175P-Utility of artificial intelligence (AI) in Ki-67 scoring of a breast cancer (BC) patient population

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Background

Ki-67 is an important breast cancer (BC) marker, especially for adjuvant treatment in HR+, HER2- cases. Working groups have provided guidance for Ki-67 immunohistochemistry (IHC) BC scoring to limit pathologist's variability, but no scoring method has been universally accepted. Rapid and reliable image analysis solutions to support scoring have surfaced for the Ki-67 assessment. We compared Ki-67 scoring with Aiforia® platform (AI deep learning image analysis), Halo® (image analysis supervised software) and two independent pathologists (patho) in a breast cancer population.

Method

We stained 114 breast cancer tumors for Ki-67 (Ki-67 clone MIB-1, ref GA626-Agilent) on the Dako Omnis platform. Three methodologies were used to quantify Ki-67+ tumor cells:

1) A deep learning approach model was trained for breast cancer detection and the Ki-67 MIB-1 clone by Aiforia®;

2) Two pathologists (Patho 1 and Patho 2) were trained following the International Ki67 Working Group (IKWG) guidelines (1,2). Intra-analysis assessment was done for one pathologist. The selected pathologist re-read the samples after a three week washout period;

3) The random forest classifier from Halo® was used to separate the image into tumor, non-tumor and background with pathologist approval. After cell segmentation, Ki67 positivity was assessed by thresholding (3).

4) The time needed to complete the analyses was recorded for each method.

Workflow

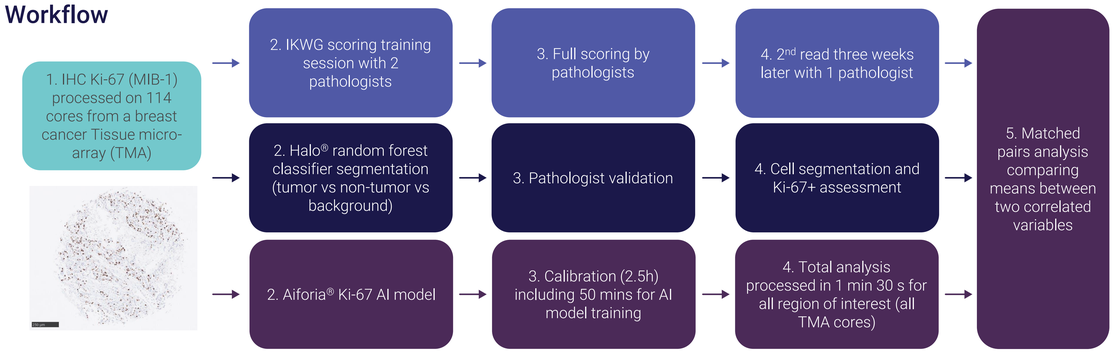

Fig 1. Example of an IHC Ki-67 staining workflow from a breast cancer specimen (invasive carcinoma).

Results: Image analysis illustrations

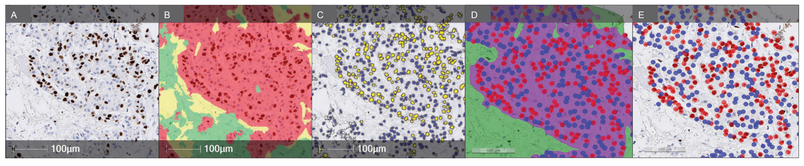

Fig 2. Image analysis illustration. From left to right: Ki-67 IHC, DAB detection (brown), hematoxylin counterstain (A). The Halo classifier with the tumor area in red, the non-tumor area in green and the background in yellow (B). Halo analysis markup Ki-67, (blue: nuclei and in yellow: positive cells (C)). Aiforia tissu detection with the tumor area in purple, the non-tumor area in green (D). Aiforia analysis markup Ki-67 (blue: negative cells and in red: positive cells (E)). Scale bar 100µm.

Results: Ki-67 quantification results on breast cancer

Out of 114 cores, only 109 were analyzed due to absence of tissue and/or pathologists unable to score. Ki-67+ cells were detected in 7.79 – 12.33% of tumor cells on average depending on the analysis approach applied (table 1). Our study shows a very high consistency of results obtained for Ki-67 scoring between the two image analysis softwares, Aiforia® and Halo® (r^2=0.93), on breast tumors analyzed. The correlation obtained between the pathologists was, however, weaker (mean r^2=0.86), despite appropriate training and following of guidelines, but remains within an acceptable range (table 2).

n=109	Mean %Ki-67+
Aiforia®	10.06
Halo®	7.79
Patho 1	8.41
Patho 2	12.33
Patho 1 (2^{nd} read)	9.03

Table 1: Ki-67 quantification results on breast cancer tumors analyzed.

Disclosures: XP, SI & AF are Cerba Research employees. RG is a consultant and DK & SR are Aiforia Technologies Plc employees. Study is sponsored by Cerba Research.

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Results: Matched pairs analysis of Ki-67 quantification on breast cancer

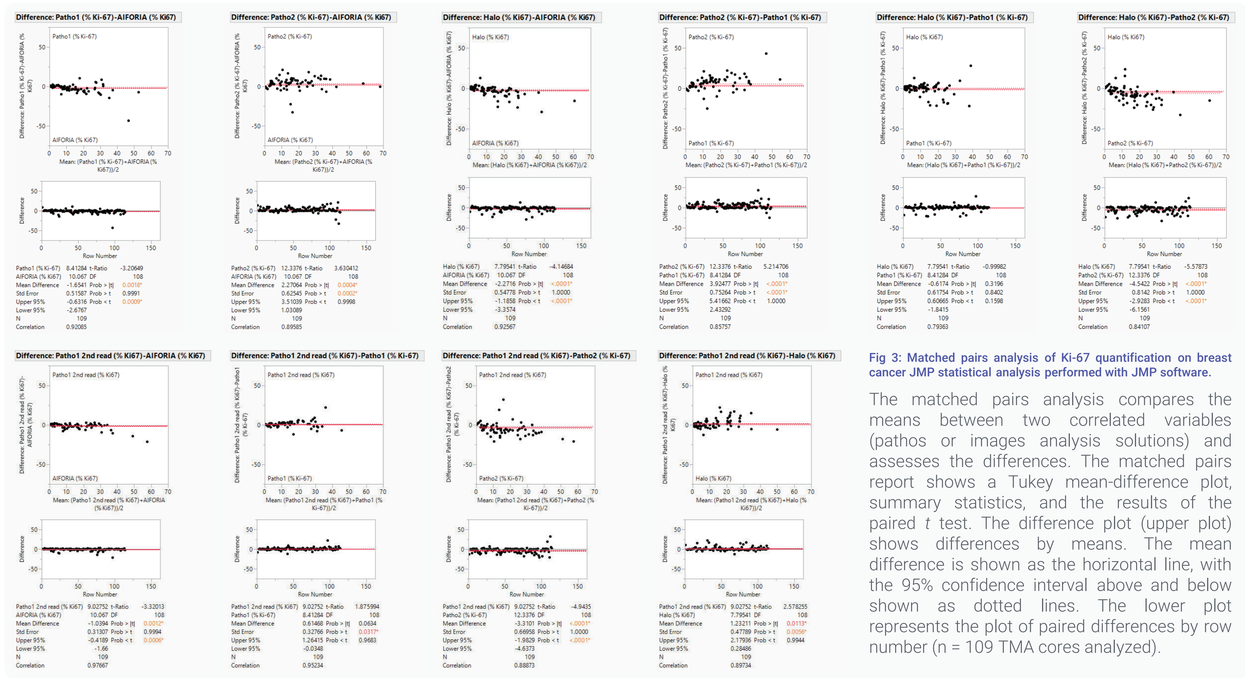

Fig 3: Matched pairs analysis of Ki-67 quantification on breast cancer JMP statistical analysis performed with JMP software.

The matched pairs analysis compares the means between two correlated variables (pathos or images analysis solutions) and assesses the differences. The matched pairs report shows a Tukey mean-difference plot, summary statistics, and the results of the paired *t* test. The difference plot (upper plot) shows differences by means. The mean difference is shown as the horizontal line, with the 95% confidence interval above and below shown as dotted lines. The lower plot represents the plot of paired differences by row number (n = 109 TMA cores analyzed).

Results: Summary of Ki-67 quantification analysis on breast cancer

Matched pairs analysis (n=109)	Mean difference of %Ki-67+	Prob > ItI	Std Err	Prob > t	r^2
Halo-Aiforia	-2.27	<0.0001*	0.55	1.000	0.93
Patho1-Aiforia	-1.65	0.0018*	0.51	0.9991	0.92
Patho 2-Aiforia	2.27	0.0004*	0.62	0.0002*	0.89
Patho 2-Patho 1	3.92	<0.0001*	0.75	<0.0001*	0.86
Halo-Patho 1	-0.62	0.3196	0.62	0.8402	0.79
Halo-Patho 2	-4.54	<0.0001*	0.81	1.0000	0.84
Patho 1 (2^{nd} read)-Aiforia	-1.04	0.0012*	0.31	0.9994	0.98
Patho 1 (2^{nd} read)-Patho 1	0.61	0.0634	0.33	0.0317*	0.95
Patho 1 (2^{nd} read)-Patho 2	-3.31	<.0001*	0.67	1.000	0.89
Patho 1 (2^{nd} read)-Halo	1.23	0.0113*	0.48	0.0056*	0.90

Table 2: Summary of matched pairs analysis of Ki-67 quantification on breast cancer tumors (n=109). Cell color coding for r^2: green >0.90; orange: 0.90 - 0.80; yellow: 0.80 - 0.75

As indicated in table 2 and figure 3, intra-pathologist analysis showed a very high reproducibility (r^2=0.95) while matched pair analysis between two pathologists was lower (r^2=0.86) despite following guidelines. Our study also shows a high consistency of Ki-67 results between AI and the other methods (patho A-AI, r^2=0.92; B-AI, r^2=0.90; Halo-AI, r^2=0.93). The correlation obtained between Halo scoring was not as good, but within an acceptable range (Halo-A, r^2=0.79, Halo-B, r^2=0.84).

Results: Time needed to complete each analysis

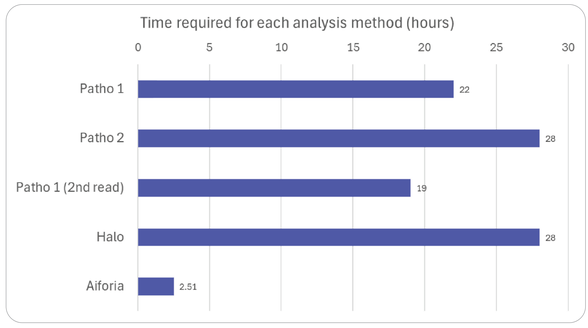

Fig 4: Comparison of the process times required for each method for Ki-67 quantification in hours.

The deep learning AI approach was the quickest by far even when including the model training (total time: 2hrs 51min). Pathos time ranged from 22 to 28hrs without a major gain in analysis time in the second review. Halo took 28 hours including application development, pathologist verification, and analysis.

Conclusion

Overall, the Ki-67 tumor analysis approaches were quite comparable which is similar to our previous analysis with the Ki-67 30-9 clone (4). AI-based image analysis tools offer valuable assistance in Ki-67 scoring and could reduce inter-pathologist variability. These results demonstrate a significant time benefit of using an AI-driven method for Ki-67 analysis in breast cancer ensuring that Ki-67 services are delivered efficiently and effectively.

References:

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[4] Pichon X et al. ESMO 2023.