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Feasibility of artificial intelligence for predicting live birth without aneuploidy from a blastocyst image

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Abstract

Purpose: To make the artificial intelligence (AI) classifiers of the image of the blastocyst implanted later in order to predict the probability of achieving live birth.

Methods: A system for using the machine learning approaches, which are logistic regression, naive Bayes, nearest neighbors, random forest, neural network, and support vector machine, of artificial intelligence to predict the probability of live birth from a blastocyst image was developed. Eighty images of blastocysts that led to live births and 80 images of blastocysts that led to aneuploid miscarriages were used to create an AI-based method with 5-fold cross-validation retrospectively for classifying embryos.

Results: The logistic regression method showed the best results. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 0.65, 0.60, 0.70, 0.67, and 0.64, respectively. Area under the curve was 0.65 ± 0.04 (mean \pm SE). Estimated probability of belonging to the live birth category was found significantly related to the probability of live birth ($P < 0.005$).

Conclusions: Classifiers using artificial intelligence applied toward a blastocyst image have a potential to show the probability of live birth being the outcome.

KEYWORDS

artificial intelligence, blastocyst, live birth, machine learning

1 | INTRODUCTION

Securing live birth with no chromosomal abnormality is considered to be the preferable ultimate goal in assisted reproductive technology. Failure of embryo development, or miscarriage, results in loss of time and cost. Moreover, in order to avoid ongoing aneuploid gestations, it is preferable to distinguish euploid embryos from aneuploid or mosaic embryos when possible. Reliable selection of embryos prior to embryo transfer has been investigated.

Morphological structures such as meiotic spindles, zona pellucidae, vacuoles or refractile bodies, and polar body shapes have been

investigated, but none of these features have been conclusively assessed as having prognostic value for the further developmental competence of oocytes.¹ Conventional morphological evaluation has had limited success at identifying aneuploid embryos.²⁻⁶ Several observational studies have proposed time-lapse parameters as predictive of aneuploidy, though these have had diverging conclusions. Researchers have generally concluded that aneuploidy is reflected in cell cycle parameters up to day 2 of development because euploid embryos have been found to display more tightly clustered timings compared with aneuploid embryos.^{2,7-9} However, it is well-documented that embryos of good morphological quality may well be

Clinical Trial Registry: This study is not a clinical trial.

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aneuploid and suboptimal embryos may be euploid.^{2,10,11} The morphological classification of aneuploidy or euploid, however, is not established. Strict evidence may still be too weak to justify introducing time lapse in routine clinical settings.²

Preimplantation genetic testing for aneuploidy (PGT-A)^{12,13} is another method for examining chromosomal profiles. Performed on a small embryo biopsy prior to transfer, PGT-A is an invasive technique for the embryo, which brings with it considerable ethical arguments. Transfer of the embryo after the biopsy is prohibited in some countries, including Japan. Moreover, the chromosomal profiles are not always uniform and differ at the blastocyst sites. The chromosomal profile of the biopsy specimen does not always represent the profile of the rest of the embryo because of this genetic heterogeneity. A mosaicism in the trophectoderm (TE) is observed much more than has been appreciated, and a single TE biopsy apparently may not be representative of the complete TE.¹⁴ A global Internet-based survey indicated more randomized controlled trials are needed to legitimize use of PGT-A.¹⁵

There is now clear need for a means of noninvasively predicting live birth of euploid or not. We therefore created a system applying the machine learning approach of artificial intelligence (AI) and applied it to blastocyst images to seek a solution for this challenge as a pilot study. Our image analysis via AI was able to detect and recognize information that the conventional methods could not. We studied comparisons of six types of machine learning methods on blastocyst images and then made a classifier program that retrospectively shows the probability of live birth. Confidence score that is the estimated probability of belonging to the live birth category can be viewed in terms of ranking of blastocysts; thus, it will be easier for embryologist to select superior blastocysts for transfer. Herein, we present the feasibility of using the classifier in our system for predicting the probability of live birth.

2 | MATERIAL AND METHODS

2.1 | Blastocyst images

This study used fully de-identified data and was approved by the Institutional Review Board (IRB) at Okayama Couples' Clinic (IRB no. 18000128-04). This study carried out with explanation to the patients and a Web site with additional information and including an opt-out option was set up for the study. After blastocyst formation followed by fertilization from May 2008 to January 2017 in Okayama Couples' Clinic, an image of the incubated blastocyst was captured approximately 115 hours after insemination and saved on a USB storage device in JPEG format containing no data that could be used to identify the individual. The de-identified image data were transferred to the AI system off-line. Eighty images of blastocysts that led to live births and 80 images of blastocysts that led to aneuploid miscarriages were used to create a machine learning based method for classifying embryos. These were respectively defined as in the normal category or abortion category. In other words, blastocysts in the normal category in this study would become live birth

with unknown chromosomal status and those in the abortion category would result in abortion due to chromosomal abnormalities confirmed with genetic testing of chorionic villus samples. Then, this algorithm was applied to a random sampling of embryos that led either to live birth or to aneuploid miscarriage.

2.2 | Preparation for AI

All de-identified images stored off-line were transferred to our AI-based system. Each image that had the artifacts outside the blastocyst deleted to the greatest possible extent was cropped as a square and then saved in 100 × 100 pixel size. One-fifth of images from each category were randomly selected as test dataset and the rest used as training dataset. In this way, the test dataset could potentially be used for validation, as the training dataset contained no test data. The number of training dataset items could be augmented as often seen in computer science because the blastocyst image processing of the arbitrary degrees' rotation led to being in the same category of the different vector data. For example, if an image was rotated at intervals of 90 degrees, four images with different vectors were generated.

2.3 | AI classifier

We developed a classifier program using machine learning with L2regularization^{16,17} to categorize blastocyst images as either in the normal or abortion category and to obtain the mathematical probability for predicting normal category (as well as abnormal category). The analysis used supervised machine learning methods: logistic regression,¹⁸ naive Bayes,¹⁹ nearest neighbors,²⁰ random forest,²¹ support vector machine,²² and neural network²³ with automatic option for hyper-parameters to find best classifier in each method. The automatic option of the neural network included activation function to use between layers, the parameter multiplying the L2 term, the type of network module to use, the depth of the network, the total number of the network's trainable parameters, and the optimization method such as ordinary stochastic gradient descent with momentum or stochastic gradient descent using an adaptive learning rate that is invariant to diagonal rescaling of the gradients. We applied cross-validation,²⁴⁻²⁶ a powerful method for model selection, to identify the optimal method of machine learning. The suitable number of images for the training data was investigated by evaluating accuracy and variances using the 5-fold cross-validation method, in which test data were analyzed using the training data, as follows. First, the test data were the initial one-fifth of the images of each category's collection. Then, the test data were changed to the next one-fifth of the images. This procedure was repeated five times to encompass all images as potential test data. The number of augmented training images was analyzed until the accuracy and variance were likely to show the maximum and minimum value, respectively (Figure 1). When the optimal number of training data was obtained, the histogram of the probability for prediction was investigated.

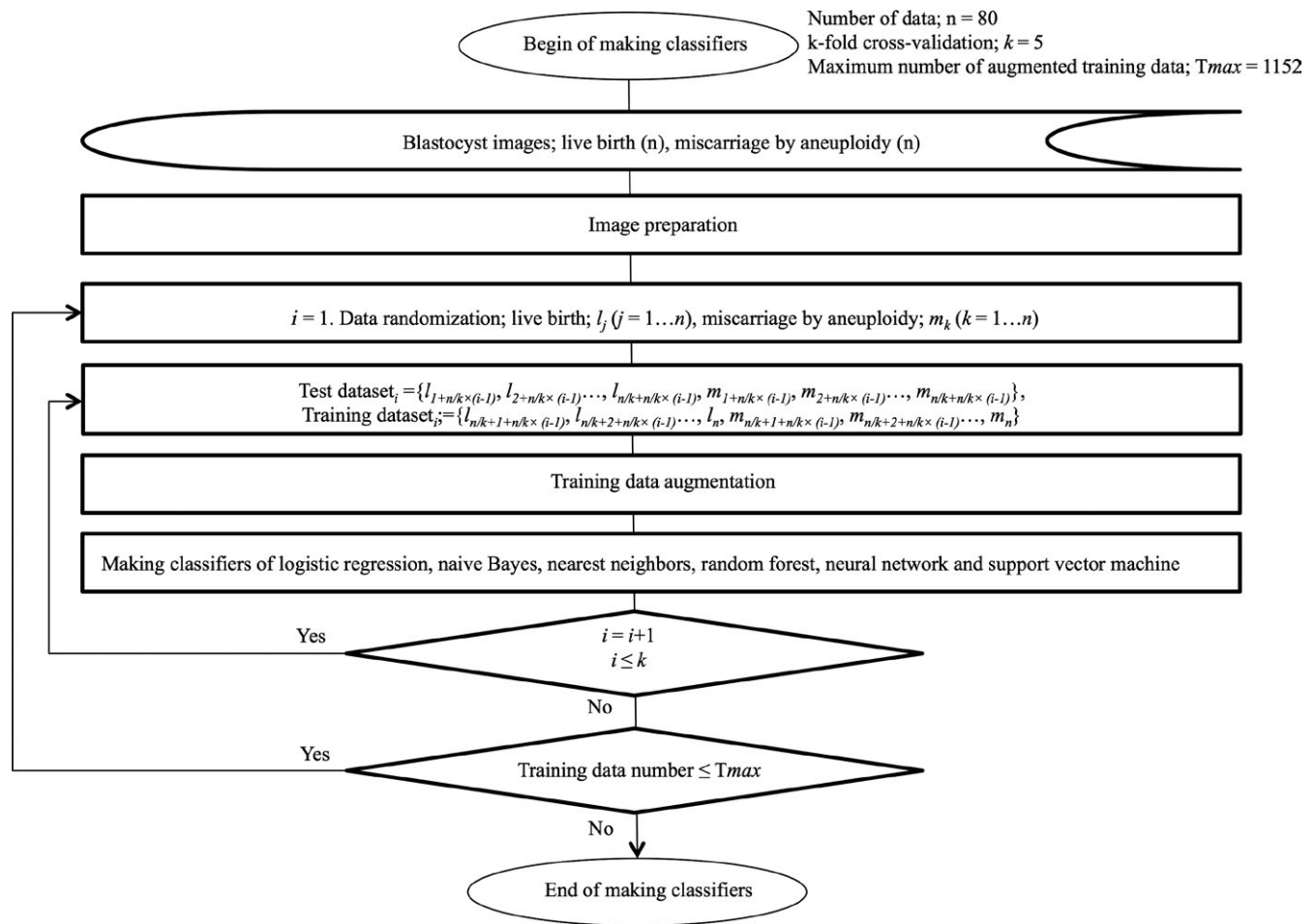


FIGURE 1 The flow chart of making classifiers for blastocysts that were implanted and led to live birth or aneuploid miscarriages

2.4 | Development environment

The development environment used in the present study was as follows: a Mac (CPU; 2 x 2.8 GHz Quad-Core Intel Xeon, RAM; 20 GB) running OS X 10.11.6 (Apple, Inc, Cupertino, CA, USA); Mathematica 11.3.0.0 (Wolfram Research, Champaign, IL).

2.5 | Statistics

Mathematica 11.3.0.0 (Wolfram Research, Champaign, IL, USA) was used for statistical analysis.

3 | RESULTS

3.1 | Logistic regression as machine learning

The preliminary calculations revealed logistic regression was the best among the abovementioned machine learning methods. The accuracy by six types of machine learning methods (logistic regression, naive Bayes, nearest neighbors, random forest, neural network, and support vector machine) is shown in Figure 2, respectively. As the number of the training data became larger, the average of the

accuracies showed the maximum and the standard deviation (SD) of the accuracies showed the minimum simultaneously in each method. The best accuracy of all with small SD was 0.650 ± 0.075 (mean \pm SD) when the number of the training data was 640 in logistic regression. Therefore, the logistic regression should be selected as the best method among the machine learning methods and the results for both accuracy and SD suggested 640 as the suitable number of training images and selected as the number for this study. Consequently, further investigations were carried out with logistic regression.

3.2 | AI classifier

Table 1 shows the results of the best classifier. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 0.650 ± 0.075 , 0.600 ± 0.105 , 0.700 ± 0.103 , 0.669 ± 0.085 , and 0.638 ± 0.069 (mean \pm SD), respectively. Classifying an image took only less than one second on average. A probability of 0 or 1 meant the image was categorized in the abortion category or normal category, respectively. When the probability was ≥ 0.5 , the image was put in the normal category; otherwise, it was in the abortion category. The histogram of the confidence score is shown in Figure 3.

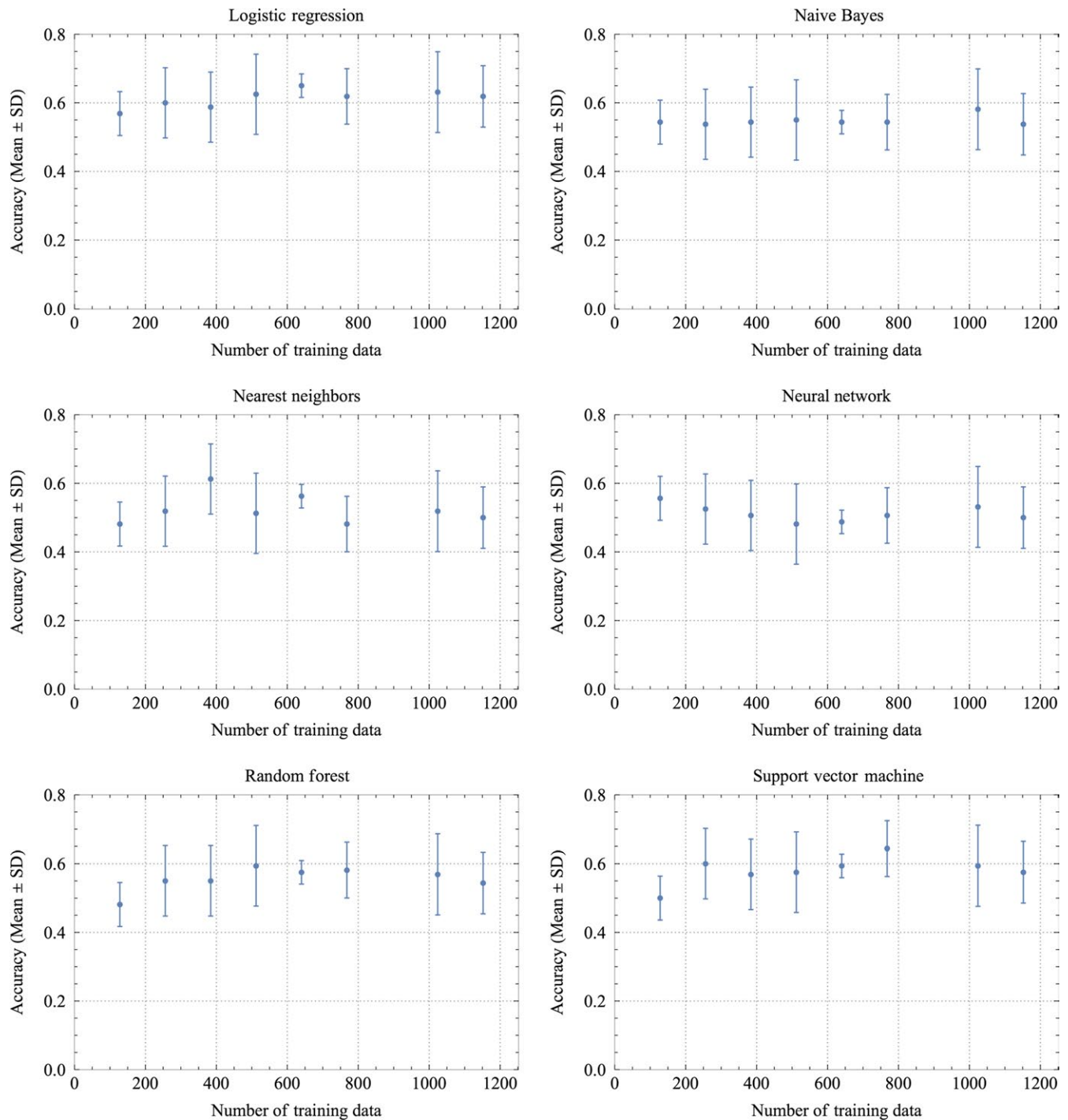


FIGURE 2 The relationship of the number of training files and accuracy in regard to resulting in live birth or abortion by machine learning with logistic regression method, naive Bayes method, nearest neighbors method, neural network method, random forest method, and support vector machine method as shown in each panels. Mean \pm SD of accuracy at the number of the training data is shown in each panel. Accuracy is likely to approach a maximum of 0.65 with the minimum of the standard deviation of 0.075 when there are 640 files in the logistic regression method

The confidence score increased, while the incidence of becoming live birth increased. A significant relationship was seen between the confidence score by the AI and the probability of incidence derived from the histogram ($P < 0.005$ by Cochran-Armitage test). The linear regression model that fits the incidence are constructed as follows:

$y = 0.822 (\pm 0.224) x + 0.128 (\pm 0.129)$ (mean \pm SE), x ; the confidence score by the AI, y ; the probability of incidence of becoming live birth. The area under the curve (AUC) of the receiver operating curve was 0.6594 ± 0.043 (mean \pm SE), and the 95% confidence interval ranged 0.575-0.743 as shown in Figure 4.

TABLE 1 Discrimination ability of the best classifier. A classifier using a logistic regression method with L2 regularization with 640 selected images as the training data showed the best results

	Mean \pm SD	Median
Accuracy	0.650 \pm 0.075	0.656
Sensitivity	0.600 \pm 0.105	0.625
Specificity	0.700 \pm 0.103	0.750
Positive predictive value	0.669 \pm 0.085	0.647
Negative predictive value	0.638 \pm 0.069	0.667

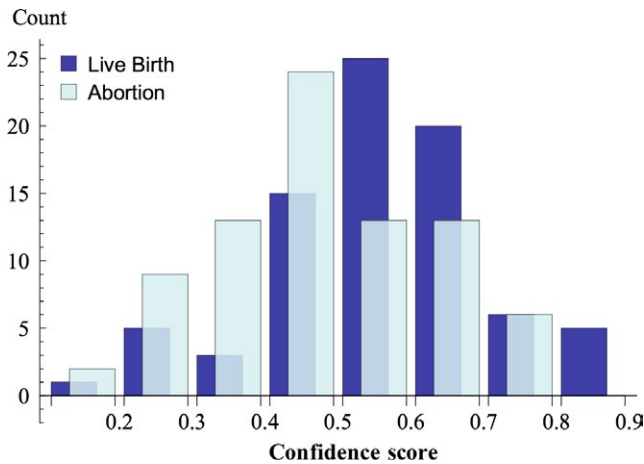


FIGURE 3 The histogram of confidence score; the probability that is likely to be live birth class of blastocyst images of which the outcome had revealed as either live birth or abortion with aneuploid. The probability of 1 and 0 means that the image is very likely to belong to the live birth class and the abortion class, respectively

4 | DISCUSSION

We obtained the classifier of the machine learning program using logistic regression with L2 regularization to classify blastocysts that were implanted and led to live birth or aneuploid miscarriages. The best classifier with 640 selected training images showed the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for predicting live birth were 0.650 ± 0.075 , 0.600 ± 0.105 , 0.700 ± 0.103 , 0.669 ± 0.085 , and 0.638 ± 0.069 (mean \pm SD), respectively (Table 1). One study found the live birth rate per transfer was 0.668, by using clinical factors such as age and body mass index.²⁷ Another study reported that the grading of the TE was the only statistically significant independent predictor of live birth outcome, and the live birth probabilities of grade A, B, or C of the TE were 0.499, 0.339, and 0.080, respectively.²⁸ These reports cannot be directly compared with our results because all of the miscarriage causes were not aneuploidy. But they suggest a classifier with no harm inflicted, owing to the use of AI in this study, is superior to those clinical factors and the examinations of conventional morphology.

There are several reports of AI²⁹ with using machine learning, which is mainly deep learning³⁰ with the convolutional neural

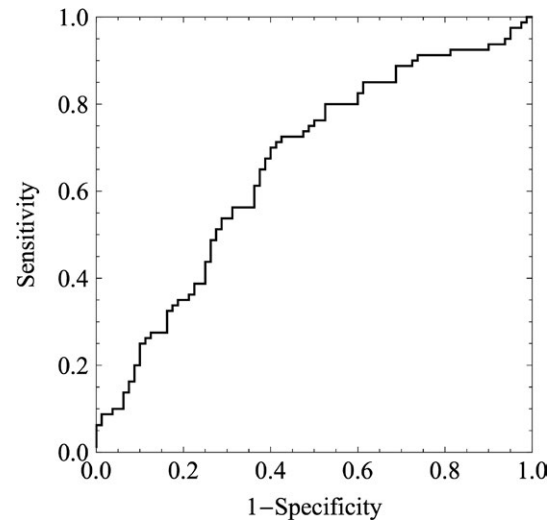


FIGURE 4 The area under the curve of the best classifier for predicting live birth by the logistic regression method. The value of the curve is 0.659 ± 0.043 (mean \pm SE), and the 95% confidence interval ranged 0.575-0.743

networks for medicine.³¹ The deep learning required a lot of data such as more than several thousands to make a classifier. Because there are 160 images in this study, we studied machine learning except deep learning. The accuracies with the deep learning have been reported such as 0.997 for histopathological diagnosis of breast cancer,³² 0.90-0.83 for the early diagnosis of the Alzheimer's disease,³³ 0.83 for urological dysfunctions,³⁴ 0.72,³⁵ and 0.50³⁶ for the colposcopy, 0.83 for the diagnostic imaging of orthopedic trauma.³⁷ In practical sterility, there are some clinical disincentives for the embryo to achieve live birth; the uterine factors³⁸—(intrauterine adhesions,^{39,40} uterine myomas,⁴¹ and endometrial polyps),⁴² endometriosis,⁴³ ovarian function,⁴⁴ oviduct obstruction,^{45,46} female diseases such as diabetes mellitus,⁴⁷ immune disorder,^{48,49} and uterine microbiota.⁵⁰ Because these factors cannot be detected by the AI classifier from the image of the blastocyst, the accuracy, the sensitivity, and the specificity for live birth cannot reach to 1. These clinical characteristics of the blastocyst prevent the accuracy to predict live birth by any means from as close to 1. But we think the accuracy of 0.650 by the AI for predicting live birth distinguishing from abortion or miscarriage is feasible.

In our repeated calculations, the logistic regression continually showed the best result among the six machine learning methods examined. In short, the logistic regression models the log probabilities of each category with logistic functions of a linear combination of numerical features. However, further investigation in the future may prove other machine learning methods superior. Though we preliminarily tested the deep learning method of the convolutional neural networks with training data increased to 20 000, this did not show better accuracy than logistic regression. However, the deep learning might be able to provide better accuracy if a greater number of training images can be obtained.

We found 640 to be a suitable number for the training data because the maximum value of accuracy was obtained, while the error was close to the minimum value, as shown in Figure 2. L2 regularization seemed to sufficiently control over-fitting for reducing the error. This was a key process in that the smaller size of both error and bias may yield a good classifier. Only a few seconds were needed to finish calculation for an image once the classifier was established. We therefore can envision the classifier being applied for clinical use.

In one report, embryos categorized using a model in which the two morphokinetic variables are applied to predict chromosomal content by blastomere biopsy on day 3, followed by array-comprehensive genomic hybridization, showed a significant decrease in the percentage of chromosomally normal embryos for each decreasing category (A, 35.9%; B, 26.4%; C, 12.1%; D, 9.8%; $P < 0.001$).⁵¹ Our method appears more viable than this because the classifier in this study induces no harm, and it shows a wider range of percentage for category prediction.

The receiver operating curve of the classifier shows the AUC value is 0.659 ± 0.043 (mean \pm SE). Regarding the AUC of preimplantation genetic screening, a study reported a prediction model to classify embryos into high-, medium-, or low-risk categories, with an AUC of 0.72.⁵² The model could be useful for ranking embryos and for prioritizing them for PGT-A. However, it does have limited predictive value for patients undergoing IVF in general.⁵³ In terms of the discriminative ability of an examination, the classifier using AI seems inferior to PGT-A; therefore, the classifier in this study may need to be improved. Though the ability of the classifier in this study shows viability for classifying blastocysts, the histogram of the probability of live birth and abortion categories suggests correct assigning to the classifier was difficult for some images. More precise recognition of atypical images would improve our classifier and increase accuracy.

There are further potential ways of improving the classifier. First, more images for both the normal and abortion categories may be needed. In this pilot study, the analysis is restricted to simply evaluating a pregnancy once it has been detected. As the blastocysts images are required prior to transfer, a further study with blastocyst images including images failed to implant is required in order to classify all embryos suitable for transfer by AI following this pilot study. It may also be important to statistically investigate the relationship of the probability given by the classifier with other clinical and morphological information, such as maternal age, body mass index, and TE grading. The data in this pilot study were not big and not stratified by such as maternal age or cycle history. The further investigation including the statistical stratification with more number of data might result in better results. Though we used images of blastocyst on only day 5 in order to reduce bias in this pilot study, the further investigation might be considered to prepare dataset by adding images of day 6 blastocyst that seem to grow late. Predictive ability could be improved for when the image and certain information are combined, and the outcome is investigated by statistical analysis. The proper conditions of capturing images should also be investigated and a standard determined so

the classifier can be easily implemented at any institute. Blastocyst images showing chromosomal mosaicism or aneuploids confirmed by the PGT-A were not included in this study. In further work, we would be able to develop an advanced classifier that can classify blastocyst images into three or more categories such as live birth, aneuploid, mosaic, and abortion.

Biologically, this method shows capabilities at least as good as other modes of examination. Ethically speaking, it inflicts no harm on the blastocyst. It offers economic savings for patients and/or clinical institutes, gives quick and efficient diagnosis of the classification, and permits examination over distances when the image is transferred via the Internet.

We applied machine learning in the realm of AI to develop a classifier for predicting from an image of the blastocyst that was implanted. The classifier can predict the probability of becoming live birth with the accuracy of 0.65. The further validation to test the feasibility of a classifier by machine learning using the data of the images and conventional methods might be conducted. Only less than one second are needed to complete analysis of each image. This method does not harm the embryo, which can be transferred after establishing the prediction. Though further study may be required to validate the classifier, the system showed a possibility that the AI would be feasible for clinical use and may bring benefits to both patients and medical personnel.

The contents in this manuscript were approved as a patent in Japan; patent 6422142.

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DISCLOSURES

Conflict of interest: Yasunari Miyagi, Toshihiro Habara, Rei Hirata, and Nobuyoshi Hayashi declare that they have no conflict of interest. *Human rights statements and informed consent:* Human rights statements and informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article. A Web site with additional information including an "opt-out" option was set up for the study. *Animal studies:* No animals were used in this study. *Approval by ethics committee:* The protocol for the research project including human subjects has been approved by the Institutional Review Board at Okayama Couples' Clinic (IRB no. 18000128-04).

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