

## Geri Assess® 2.0

### A consistent approach to selecting the most viable embryos

The advent of time-lapse technology has created an increase in data that clinics use to assess and grade embryos, thus there is a need for a time-saving tool to assist embryologists to determine the best embryo to transfer or freeze. Using the best focal plane, embryo-cropped video from Geri®, Geri Assess® 2.0 is an embryo assessment tool that automatically detects and annotates key embryo development events from PN appearance to hatching blastocyst, as well as the observations of fragmentation and reverse cleavage. Geri Assess® 2.0 helps improve efficiencies in the clinic and provides consistency in assisting in embryo selection.

#### Principles of Geri Assess®

Geri® software over time is able to determine the best focussed image and will “re-focus” as recording progresses. The combination of the best focal plane, embryo-cropped video and the ability to move through the up to 11 z-stacks of video on Geri Connect® & Geri Assess® is analogous to the standard clinical practice of focussing the microscope while assessing the embryo. Any additional events and observations can be added or removed providing traceability for auditing purposes.

The purpose of the Automated Annotations is to detect key embryo developmental events from pronuclei appearance to hatching blastocyst, as well as the observations of fragmentation and reverse cleavage, using the best focal plane, embryo-cropped video. Geri Assess® 2.0 does this by receiving images, classifying the images into a category and then providing the classification result.

Geri Assess® 2.0 uses a convolutional neural network (CNN) to classify the images of embryos into classes, such as 1-cell, 2-cell, 3-cell etc. Analysis of these images were done using an artificial neural network, which is a computing system that is inspired by biological neural networks.

For Geri Assess® 2.0 to automatically annotate, each embryo developmental event must fall within a specified range to be included on the Timeline Bar. If an embryo developmental event falls outside the specified range, a yellow triangle is marked in the Geri Assess® 2.0 tab and the time stamp is shown in red.

Custom scoring algorithms, which can be applied to the automated annotations of Geri Assess® 2.0, are a set of

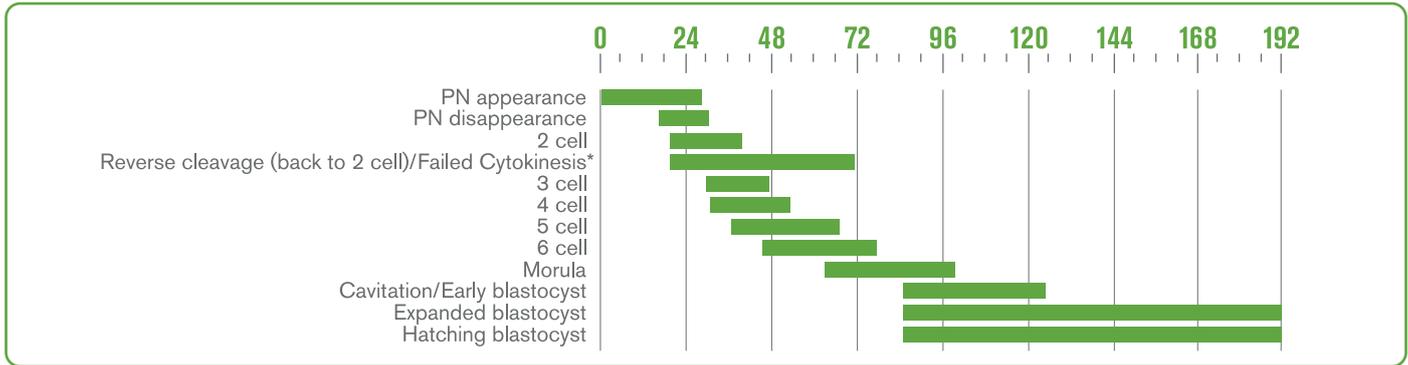
conditions that assess the timing of annotations of the developmental timeline and if the conditions are met, a final embryo score is shown. The end-user defines these conditions as well as the final score in a file that is uploaded to Geri Connect® & Geri Assess® by the service engineer. The desired algorithm or an average of all the uploaded algorithms can be selected in the Patient Details page of Geri Connect® & Geri Assess®.

#### Comparing Automated Annotations to Manual Annotations

Performance of the automated annotations module was extensively tested using five Geri® systems in two Genea clinics, comparing the automated annotations to manual annotations made independently by up to three experienced embryologists. The events compared were the cell division events and the observations of reverse cleavage/failed cytokinesis and embryo fragmentation. Additional tests were conducted to assess the performance of reverse cleavage (back to 2-cell)/failed cytokinesis, comparing the automated annotations to the mean of three manual annotator annotations.

Embryo fragmentation is annotated as being present or not and is displayed as a blue bar above the Timeline Bar in the Patient Review Page and in the Patient Summary Page, shown in Figure 2. The threshold for detection of fragmentation is approximately 15% of the embryo volume. Fragmentation False Alarm was tested by one manual annotator reviewing the automated fragmentation annotations in different quality embryos and developmental stages (utilised and non-utilised, before and after morula stage) and either agreeing or disagreeing with the automated annotations.

*The ranges were determined by literature review of 1) Balaban, B. et al. (2011) “Istanbul consensus workshop on embryo assessment: proceedings of an expert meeting.” Reproductive BioMedicine Online 22 (6): 632-646; 2) Ciray, H.N. et al. (2014) “Proposed guidelines on the nomenclature and annotation of dynamic human embryo monitoring by a time-lapse user group.” Human Reproduction 29 (12): 2650-2660 and 3) experienced embryologists at Genea Australia Clinics.*



**Figure 1:** Detection periods as defined in the Automated Annotations module of Geri Assess® 2.0.

\* As reverse cleavage is an observation, if it falls outside the range depicted here, it will still be presented on the Timeline Bar

PNa	PNd	2-cell	3-cell	4-cell	5-cell	6-cell	M	EB	XB <sup>3</sup>	HgB <sup>3</sup>
<b>Detection rate<sup>1</sup></b>										
70/71	131/136	143/144	122/140	165/188	129/139	145/187	122/137	116/127	46/58	74/89
99%	96%	99%	87%	88%	93%	78%	89%	91%	79%	83%
Pass <sup>4</sup>	Pass	Pass <sup>4</sup>	Pass <sup>4</sup>							
<b>Automated Annotations Accuracy<sup>2</sup></b>										
41/70	121/131	139/143	114/122	141/165	112/129	126/145	100/122	107/116	41/46	43/74
59%	92%	97%	93%	85%	87%	87%	82%	92%	89%	58%
Pass <sup>4</sup>	Pass	Pass <sup>4</sup>	Pass <sup>4</sup>							

**Table 1:** Detection Rate<sup>1</sup> and Automated Annotations Accuracy<sup>2</sup> outcomes for all embryo development events at the final fixed time point.

**NOTE:** The acceptance criteria for a **pass** consists of minimum required detection rate, minimum required annotation accuracy and maximum allowed false positive detection rates. Genea Biomedx, 2018 QRTF285. Unpublished internal document

<sup>1</sup> Detection Rate examines if Geri Assess® 2.0 successfully detected and annotated an event considered to be a 'true' observed event within the specified ranges, based on it being manually annotated by 3 annotators.

<sup>2</sup> Automated Annotations Accuracy was determined by two independent criteria: 1) direct comparison of the time difference between the automated annotation and the average of 3 manual annotation values; and 2) inter-observer error comparing the average difference between the automated annotation and each of the 3 manual annotation values.

<sup>3</sup> Includes all embryos, including PGD/biopsied embryos.

<sup>4</sup> Assigned as a Pass despite the number of events being below those planned, due to achieved and accepted true Confidence Intervals.

Detection Rate				
Embryos	True Events	True events not annotated by GA 2.0	True events annotated by GA 2.0	Detection Rate
85	25	7	18	72%

Automated Annotations Accuracy			
Embryos	True events not annotated by GA 2.0	Time difference between Annotators' Mean & GA 2.0 ≤ 75min <sup>1</sup>	% within the time limit
85	18	13	72%

**Table 2:** Detection Rate and Automated Annotations Accuracy outcomes for additional Reverse Cleavage/Failed Cytokinesis testing

Test	Period of embryo development					
	Before Morula stage	After Morula stage				
<b>False positives</b>						
Annotator & Geri Assess 2.0 accord / Total Number	53/54	57/62				
% of Annotator & Geri Assess 2.0 accord	98%	92%				
Pass/Fail	Pass	Pass				
<b>False negatives</b>	24-48h	48-72h	72-96h	96-120h	120-144h	Total
Annotator & Geri Assess 2.0 accord / Total Number	9/12	9/12	11/12	9/12	12/12	50/60
% of Annotator & Geri Assess 2.0 accord	75%	75%	92%	75%	100%	83%
Pass/Fail						Pass

**Table 3:** Fragmentation results



**Figure 2:** Timeline Bar showing finalised automated annotations and fragmentation as blue bars above the Timeline Bar.

## Conclusion

The ability to routinely select the best embryo relies on the consistent performance of the automated annotations module. The main advantages of using automated annotations for embryo development in a busy IVF clinic are:

- Improves consistency and standardises embryo assessment
- Ease and time-saving

Although, the main function of the automated annotations module is not to perform embryo grading, but it is intended to be used as a tool to assist with embryo grading.