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ASSISTED REPRODUCTION TECHNOLOGIES

Clinical implementation of algorithm-based embryo selection is associated with improved pregnancy outcomes in single vitrified warmed euploid embryo transfers

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Abstract

Purpose To assess whether utilization of a mathematical ranking algorithm for assistance with embryo selection improves clinical outcomes compared with traditional embryo selection via morphologic grading in single vitrified warmed euploid embryo transfers (euploid SETs).

Methods A retrospective cohort study in a single, academic center from September 2016 to February 2020 was performed. A total of 4320 euploid SETs met inclusion criteria and were included in the study. Controls included all euploid SETs in which embryo selection was performed by a senior embryologist based on modified Gardner grading (traditional approach). Cases included euploid SETs in which embryo selection was performed using an automated algorithm-based approach (algorithm-based approach). Our primary outcome was implantation rate. Secondary outcomes included ongoing pregnancy/live birth rate and clinical loss rate.

Results The implantation rate and ongoing pregnancy/live birth rate were significantly higher when using the algorithm-based approach compared with the traditional approach (65.3% vs 57.8%, $p<0.0001$ and 54.7% vs 48.1%, $p=0.0001$, respectively). After adjusting for potential confounding variables, utilization of the algorithm remained significantly associated with improved odds of implantation (aOR 1.51, 95% CI 1.04, 2.18, $p=0.03$) ongoing pregnancy/live birth (aOR 1.99, 95% CI 1.38, 2.86, $p=0.0002$), and decreased odds of clinical loss (aOR 0.42, 95% CI 0.21, 0.84, $p=0.01$).

Conclusions Clinical implementation of an automated mathematical algorithm for embryo ranking and selection is significantly associated with improved implantation and ongoing pregnancy/live birth as compared with traditional embryo selection in euploid SETs.

Keywords Embryo selection · Morphologic grading · Preimplantation genetic testing · Mathematical modeling · In vitro fertilization

Introduction

One of the most important aspects of assisted reproductive technology (ART) is the selection of an optimal embryo for transfer. Modern ART centers commonly utilize a treatment strategy that extends embryo culture to blastulation, which allows for trophectoderm biopsy for preimplantation genetic testing for aneuploidy (PGT-A). PGT-A has developed as a means of identifying and excluding chromosomally abnormal embryos in order to improve embryo selection prior to transfer. However, morphologic grading remains a significant metric for consideration, especially among patients with more than 1 euploid embryo available at the time of transfer [1–3]. In papers published by Nazem et al [1] and Irani et al [2], a better morphologic grade was associated with a higher ongoing pregnancy/live birth rate, even among euploid embryos. However, the optimal method for integrating morphologic parameters into embryo selection in patients who have multiple euploid embryos available requires further investigation.

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A growing number of studies have focused on developing mathematical models that incorporate morphologic or morphokinetic data to predict which embryo would be optimal for selection and result in the best transfer outcome [4–7]. However, the objective in each of these studies was to validate models that were developed using prior transfer cycles with known clinical results. To our knowledge, there is no published research comparing embryo selection by a skilled embryologist with the clinical implementation of an automated, algorithm-based ranking system for embryo scoring and selection in single vitrified warmed euploid embryo transfer cycles. Therefore, this study sought to assess whether clinical implementation of automated, algorithm-based embryo selection was associated with improved reproductive outcomes in single vitrified warmed euploid embryo transfers.

Materials and methods

Study design

This retrospective cohort study included patients who underwent controlled ovarian hyperstimulation (COH), in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI), and subsequent vitrified warmed euploid single embryo transfer (euploid SET) at an academic, private medical center from September 2016 to February 2020. All embryos underwent PGT-A prior to transfer. Of note, all PGT-A was performed using next-generation sequencing (NGS).

Controls included euploid SETs in which a senior embryologist selected the embryo for transfer based on a site-specific modified Gardner grading system and day of biopsy (traditional approach). Cases included euploid SETs in which the embryo was selected using an automated algorithm-based approach (algorithm-based approach). Only medicated endometrial preparation cycles for autologous embryo transfer were included. From September 2016 to July 2017, the algorithm-based approach had not yet been implemented, and therefore only the traditional approach was utilized. From February 2018 to February 2020, the algorithm-based approach was exclusively implemented. From July 2017 to January 2018, a hybrid model was used in which the traditional and algorithm-based approaches were both utilized, without distinction or documentation as to which method was used for embryo selection; cycles from this time period were therefore excluded from the study. Cycles in which more than one embryo was transferred, cycles utilizing untested and/or fresh embryos, donor/recipient cycles, and patients with a diagnosis of uterine factor were also excluded from the analysis. Demographic data was collected, including female patient age, body mass index (BMI), ovarian reserve testing (day 3 follicle stimulating hormone (FSH) and anti-Mullerian hormone (AMH)), year of embryo transfer, obstetric history, endometrial thickness at the time of embryo transfer, and progesterone level at the time of embryo transfer.

Stimulation protocol and laboratory procedures

Controlled ovarian hyperstimulation and subsequent embryology laboratory techniques were performed as described previously [8]. Briefly, patients received a combination of recombinant FSH and human menopausal gonadotropin with either a gonadotropin releasing hormone (GnRH) antagonist protocol, in which a flexible GnRH antagonist was initiated for luteal hormone suppression, or a GnRH agonist long or short protocol. When at least two follicles reached 18mm in diameter or greater, final oocyte maturation was triggered via either human chorionic gonadotropin (Novarel, Ferring Pharmaceuticals, Parsippany, NJ, USA) or recombinant human chorionic gonadotropin (Ovidrel, EMD Serono, Rockland, MA, USA) alone or hCG in combination with 40IU of a GnRH agonist (Lupron, AbbVie Laboratories, Chicago, IL, USA). Transvaginal oocyte retrieval was then performed approximately 36 h later. Retrieved oocytes were then evaluated for maturity, and those oocytes that reached metaphase II underwent ICSI approximately 5 h post-retrieval. Assisted hatching was performed on day 3 of development, and extended culture with sequential media was performed until embryos reached the blastocyst stage; trophectoderm biopsy was performed on day 5 or 6 of development when the embryo reached a morphologic grade of 4CC or greater (modified Gardner score) [9].

For vitrified warmed embryo transfer cycles, endometrial preparation was performed as follows: patients initiated 2mg micronized oral estradiol (Estrace, Teva Pharmaceuticals, NJ, USA) on day 3 of a subsequent menstrual cycle, utilized twice daily for 4 days and then increased to three times daily thereafter. After approximately 11 days, patients underwent transvaginal sonography to evaluate the endometrial pattern and thickness. Once the endometrial thickness was 7mm or greater, patients were initiated on progesterone, administered either via intramuscular injection (Watson Pharma, Parsippany-Troy Hills, NJ, USA) or a combination of oral (Prometrium; Solvay Pharmaceuticals, Princeton, NJ, USA) and vaginal (Endometrin; Ferring Pharmaceuticals, Parsippany, NJ) supplementation per patient preference. After 5 days of progesterone administration, embryo transfer was performed, and estradiol and progesterone were continued thereafter.

Embryo grading

Blastocysts were graded based on a center-specific modified Gardner's scoring system which evaluated the main components of the blastocyst: the inner cell mass (ICM), the trophectoderm (TE), and the degree of blastocyst expansion,

as described by Hernandez-Nieto et al [9]. Grading was performed only by senior embryologists at the fertility center. The ICM was graded as follows: A, many cells tightly compacted; B, some cells tightly compacted or organizing; C, some cells disorganized; and D, few cells disorganized. TE grading was as follows: A, many cells forming a cohesive epithelium; B, moderate cells forming a loose epithelium; C, some cells forming a loose epithelium; and D, very few cells. Finally, grading of blastocyst expansion was categorized as follows: 1, blastocyst cavitation initiated; 2, cavitation is less than 50% of the full embryonic volume; 3, cavity completely fills the embryo; 4, expanded blastocyst, cavity volume exceeds the volume of embryo in *zona pellucida*, with at least four to five cells herniating out of the zona; 5, hatching blastocyst, at least 50% the trophectoderm has herniated out of the zona; and 6, hatched blastocyst, blastocyst has extruded entirely out of the zona.

Algorithm development

To create the algorithm, a mixed effect logistic model for the outcome of implantation was created by analyzing the outcomes of 1924 single vitrified warmed euploid embryo transfers from 1431 unique patients from March 2012 to April 2017. Of note, the embryo grade utilized for the model was obtained at the moment prior to vitrification. At cryopreservation, all embryos had an expansion grade of 4, 5, or 6; an ICM grade of A, B, or C; and a TE grade of A, B, or C and were biopsied and cryopreserved on either day 5 or day 6 of development. Embryo transfers were included in the model if the endometrial thickness at the time of transfer was at least 7mm. Within the model, the independent variables included ICM grade, TE grade, expansion grade, and day of TE biopsy and cryopreservation, using as a reference for comparison an embryo with expansion grade 6, an ICM grade C, and a TE grade C that was eligible for biopsy and cryopreservation on day 6 of development (Table 1). The odds ratios from these models were then utilized as weighted multipliers in order to create a composite score for each embryo based on the following embryonic parameters: expansion grade, ICM grade, TE grade, and day of biopsy and cryopreservation. Figure 1 represents a heat map demonstrating all of the potential composite scores using all combinations of embryonic parameters. For a given patient with multiple euploid embryos available for transfer, euploid embryos were ranked according to their composite score, and the embryo with the highest score was selected for transfer.

Outcomes

The primary outcome was implantation rate. Secondary outcomes included ongoing pregnancy/live birth rate and clinical loss rate. Implantation rate was defined as the number of gestational sacs seen on transvaginal ultrasound divided by the number of single embryo transfers performed. Ongoing pregnancy/live birth rate was defined as the number of ongoing pregnancies or live births at the time of discharge from the study center recorded over the number of single embryo transfers performed. The clinical loss rate was calculated as the total number of pregnancies that failed to progress after having visualized an intrauterine gestational sac over the total number of transfers with a subsequent positive hCG.

Table 1 Odds of embryo implantation integrated into the final scoring algorithm

	OR (95% CI)*
Day 5 Embryo Biopsy/cryopreservation	1.33 (1.07, 1.66)
Day 6 Embryo Biopsy/cryopreservation	Reference
Expansion Grade 4	1.16 (0.82, 1.64)
Expansion Grade 5	1.10 (0.78, 1.56)
Expansion Grade 6	Reference
ICM Grade A	2.51 (1.72, 3.68)
ICM Grade B	1.69 (1.14, 2.51)
ICM Grade C	Reference
TE Grade A	1.21 (0.90, 1.62)
TE Grade B	1.21 (0.98, 1.69)
TE Grade C	Reference

*Embryo with an Expansion Grade 6, ICM Grade C, TE Grade C, biopsied and cryopreserved on day 6 used as reference

Statistical analysis

Measures of central tendency and dispersion were analyzed, and the normality of all variables was determined. Continuous data was analyzed using either Student's *T*-test for normally distributed data or Mann-Whitney *U* test for skewed data. Chi-square was used to analyze categorical data. In addition, logistic multivariable generalized estimating equation (GEE) regression models were used to calculate odds ratios (OR) and to adjust for potential confounding factors and repeated measures; variables were included in the models if they showed statistical significance and/or were perceived to be clinically pertinent. Results were expressed as mean and standard deviation (SD), percentages, and adjusted odds ratios (aORs) with 95% confidence intervals (CIs). All *p*-values were two sided with a clinical significance level set at $p<0.05$. To assess whether our study was adequately powered to detect the difference noted in our primary outcome, a post hoc power analysis was performed. In order to ensure a power of 80% for detecting an effect size of 8% in implantation rate, 593 embryo transfers in each cohort were required (alpha 0.05). Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc. Cary, North Carolina).

		Day of Biopsy							
		5			6				
ICM Grade	A	4.685638	4.659984	3.872428	3.523036	3.4776	2.9116	4	Expansion Grade
	B	3.154872	3.106656	2.607332	2.372084	2.3184	1.9604		
	C	1.866788	1.8492	1.5428	1.4036	1.38	1.16		
	A	4.443277	4.376333	3.67213	3.34081	3.26592	2.761	5	
	B	2.991689	2.917555	2.47247	2.24939	2.17728	1.859		
	C	1.77023	1.73664	1.463	1.331	1.296	1.1		
	A	4.039343	4.05216	3.3383	3.0371	3.024	2.51	6	
	B	2.719717	2.70144	2.2477	2.0449	2.016	1.69		
	C	1.6093	1.608	1.33	1.21	1.2	1		
		A	B	C	A	B	C		
		Trophectoderm Grade							

Fig. 1 Heat map depicting calculated composite scores of embryos using the automated algorithm

Ethical approval

The study was approved by an academic Institutional Review Board (IRB# 18-00452). Patient information was de-identified before data analysis.

Results

A total of 4320 vitrified warmed single euploid embryo transfers were performed in the study period and met inclusion criteria. Among these, 1090 cycles utilized a traditional approach for selection, while 3230 cycles employed the algorithm-based approach. Patients in which the traditional approach was utilized were older (35.9 ± 3.9 vs 35.5 ± 4.0, p=0.003), had a thinner endometrium at time of transfer (9.4 ± 2.0 vs 9.8 ± 3.1, p<0.0001), and had a lower serum progesterone level at time of transfer (26.0 ± 12.0 vs 32.8 ± 16.5, p<0.0001); demographic data were otherwise comparable between the cohorts (Table 2). In an unadjusted analysis, the implantation rate was significantly higher when the automated algorithm-based approach was utilized (65.3% vs 57.8%, p<0.0001). The ongoing pregnancy/live birth rate was also significantly higher in cycles in which the automated algorithm-based approach was used (54.7% vs 48.1%, p=0.0001). We performed a sub-analysis assessing only the first embryo transfer cycle of each patient in both groups; again, patients in the algorithm-based cohort had a significantly higher implantation rate (68.1% vs 58.1%, p <0.0001) and ongoing pregnancy/live birth rate (57.6% vs 49.6%, p=0.0004) as compared with patients in the traditional cohort. Finally, we performed an additional sub-analysis evaluating exclusively patients with at least 2 euploid embryos available for selection. Again, the implantation rate (67.5% vs 60.4%, p=0.0002) and the ongoing pregnancy/live birth rate (56.8% vs 50.5%, p=0.002) remained significantly higher in the algorithm-based cohort.

Logistic multivariable GEE regression models were then performed adjusting for the following co-variates: female patient age, BMI, AMH, obstetric history, endometrial thickness at time of transfer, and progesterone level at time of transfer (Table 3). The year of transfer was also included as a covariate in order to control for changes in practice over time. In this adjusted multivariable model, utilization of the automated algorithm-based approach remained significantly associated with improved odds of implantation (aOR 1.51, 95% CI 1.04, 2.18, p=0.03) compared to the traditional approach. After adjusting for the same co-variates, the automated algorithm-based approach to embryo selection also remained significantly associated with improved odds of ongoing pregnancy/live birth (aOR 1.99, 95% CI 1.38, 2.86, p=0.0002) and with decreased odds of clinical loss (aOR 0.42, 95% CI 0.21, 0.84, p=0.01).

Discussion

Optimal embryo classification and selection prior to embryo transfer remains of paramount importance in ART cycles. This study evaluated the clinical implementation of an automated algorithm-based approach in embryo selection compared with traditional selection processes of single vitrified warmed euploid embryos prior to transfer. Our results demonstrate that utilization of a mathematical model that integrates morphologic parameters optimizes euploid embryo selection for transfer as evidenced by improved implantation rate and ongoing pregnancy/live birth rate as compared with traditional selection approaches. These findings are of particular importance for patients with more than one euploid embryo available for transfer.

Without an algorithm to drive embryo selection, embryologists may weigh the variables in choosing an embryo for transfer differently, with some putting a higher emphasis on day of biopsy, while others may favor ICM or TE grade.

Table 2 Demographic and cycle characteristics of the populations analyzed

	Traditional ($N = 1090$)	Algorithm ($N = 3230$)	p-value
Age (years)	35.9 ± 3.9	35.5 ± 4.0	0.003
BMI (kg/m^2)	23.9 ± 4.3	24.1 ± 4.5	0.11
Day 3 FSH	6.2 ± 3.1	6.3 ± 3.2	0.25
AMH (ng/mL)	3.9 ± 4.5	3.3 ± 3.2	0.11
Gravidity	1.2 ± 1.4	1.1 ± 1.2	0.19
Parity	0.5 ± 0.8	0.5 ± 0.7	0.41
Endometrial thickness at time of transfer (mm)	9.4 ± 2.0	9.8 ± 3.1	<0.0001
Progesterone at time of transfer (ng/mL)	26.0 ± 12.0	32.8 ± 16.5	<0.0001
Implantation rate	630/1090 (57.8%)	2108/3230 (65.3%)	<0.0001
Ongoing pregnancy/live birth rate	524/1090 (48.1%)	1768/3230 (54.7%)	0.0001
Clinical loss rate	106/770 (13.8%)	340/2529 (13.4%)	0.82

Within a cohort of embryos with different morphologic grading, embryologist selection is not always standardized. Importantly, prior studies have demonstrated that embryo grading and scoring may vary frequently between embryologists; this is likely secondary to the inherent subjectivity in the scoring and interpretation of embryo quality [4, 10]. Thus, previous work has focused on the validation and accuracy of mathematical models and artificial intelligence (AI) for embryo scoring. Khosravi et al [4] utilized time-lapse images of human embryos to develop convolutional neural networks. This deep learning algorithm was then assessed for its ability to successfully predict the quality of human embryos by studying blastocysts with known clinical outcomes. The authors found that the deep neural network gave a predictive accuracy with an area under the curve (AUC) of 0.987 for successfully categorizing embryos as "good-quality" or "poor-quality." In a similar study, Dimitriadis et al. [11] evaluated a convolutional neural network and sought to determine its accuracy in correctly identifying an embryo's developmental stage as well as discerning the top quality embryo within a given patient's cohort of embryos. That algorithm successfully categorized 182 embryos based solely on their morphology with an accuracy of 89.1%; in addition, the model identified the "top choice" within a cohort of embryos with 95% accuracy, which was not significantly different from the 98.3% accuracy noted when skilled embryologists classified the embryos.

In addition to embryo classification, several studies have also validated the use of mathematical models in predicting clinical outcomes. VerMilyea et al [12] investigated the clinical potential of an AI-based model that used images of human embryos captured with optical light microscopy. Those researchers assessed the model's ability to accurately predict the viability of day 5 blastocysts with known clinical outcomes. The model demonstrated a sensitivity of 70.1% and specificity of over 60.5% in accurately predicting successful implantation, as defined via visualization of a fetal heartbeat. This improvement in accuracy was demonstrated to be 24.7% over the accuracy of embryologists' predictions alone. Similarly, Tran et al [13] interrogated an AI tool based on time-lapse videography of embryos at various developmental stages that were grown in different culture conditions. Similar to VerMilyea et al. [12], these authors sought to validate the accuracy of the AI tool in its prediction of the probability of a clinical pregnancy based on time-lapse videography. They found that the AUC for the model was 0.93 for predicting a clinical pregnancy with fetal heart tones present. Finally, Bori [14] evaluated the clinical utility of an algorithm in predicting embryonic ploidy status. That study found a significant association between embryo scores and the embryo's chromosomal composition. In addition, the researchers found that embryos with a higher score were significantly associated with improved implantation and live birth compared with embryos that had a lower score.

Table 3 Multivariable logistic GEE regression models by decision-making tool

	Traditional	Algorithm	
	Reference	Adjusted OR (95% CI)	P-value
Implantation rate	Reference	1.51 (1.04, 2.18)	0.03
Ongoing pregnancy/live birth rate	Reference	1.99 (1.38, 2.86)	0.0002
Clinical loss rate	Reference	0.42 (0.21, 0.84)	0.01

The results of these studies, in sum, support the utilization of mathematical models in the classification of embryos and for their prediction potential as it pertains to clinical outcomes. Similar to prior studies, the current study's algorithm was developed as a means of creating a more standardized approach to embryo ranking in order to optimize embryo selection prior to transfer in women with multiple euploid embryos available. However, unlike prior studies, in which the purpose was validation of an algorithm by studying prior embryo transfers with known cycle results, the current study investigated whether clinical implementation of the algorithm was associated with improved outcomes. Given the importance of optimal embryo selection prior to transfer, this study's findings are of particular importance and suggest that, particularly in women with multiple euploid embryos available for transfer, utilization of an automated algorithm-based embryo scoring system may improve clinical outcomes.

This study has several strengths. The cohort of patients all underwent single, vitrified warmed euploid embryo transfer cycles, thereby reducing potential variability that may occur with inclusion of fresh transfers or multiple embryo transfers or cycles which utilized untested embryos. In addition, all embryos were PGT-A tested uniformly using next-generation sequencing, which may reduce any variability in findings due to use of differing genetic testing platforms. Based on our post hoc power analysis, our study was adequately powered to detect the statistical differences in clinical outcomes found between cohorts. Finally, this study was performed at a single, large academic center, with a team of embryologists trained in the same systematic fashion, which may decrease the variability that may occur with multicenter studies.

However, this study is not without limitations. One notable limitation of this study is its retrospective design, which can result in selection bias and therefore may lead to reduced generalizability. Adjusted multivariable logistic GEE regression models were utilized to minimize bias and to adjust for potential confounders and repeated measures. Although differences were noted in patient age and endometrial thickness between the groups, after adjusting for these confounders, the study findings remained unchanged; moreover, these differences are unlikely to be clinically relevant. In addition, although all senior embryologists are trained for morphologic grading in the same fashion, there remains inherent subjectivity in morphologic grading which cannot be accounted for in this study. Studies utilizing time-lapse technology may be better able to reduce this inherent inter-observer variability. The authors also acknowledge that the algorithm was developed based on our center's patient population and may therefore have limited generalizability to other ART centers. In addition, the algorithm was developed based on outcomes from a time period during which more than one PGT-A platform was utilized, namely, qPCR and aCGH in addition to NGS. As of September 2016, NGS was exclusively utilized for PGT-A. Future algorithm development should utilize embryos exclusively tested via NGS, as this would help to minimize the inherent variability that may exist between PGT platforms. Finally, in the current study, the traditional and algorithm-based embryo selection approaches were used at different time points at our facility. Our study therefore lacked a true direct comparison between the cohorts. In an attempt to account for this, our regression models included the year of embryo transfer in order to control for the difference in time between the two cohorts. Prospective, head-to-head randomized trials comparing the implementation of a mathematical model for embryo selection with traditional embryologist-based embryo selection would better define the role of the algorithm in improving euploid embryo selection prior to transfer.

In conclusion, to our knowledge, this is the first study to compare the clinical implementation of a mathematical model for embryo selection with traditional selection by senior embryologists in single vitrified warmed euploid embryo transfers. Our results demonstrated that utilization of an automated algorithm-based approach for ranking and selection of a euploid embryo prior to transfer is associated with improved clinical pregnancy outcomes. Future studies will benefit from integrating time-lapse technology with real-time deep learning algorithms and AI in prospective, randomized trials that may more definitively delineate the role of automated models in choosing the optimal euploid embryo for transfer.

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Code availability Not applicable.

Author contribution J.F., C.H.N., A.C., and T.N. provided substantial contribution to the design of the study. J.F., C.H.N., D.G. R.M.R, R.S., and C.B.J. collected and analyzed the data. J.F., C.H.N., J.A.L., A.C., and C.B.J. drafted the manuscript. All authors interpreted the data, revised the work, and approved the final submitted version. All authors contributed to the study conception and design. Material preparation and data collection was performed by Jenna Friedenthal, Dmitry Gounko, Rose Marie Roth, and Richard Slifkin. Formal analysis was performed by Jenna Friedenthal, Carlos Hernandez-Nieto, and Dmitry Gounko. Original draft preparation was performed by Jenna Friedenthal; review and editing was performed by all authors. Christine Briton-Jones, Taraneh Nazem, Joseph A. Lee, and Alan Copperman made significant editorial contributions to the manuscript.

Data Availability The data underlying this article may be obtained upon reasonable request.

Declarations

Ethics approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB# 18-00452) of the Icahn School of Medicine at Mount Sinai approved this study.

Consent to participate Not applicable. The Human Investigation Committee (IRB# 18-00452) of the Icahn School of Medicine at Mount Sinai approved this retrospective chart review study.

Consent to publish Not applicable. The Human Investigation Committee (IRB# 18-00452) of the Icahn School of Medicine at Mount Sinai approved this retrospective chart review study.

Conflict of interest Alan Copperman is a board member of Sema4 Genomics and Progyny and possesses stock/stock options in Sema4 Genomics and Progyny. The other coauthors declare no conflicts of interest.

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