

=====**Submit Journal**=====

Manuscript Number: XAGR-D-22-00492

Manuscript Title: Embryo Ploidy Status Classification Through Computer-Assisted Morphology Assessment

Journal: AJOG Global Reports

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=====**Revision 1**=====
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Manuscript Number; XAGR-D-22-00492
Entitled; Embryo Ploidy Status Classification Through Computer-Assisted Morphology Assessment

Dear Mr. Danardono:

Your manuscript cited above has received reviews by the consultants of AJOG Global Reports. We are interested in giving your paper further consideration, once you and your co-authors have addressed the comments of the reviewers.

If you choose to revise your manuscript, please submit all items on the following checklist at the AJOG Global Reports Editorial Manager website. Revisions submitted after the designated due date may be considered a new submission and undergo an additional peer review process.

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REVIEWER 1, POINT 1

A. Point made by the reviewer/editor.

B. Reply to the reviewer/editor (by the authors) - you may agree or disagree with the

comment - if you disagree, it is necessary to explain the reasons and provide evidence in the form of references, if necessary, in support of your point.

C. Provide the specific page and line on which any changes were made.

D. Provide the textual change in quotations.

REVIEWER 1, POINT 2

(follow same A, B, C, D format)

REVIEWER 2, POINT 1

(follow same A, B, C, D format)

EDITOR COMMENT, POINT 1

(follow same A, B, C, D format)

2. TRACK CHANGES, EDITED MANUSCRIPT - Submit a copy of the revised manuscript using the "track changes" feature on Microsoft Word or, if this feature is unavailable, underline all changes

3. REVISED MANUSCRIPT - Submit a clean, non-edited final version of the revised paper

4. SUBMITTING THE REVISION -

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B. Ensure that all requirements have been completed in accordance with the AJOG Global Reports Guide for Authors, with particular attention to Editorial Policies (ie IRB information, conflict of interest statements, and that ALL authors have signed a Statement of Authorship form

C. Submit figures and tables ONLY if the originals have been revised (if so, remove previous versions). We encourage the use of color whenever possible in both figures and tables (this is a free service)

D. Upload each figure in a separate file. Do not paste figure within the manuscript text

E. Please be sure to upload a copy of the revised manuscript with changes highlighted and a clean copy of the revised manuscript.

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The Editors

AJOG Global Reports

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EDITOR/REVIEWER COMMENTS:

Editor Comment(s):

In its current state, the level of English throughout your manuscript does not meet the journal's required standard. You may wish to ask a native speaker to check your manuscript for grammar, style and syntax, or use the professional language editing options available from Elsevier Author Services: <https://webshop.elsevier.com/>

Reviewer #1: This study developed a machine learning model for a non-invasive ploidy status prediction and the model has the ability to predict aneuploid embryo with high confidence level.

- 1.The sample size of this study was relatively small, especially in euploid group.
- 2.Lack of baseline for inclusion population.
- 3.The inclusion and exclusion criteria for images should be described in detail.

Reviewer #2: The study aimed to develop an artificial intelligence model to predict ploidy status in human embryos. This is a topic of interest, and I appreciate that results of two case study comparisons were presented. However I do have some concerns

please see as the following:

1. As the authors mentioned, an optimal model should be able to classify different classes with similar accuracy, precision and recall. While the most robust prediction model, using Gradient Boosting algorithm, yielded good precision and recall in predicting uploidy, it has very poor precision and recall in predicting euploidy (0.35 and 0.33 respectively). It seems the model has little value in predicting euploidy, this is confusing.
2. I think the proportion of mosaic embryos in the study was relatively high ($416/1123=37\%$). Please describe what method was used for PGT-A (NGS? SNP array? etc.); and how euploid, aneuploid, and mosaic was defined. Please also provide more information on the study population.
3. For the binary classification of the embryos, I have some concerns with putting mosaic embryos and aneuploid embryos into one classification. Recent studies have shown that mosaic embryos could result in normal live births, especially low-level mosaic embryos. As over one third of the embryos included in the model was designated as mosaic, this could have a great impact on the model.
4. To help evaluate performance of the model, please add the receiver-operating characteristic curve and precision-recall curve (with AUC value).

Editor: 1. Please address the points raised by the Reviewers, such as inclusion criteria and mosaic embryo classification, etc.

2. Could you please discuss more about the unique of your AI model compared with those preciously developed models?
3. Is it possible to test the performance of the AI model in another separate embryo database?.

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=====**Revision 2**=====
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Manuscript Number; XAGR-D-22-00492R1
Entitled; Embryo Ploidy Status Classification Through Computer-Assisted Morphology Assessment

Dear Mr. Danardono:

Your manuscript cited above has received reviews by the consultants of AJOG Global Reports. We will be pleased to accept this paper for publication, once you and your co-authors have addressed the comments of the reviewers.

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HEADINGS (Reviewer #, Point #) and BULLETS (A, B, C, and D) are REQUIRED.

REVIEWER 1, POINT 1

A. Point made by the reviewer/editor.

B. Reply to the reviewer/editor (by the authors) - you may agree or disagree with the comment - if you disagree, it is necessary to explain the reasons and provide evidence in the form of references, if necessary, in support of your point.

C. Provide the specific page and line on which any changes were made.

D. Provide the textual change in quotations.

REVIEWER 1, POINT 2
(follow same A, B, C, D format)

REVIEWER 2, POINT 1
(follow same A, B, C, D format)

EDITOR COMMENT, POINT 1
(follow same A, B, C, D format)

2. TRACK CHANGES, EDITED MANUSCRIPT - Submit a copy of the revised manuscript using the "track changes" feature on Microsoft Word or, if this feature is unavailable, underline all changes

3. REVISED MANUSCRIPT - Submit a clean, non-edited final version of the revised paper

4. SUBMITTING THE REVISION -

A. Please re-enter in EM the title of your paper if changes have been made to the original title.

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Sincerely yours,

The Editors

AJOG Global Reports

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EDITOR/REVIEWER COMMENTS:

Editor Comment(s):

Reviewer #2: Please consider adding method of PGT-A and threshold for euploid, aneuploid and mosaic in the method section.

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=====**Accepted**=====
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Dear Mr. Danardono:

We are pleased to inform you that your submission number XAGR-D-22-00492R2 entitled, "Embryo Ploidy Status Classification Through Computer-Assisted Morphology Assessment," is accepted for publication in AJOG Global Reports.

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AJOG Global Reports

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With best regards,

Hazel Gret Celis
Researcher Support – Open Access
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Article title: Embryo Ploidy Status Classification Through Computer-Assisted Morphology Assessment

To be published in: AJOG Global Reports

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