7.4)
Somewhat difficult	56 (32)	10 (37)
Very difficult	8 (5)	2 (7.4)
Unsure	15 (9)	0
Understanding benefits/limitation of TME	n = 173	n = 27
Very easy	0	0
Somewhat easy	17 (9.8)	2 (7.4)
Neither easy nor difficult	9 (5.2)	2 (7.4)
Somewhat difficult	89 (51.4)	13 (48.1)
Very difficult	49 (28.3)	9 (33.3)
Unsure	9 (5.2)	1 (3.7)
Deciding whether to pursue TME	n = 174	n = 27
Very easy	1 (0.6)	0
Somewhat easy	2 (01.1)	3 (11)
Neither easy nor difficult	8 (4.6)	2 (7)
Somewhat difficult	56 (32.2)	8 (30)
Very difficult	95 (54.6)	14 (52)
Unsure	12 (6.9)	0

Table 7: Patient education and decision-making

Figure 4 summarizes the resources reported as influential to providers' personal feelings and/or clinical practice with regard to transfer of mosaic embryos. The resource that influenced the greatest number of respondents was the PGDIS position statement published in 2016 (75%) followed by laboratory reporting policies (71%). However, 60-80% of those who reported that the PGDIS position

statement influenced their practice did not select the factors it recommended for prioritization of mosaic embryos (which chromosome is involved, trisomy vs. monosomy and the level of mosaicism). The resource that was most commonly reported to have no influence was personal practice experience (30%). Between most of the articles/position statements (except the PGDIS position statement), there was a comparable percentage of respondents who indicated they had not read that resource (35-45%). There was also a comparable percentage of respondents who indicated that the resource influenced them across the various articles/position statements listed (45-55%). Additionally, there was a small group of respondents (less than 10%) who indicated they had read the resource and it did not influence them. From this, we could infer that among those who had read a resource, the vast majority of them felt it influenced them in some way.

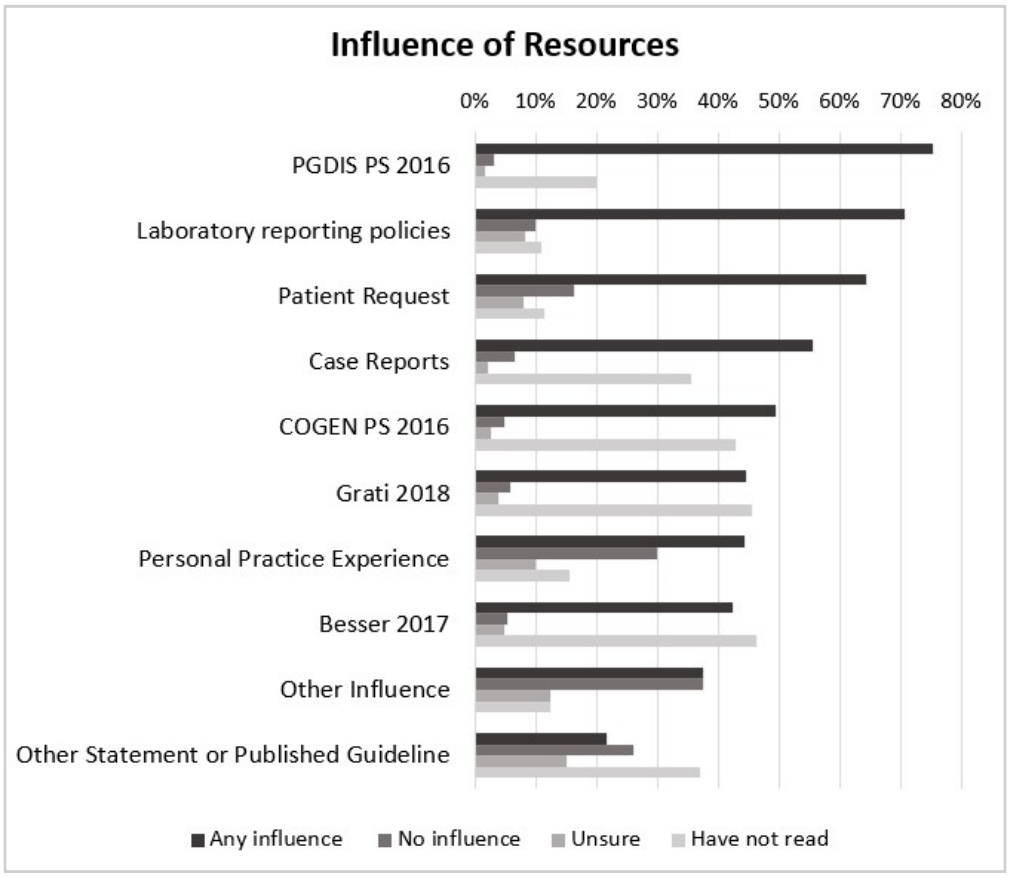

Figure 4: Influence of resources

Lastly, the respondents were asked to indicate whether they believe additional consensus/guidance is needed for a list of various topics regarding transfer of mosaic embryos (Figure 5). Depending on the topic in question, a large majority of respondents (67-84%) indicated that additional consensus/guidance is needed. Of note, 20% of respondents indicated that they thought no additional consensus/guidance is needed regarding when to discuss the possibility of mosaic embryos or when to consent for transfer of mosaic embryos. Those who indicated that no additional guidance was needed for these two topics were more likely to say they thought patients found it very easy or somewhat easy to decide whether to transfer mosaic embryos ($p<0.001$). Within two of the topics listed (prioritization when multiple mosaic embryos are present and the appropriate number of mosaic embryos to transfer), those who reported higher levels of comfort discussing transfer of mosaic embryos were more likely to report that they do not think additional consensus or clinical guidance is needed ($p<0.005$). However, there was no correlation between those who indicated additional consensus and/or guidance was needed and comfort level discussing transfer of mosaic embryos on these two topics.

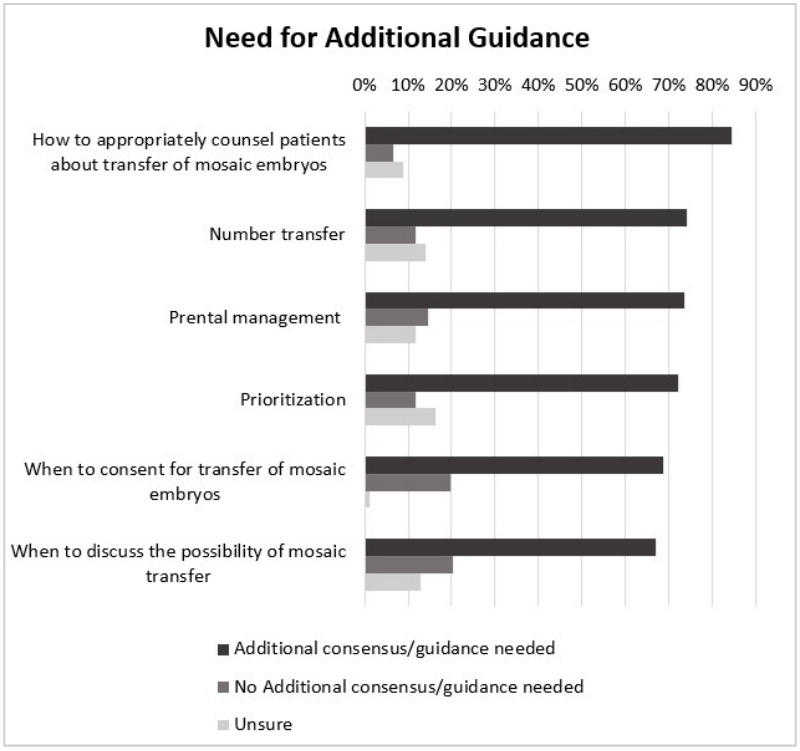

Figure 5: Need for additional consensus of guidance on various topics related to transfer of mosaic embryos

Discussion

Limited published guidance along with a lack of formal consensus regarding the transfer of mosaic embryos after IVF with PGT-A presents a complex clinical scenario for providers who are responsible for helping patients to understand their options and make reproductive decisions. The current study was conducted to describe the current practices regarding transfer of mosaic embryos, as reported by GCs and REs. Additionally, we aimed to determine GC and RE professional perspectives on patient education, informed consent, decision making and clinical guidance with regard to the transfer of mosaic embryos. The results show that overall, these providers desire additional consensus to help guide their practice.

Evaluating current practices of the GCs and REs that responded to the survey revealed a theme regarding the interaction between infertility GCs and REs. Namely, responses revealed that infertility GCs' experience and practices are more consistent with REs than with GCs of other specialties. Infertility GCs and REs working together and their relatively more frequent experience with PGT-A cases and results compared to non-infertility GCs could explain the similarities in their practices. Infertility GCs often differed from their prenatal colleagues in terms of the variability in responses with more variability among prenatal GCs. This could be due to less frequent experience with counseling about mosaic embryos and less familiarity with newly published data in this area among prenatal GCs. REs reported utilizing GCs more often for post-test/pre-transfer counseling than for pre-test counseling, whether that might be a lab GC, outside/contracted clinical GC or in-house GC. This may be a reflection of the lower levels of comfort among REs who participated in the study when counseling about mosaic embryos compared to counseling about PGT-A.

There were only two of six topics regarding transfer of mosaic embryos posed to respondents (prioritization of multiple mosaic embryos and the appropriate number of mosaic embryos to transfer) that had a statistically significant relationship between whether respondents thought additional guidance was needed on that topic and a providers' comfort level discussing transfer of mosaic embryos. Those reporting a lower level of comfort discussing transfer of mosaic embryos were more likely to be unsure

of whether additional guidance was needed on certain topics. It is hypothesized that those who were unsure may be less familiar with transfer of mosaic embryos and therefore, have not formed an opinion about whether additional guidance is needed. However, no correlation between the number of mosaic cases seen and comfort level discussing transfer of mosaic embryos was seen. Those who had higher levels of comfort discussing transfer of mosaic embryos were more likely to indicate that they did not think additional guidance was needed. However, even within these two topics, there was no statistically significant difference amongst those who indicated additional guidance was needed and comfort level discussing transfer of mosaic embryos. For all of the other four topics listed, there were no correlations found between comfort level and whether additional guidance was needed. Therefore, regardless of current practices and comfort level discussing transfer of mosaic embryos, the large majority of respondents agreed that additional consensus and clinical guidance is needed regarding how to appropriately counsel and manage cases involving mosaic embryos. This was reflected when analyzing how respondents prioritize multiple mosaic embryos when several are available for transfer. Although the REs had some consistency in their responses, there was no clear trend that indicated that GCs and REs have any set criteria or consensus for how they are prioritizing multiple mosaic embryos for transfer.

Responses regarding the influence of several applicable resources regarding transfer of mosaic embryos showed that the majority of providers who read publications on this topic feel as though those resources influenced their practice in some regard. Interestingly, the majority of those indicating that the PGDIS position statement influenced them did not report using the factors recommended in this position statement for prioritization. One possibility is that these resources influenced them in the past, but they no longer abide by these recommendations given conflicting data that has been published since the recommendations were established. Another possible explanation would be that the guidelines were misinterpreted by readers or were unclear in their recommendations. Respondents were asked whether the resources listed influenced them at all but were not specifically asked if they influenced them in

regard to each specific factor. Therefore, it is possible that respondents did feel like the PGDIS position statement influenced them but not in a way that aligned with its recommendations.

One aim was to identify how comfortable or confident respondents report feeling when counseling about PGT-A and transfer of mosaic embryos. The order of groups reporting the most comfort counseling to least comfort was consistent between these two topics. Infertility GCs were the most consistently comfortable group followed by REs, with non-infertility GCs most commonly reporting more discomfort. However, across all respondents, less comfort was reported regarding counseling about transfer of mosaic embryos compared to PGT-A. This may be due to less experience with cases involving mosaic embryos and/or limited consensus and clinical guidance on this topic compared to PGT-A. Regardless of the cause, this finding identifies an area for additional studies and proposed guidelines to help providers feel more confident counseling their patients. This study identified that a provider's comfort level discussing a topic is correlated with how much they think their patients struggle to understand that topic. Additionally, providers' perceptions about the level of difficulty their patients face through the IVF process reflected that the decision whether to use mosaic embryos was more challenging than decisions about whether to pursue testing of embryos.

Although the majority of respondents felt that the option of transferring mosaic embryos should be available, prenatal only GCs were less likely to simply answer "yes". They were more likely to respond that it would depend on particular variables and cited specific circumstances including, which chromosome is involved, if there are any euploid embryos available, whether the patient has had genetic counseling and the patient's threshold for acceptability and risk. However, infertility only GCs did not share the sense that it is conditional and more commonly indicated it should be an option outright. Prenatal GCs' feelings on this topic could be attributed to their relatively less frequent experience and lower comfort with cases involving mosaic embryos. The presence of a willingness to accept risks associated with new IVF treatments among infertile patients' in order to achieve a pregnancy has been described previously (Hartshorne et al., 2002). This willingness accompanied by the physical, emotional, psychological and financial burden that these patients accept throughout the IVF process demonstrates

how invested these patients are in their efforts to have a child. Given that infertility GCs work with this patient population more frequently than non-infertility patients, they may be more conditioned to their patients electing new reproductive options that have limited research and feel more comfortable about offering something less proven such as transfer of mosaic embryos.

There was less consensus among respondents when they were asked about the ideal time to counsel patients on the possibility of mosaic embryos, decide whether to transfer mosaic embryos, and obtain informed consent, as well as the most appropriate next step when a euploid embryo does not survive thawing and only mosaic embryos remain. Two thought processes emerged from these responses that can be differentiated by how much emphasis is placed on anticipatory guidance. One thought process is that the possibility of mosaic embryos does not need to be discussed and decisions on whether to transfer mosaic embryos do not need to be made until the patient is in that situation rather than having a discussion and deciding prior to beginning the IVF cycle. These respondents may feel that it is not necessary or efficient to have this conversation with all their patients who pursue PGT-A since a minority of them will only have mosaic embryos after testing. Furthermore, one with this thought process could argue the efficacy/utility of this anticipatory decision making since patients could change their minds after testing identifies mosaic embryos even if they had made a tentative decision prior to testing. Conversely, the other thought process gleaned from these questions is one with a greater emphasis on making patients aware of the concept/possibility of mosaic embryos prior to testing and having patients determine their preference whether or not to utilize mosaic embryos before the IVF cycle. This theoretically allows the patient to weigh their options more logically and rationally compared to placing this decision on the patient during an IVF cycle where they may be experiencing mood changes as a side effect of their treatment (Wallach et al., 1982). This raises a question regarding informed consent of this vulnerable population who already carries a psychological burden when asked to make these high stakes decisions with limited time (Besser et al., 2017). Whether GCs see these patients before or after testing may influence their feelings about when these conversations should be had since they may not have the opportunity to see these patients at multiple time points (before and after

testing). This was demonstrated with regard to the most appropriate step in the scenario that a euploid embryo(s) does not survive the thawing process and only mosaic embryos remain. Those seeing patients before and after testing were more likely to think they should stop the cycle. GCs may feel more strongly about the importance of providing anticipatory guidance. Furthermore, REs may view their patients as being more resilient and capable of making these critical decisions than GCs. The question of the amount of importance that should be placed on the timing of these discussions with patients' needs to be explored further by those practicing in this field with the goal of creating a broader consensus. It will also be imperative to assess patient experiences and preferences to determine when and how they would like to be presented with information.

GCs were identified as being more likely to report that they are unsure if their opinions regarding the appropriate timing and actions regarding transfer of mosaic embryos is consistent with the clinic's policy compared to REs. Some possible reasons for this uncertainty could be a lack of clarity and transparency of the IVF clinic's policies or limited communication between referring REs and their contracted/outside GC providing counseling to the patient. This shows a need for more communication between REs and GCs who are working together. It is imperative for GCs to at least be aware of the clinic's policies, if not also being involved in creating such policies, so as not to provide conflicting/misleading information in the counseling session as that could lead to confusion, frustration and/or disappointment for patients.

Future research should investigate patients' perspectives on transfer of mosaic embryos. Ideally, a paired study with the patient and their provider could be conducted with a survey before and after PGT-A as well as before and after transfer of a mosaic embryo(s). This would allow researchers to compare provider and patient perspectives and provide valuable insight into best practices. Further studies could help provide an evidence-based approach to care for patients who are identified to have mosaic embryos after IVF and PGT-A. Presently, there may be barriers to conducting this research such as availability of data from IVF centers and from providers. Given that there may be multiple providers involved in the care of one patient throughout the IVF and PGT-A process, there needs to be efforts to determine how

these providers can collaborate to collect and organize data regarding how these patients were counseled, their decisions and outcomes.

Our study limitations had a significant impact on our ability to detect certain differences between groups and the generalizability of our results. One such limitation of this study was the low statistical power due to the total number of respondents and the comparatively few REs compared to GCs. Unlike the GCs, REs were unable to be reached by listserv and instead were contacted personally via email by the principal investigator or by a GC that forwarded them the survey. Allowing GCs to forward the survey to REs they work with helped to collect responses but does introduce a bias in the RE cohort. The REs included in this study may be more likely to work with or know a GC and therefore, their responses may not be generalizable to all REs. Additionally, the majority of RE respondents' practice in Texas with a low response rate from other states which may make it more difficulty to generalize these results to all REs. Since the survey was anonymous, we were unable to determine whether or not we received multiple RE responses from the same clinic. This represents the potential that our RE cohort is more homogeneous than the general RE population. The RE responses are further limited given that 9 were fellows with limited experience and clinical judgment. Additionally, it is unclear what percentage of practicing REs and RE fellow responded to the survey. As such the description of experience with, approaches to and views on the topics of the study may only be truly representative of the select group of REs who responded to the survey and not the larger RE population. The prenatal GC cohort in this study constituted a larger percentage of the overall GC cohort than what is reported in the NSGC PSS published in 2018. However, the proportion of GCs identifying as preconception was comparable with the PSS. Additionally, the survey tool used for this study was not validated; therefore, there was a potential for questions to be interpreted differently than intended. Given the low response rates within GC and RE cohorts, we recognize that these results may not be representative of these provider groups practices and perspectives regarding transfer of mosaic embryos. These results represent a small sampling of these groups to provide a platform for discussion and further research.

In conclusion, this research shows that providers report feeling less comfortable counseling patients regarding transfer of mosaic embryos than with pre-test PGT-A counseling. Additionally, there may be limited consensus among providers regarding their practices and perspectives surrounding transfer of mosaic embryos. The majority of these providers felt that additional consensus and clinical guidance is needed about how to counsel these patients and the appropriate timing for specific events in the counseling process such as patient education and informed consent. Additional research elucidating both patient and provider perspectives along with additional data about clinical outcomes of these transfers may help lead to a consensus in this community and therefore provide opportunities for the development of additional clinical guidance. A more consistent and evidence-based approach to patient care regarding counseling about and transfer of mosaic embryos could lead to better outcomes, more satisfied patients and could seek to minimize ethical conflicts for both patients and providers related to the use of mosaic embryos.

Appendix

Survey

*= answer required

Demographics - *All*

Q1. Consent
1. I agree
2. I do not agree >>> exit survey

Q2. What is your current area of practice? *
1. Prenatal and/or Infertility Genetic Counselor
2. Reproductive Endocrinologist
3. None of the above >>> Thank you for your participation

Q3. In what state do you currently practice?
1. Drop down with states/DC/I do not practice in the United States/Prefer not to answer

GC Experience - *Genetic Counselor (GC)*

Q4. How would you describe your work setting? (Select all that apply)
1. Academic institution
2. Non-academic institution
3. Private practice
4. IVF clinic
5. Other (free text option)

Q5. How many total genetic counselors work in your clinic/department/practice within your specialty? (free text box)

Q6. What type of GC do you identify as? (Please select all that apply) *
1. Prenatal
2. Preconception
3. Infertility/ART
4. Other (free text option)

Q7. How many total years have you spent providing prenatal, preconception and/or infertility counseling? (response requested if left blank)

Definition of PGS/PGT-A: Preimplantation genetic screening (PGS) or Preimplantation genetic testing for aneuploidy (PGT-A) refers to genetic testing of embryos for chromosomal abnormalities following IVF and prior to embryo transfer. It will be referred to as PGS/PGT-A throughout the remainder of the survey.

Q8. Select the option that best describes how often you personally see preconception patients to discuss preimplantation genetic screening/testing for aneuploidy (PGS/PGT-A)? *
1. Never
2. At least once per year
3. At least twice per year
4. At least once per month
5. At least once per week
6. Other (free text option)

All that answered something other than 'never' continue to 5a

Q9. When do you typically see patients to discuss PGS/PGT-A?

1. Before testing
2. After testing
3. Both
4. It depends (please describe in the space provided)
5. Other (free text option)

Definition of mosaicism: the presence of two or more different chromosome complements within an embryo that developed from a single fertilized egg.

Q10. Have you ever personally seen a patient to discuss the option of transferring a **mosaic** embryo(s) following PGS/PGT-A? *

1. Yes
2. No

Q11. [If yes] Approximately what how many total cases have you seen to discuss the transfer of a **mosaic** embryo(s)?

1. 1-2
2. 3-5
3. 6-10
4. 11-20
5. More than 20

Q12. [if yes conti] If you have been in the situation where there are multiple **mosaic** embryos available, what factors do you consider when prioritizing which **mosaic** embryo(s) to transfer? (Select all that apply)

1. Level of mosaicism
2. Trisomy vs. monosomy
3. Whole vs. partial chromosome (deletion/duplication) involved
4. Which chromosome is involved
5. Published scoring system
6. Internal scoring system
7. Other (free text option)
8. Unsure
9. I have not been in a situation where there are multiple mosaic embryos available
10. I do not advise the RE on which embryo(s) to consider for transfer

Q13. Please rank (if multiple) the factors selected in the previous question that you consider when prioritizing mosaic embryos from most important (1) to least important. (Carries over items selected in previous question)

Q14. [If yes conti] Approximately what percentage of the patients with whom you have discussed the option of transferring a **mosaic** embryo(s) following PGS/PGT-A elected to proceed with the transfer of a **mosaic** embryo(s)? *

1. None
2. <10%
3. 10-25%
4. 26-50%
5. 51-75%
6. 76-100%
7. Other (free text option)
8. Unknown/information not available

Q15. [If transfer of mosaic embryo] Did any of the transfers result in a viable pregnancy (heartbeat noted)?
1. Yes
2. No
3. Unsure

Q16. [If transfer of mosaic embryo] What monitoring and/or testing did you recommend for these pregnancies? (free text box)

Q17. [if no] Please indicate what factors keep you from seeing patients to discuss the transfer of **mosaic** embryos?
1. Transfer of **mosaic** embryos is against our/our referring providers' policy
2. The opportunity (**mosaic** results after PGS/PGT-A) hasn't presented itself yet
3. Our reference lab does not report **mosaicism**
4. Other (free text option)
5. Unsure

RE Experience - *Reproductive Endocrinologist (RE)*

Q18. How many years have you practiced as an RE post-fellowship? (response requested if left blank)
1. (free text box)
2. I am currently a fellow

Q19. How many total REs are there in your current clinic/practice? (free text box)

Definition of PGS/PGT-A: Preimplantation genetic screening (PGS) or Preimplantation genetic testing for aneuploidy (PGT-A) refers to genetic testing of embryos for chromosomal abnormalities following IVF and prior to embryo transfer. It will be referred to as PGS/PGT-A throughout the remainder of the survey.

Q20. Does your clinic/practice offer patients the option of preimplantation genetic screening/preimplantation genetic testing for aneuploidy (PGS/PGT-A) to screen for chromosome abnormalities? *
1. yes
2. no

Q21. [If yes] Under what circumstances do you personally offer PGS/PGT-A?
1. I offer PGS to all patients
2. I offer PGS to all patients of a certain age
3. I only offer PGS to patients who meet specific criteria (e.g. history of recurrent pregnancy loss, history of failed embryo transfers)
4. I never offer PGS

Q22. [If yes] Select the option that best describes how often you personally offer PGS/PGT-A?
1. None
2. At least once per year
3. At least twice per year
4. At least one per month
5. At least once per week
6. Other (free text option)
7. Unsure

Q23. [If yes, conti] Approximately what percentage of your patients to whom you offer PGS/PGT-A, elect PGS/PGT-A testing?
1. None

2. 1-10%
3. 11-25%
4. 26-50%
5. 51-75%
6. 76-100%
7. Other (free text option)
8. Unknown/information not available

Q24. [If yes conti] Who typically provides the PGS/PGT-A pre-test counseling for your patients? (Select all that apply)
1. I do
2. An in-house genetic counselor
3. (contracted/outside clinical genetic counselor)
4. (PGS/PGT-A laboratory genetic counselor)
5. other (free text option)

Q25. [If no] Please indicate what factors keep you from offering PGS/PGT-A: (select all that apply)
1. Clinic policy
2. Personal or professional preference
3. Clinic's inability to perform embryo biopsy
4. Other (free text option)
5. Unsure

If they answered yes to #3 above (They do offer PGS/PGT-A).
Definition of mosaicism: the presence of two or more different chromosome complements within an embryo that developed from a single fertilized egg.

Q26. Have any of your personal patients received a PGS/PGT-A report with zero normal embryos but one or more **mosaic** embryos? *
1. Yes
2. No
3. Unsure

Q27. [If yes] Approximately what percentage of your patients who pursue PGS/PGT-A are left with zero normal embryos but one or more **mosaic** embryos?
1. None
2. 1-10%
3. 11-25%
4. 26-50%
5. 51-75%
6. 76-100%
7. Other (free text option)
8. Unknown/information not available

Q28. Does your clinic/practice offer the option of transferring a **mosaic** embryo(s)? *
1. Yes
2. No

Q29. [if yes] Who typically provides the post-test/pre-transfer counseling? (Select all that apply)
1. I do
2. An in-house genetic counselor
3. (contracted/outside clinical genetic counselor)
4. (PGS/PGT-A laboratory genetic counselor)
5. other (free text option)

Q30. [if yes conti] Have you personally discussed the option to transfer a **mosaic** embryo with one of your patients? *
    1. Yes
    2. No
Q31. [If yes] Approximately how many times have you discussed the option to transfer a **mosaic** embryo with a patient?
    1. 1-2
    2. 3-5
    3. 6-10
    4. 11-20
    5. More than 20
Q32. [If yes conti] Of the patients with whom you discussed the option to transfer a **mosaic** embryo(s), approximately what percentage of these patients elected to proceed with transfer of **mosaic** embryo(s)? *
    1. None
    2. 1-10%
    3. 11-25%
    4. 26-50%
    5. 51-75%
    6. 76-100%
    7. Other (free text option)
    8. Unknown/information not available
Q33. [If transfer of mosaic embryo(s)] Did any of the transfers result in a viable pregnancy (heartbeat noted)?
    1. Yes
    2. No
    3. Unsure
Q34. [If transfer of mosaic embryo(s)] What, if any, additional monitoring and/or testing did you recommend for these pregnancies? (free text box)
Q35. [if yes conti] If you have been in the situation where there are multiple **mosaic** embryos available, what factors do you consider when prioritizing which **mosaic** embryo(s) to transfer? (Select all that apply)
    1. Level of mosaicism
    2. Trisomy vs. monosomy
    3. Whole vs. partial chromosome (deletion/duplication) involved
    4. Which chromosome is involved
    5. Published scoring system
    6. Internal scoring system
    7. Other (free text option)
    8. Unsure
Q36. I have not been in a situation where there are multiple mosaic embryos Please rank (if multiple) the factors selected in the previous question that you consider when prioritizing mosaic embryos from most important (1) to least important.
Q37. [if no] To your knowledge, has any other RE in your practice offered the transfer of a **mosaic** embryo to a patient?
    1. Yes
    2. No
    3. Unsure
    4. I am the only RE in my practice

Q38. [if no] Please indicate what factors keep you from offering the transfer of **mosaic** embryos: (please select all that apply)
    1. Clinic policy
    2. I think the risk is too high
    3. I am concerned about liability
    4. I do not think patients understand the risks
    5. The lab we use doesn't report/we do not request that information
    6. Other
    7. Unsure

Patient Education/Confidence/Decision-Making/Informed Consent– *All* – Please answer the following questions even if you have never discussed the transfer of **mosaic** embryos with a patient

Q39. Regardless of whether you have offered/discussed the option of transfer of a **mosaic** embryo(s) in your practice, do you feel as though the option of transferring **mosaic** embryos should be given?
    1. Yes
    2. No
    3. It depends (free text option)
    4. Unsure

Q40. How comfortable do you/would you feel discussing PGS/PGT-A in general with your patients?
    1. Extremely comfortable
    2. Somewhat comfortable
    3. Neither comfortable nor uncomfortable
    4. Somewhat uncomfortable
    5. Extremely uncomfortable

Q41. How comfortable do you/would you feel discussing the option of transferring a **mosaic** embryo with your patients? 1-5 scale

Q42. Ideally, when do you feel the possibility of having a **mosaic** embryo(s) following PGS/PGT-A should be discussed with a patient/couple?
    1. Never
    2. Before an IVF cycle begins
    3. After the IVF cycle has started but before PGS/PGT-A testing has been performed (before the egg retrieval)
    4. After the IVF cycle and PGS/PGT-A is complete and mosaic embryos are identified
    5. Other
    6. Unsure

Q43. Is this consistent with your clinic/practice/referring practice's policy?
    1. Yes
    2. No
    3. We/they don't have a policy
    4. Unsure

Q44. Ideally, when do you feel the decision should be made and informed consent obtained whether or not to transfer a **mosaic** embryo following PGS/PGT-A?
    1. Never
    2. Before an IVF cycle begins
    3. After the IVF cycle has started but before PGS/PGT-A testing has been performed (before the egg retrieval)
    4. After the IVF cycle and PGS/PGT-A is complete and mosaic embryos are identified

5. After the IVF cycle and PGS/PGT-A testing is complete and only mosaic embryos (but no normal) are identified
6. Other
7. Unsure

Q45. Is this consistent with your clinic/practice/ referring practice's policy?
1. Yes
2. No
3. We/they don't have a policy
4. Unsure

Q46. In your opinion, if a euploid (normal) embryo does not survive thawing, and only **mosaic** embryos remain, what is the most appropriate next step?
1. Stop the cycle, and discuss the possibility of **mosaic** transfer for a future transfer date
2. Obtain consent to thaw a **mosaic** embryo and proceed with transfer as planned
3. Other (free text option)
4. Unsure

Q47. Is this consistent with your clinic/practice/ referring practice's policy?
1. Yes
2. No
3. We/they don't have a policy
4. Unsure

Q48. In your opinion, how difficult do/would your patients find it to **understand** the benefits and limitations of PGS/PGT-A?
1. Very easy
2. Somewhat easy
3. Neither easy nor difficult
4. Somewhat difficult
5. Very difficult
6. Unsure

Q49. In your opinion, how difficult do/would your patients find it to **decide** whether or not to pursue PGS/PGT-A? Difficulty likert scale

Q50. In your opinion, how difficult do/would your patients find it is to **understand** the benefits and limitations to transfer a **mosaic** embryo(s)? Difficulty likert scale

Q51. In your opinion, how difficult do/would your patients find it to **decide** whether or not to transfer a **mosaic** embryo(s)? Difficulty likert scale

Clinical Guidance– *All* – Please answer the following questions even if you have never discussed the transfer of **mosaic** embryos with a patient

Q52. How much, if at all, have the following influenced your personal feelings and/or clinical practice with regard to the transfer of **mosaic** embryos? Influence likert scale (no influence/minimal influence/moderate influence/significant influence/unsure/have not read)
1. **2016 Preimplantation Genetic Diagnosis International Society (PGDIS) position statement** – summary: Providers can consider transfer of a mosaic embryo(s) when there are no non-mosaic euploid embryos and no option for undergoing another IVF cycle. Recommended prioritization criteria (if multiple mosaic embryos are identified) include monosomies are preferred to trisomies, percentage of abnormal cells, and which chromosome is involved in the abnormal cell line (mosaicism involving specific chromosomes are associated with adverse outcomes such as uniparental disomy or IUGR).

2. **2016 Controversies in Preconception, Preimplantation and Prenatal Genetic Diagnosis (CoGEN) position statement** – summary: consistent with PGDIS position statement outlined above
3. **2017 Besser et al. commentary (RBMO)** – summary: First commentary to address pre- and post-test genetic counseling considerations, as well as prenatal screening and diagnosis considerations.
4. **2018 Grati et al. paper (RBMO)** – summary: Proposes an evidence-based scoring system (specific risk for each specific chromosome) based on prenatal samples for prioritizing mosaic aneuploid embryos for transfer.
5. Other published statements/guidelines (open response)
6. Case reports of transfers of mosaic embryos (including NEJM 2015 letter to the editor)
7. Personal/practice experience of successful outcomes
8. Patient request
9. Laboratory reporting policies (ex. identifies and reports mosaic embryos, discloses level of mosaicism, etc.)
10. Other (free text option)
11. Other (free text option)
12. Other (free text option)

Q53. For which, if any, of the below topics do you believe additional consensus/guidance is needed? (additional consensus/guidance needed, no additional consensus/guidance needed or unsure)

1. When to discuss the possibility of **mosaic** embryo transfer
2. When to obtain patient consent for transfer of **mosaic** embryo
3. How to appropriately counsel patients about the transfer of **mosaic** embryos
4. Prioritization of **mosaic** embryos for transfer
5. How many **mosaic** embryos to transfer at a time
6. Prenatal testing and prenatal management recommendations following transfer of **mosaic** embryo(s)
7. Other (free text option)
8. Other (free text option)
9. I don't desire additional information
10. Unsure

Feedback/Gift-Card Entry

Q54. Please provide any general comments regarding your opinions and/or experiences with transfer of **mosaic** embryos (free text box)

Q55. Please enter your email address if you would like to be included in the gift card raffle (free text box)

Invitation to forward to REs – *All*

Q56. If you are aware of any reproductive endocrinologists that may be willing to participate, we invite you to forward the survey link to them (http://bit.ly/mosaic-embryos). If you would prefer, you may provide their email address(es) in the text box below, allowing the study personnel to send them an invitation to participate in the survey. (free text box)

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