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► **To cite this version:**

Yaëlle Bellahsen-Harrar, Mélanie Lubrano, Charles Lépine, Aurélie Beaufrère, Claire Bocciarelli, et al.. AI-Augmented Pathology for Head and Neck Squamous Lesions Improves Non-HN Pathologist Agreement to Expert Level. 2024. hal-04396487

**HAL Id: hal-04396487**

**<https://minesparis-psl.hal.science/hal-04396487>**

Preprint submitted on 16 Jan 2024

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## AI-Augmented Pathology for Head and Neck Squamous Lesions Improves Non-HN Pathologist Agreement to Expert Level

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### **Abstract**

**Importance:** Diagnosis of head and neck squamous dysplasias and carcinomas is challenging, with a moderate inter-rater agreement. Nowadays, new artificial intelligence (AI) models are developed to automatically detect and grade lesions, but their contribution to the performance of pathologists hasn't been assessed.

**Objective:** To evaluate the contribution of our AI tool in assisting pathologists in diagnosing squamous dysplasia and carcinoma in the head and neck region.

**Design, Setting, and Participants:** We evaluated the effectiveness of our previously described AI model, which combines an automatic classification of laryngeal and pharyngeal squamous lesions with a confidence score, on a panel of eight pathologists coming from different backgrounds and with different levels of experience on a subset of 115 slides.

**Main Outcomes and Measures:** The main outcome was the inter-rater agreement, measured by the weighted linear kappa. Other outcomes on diagnostic efficiency were assessed using paired *t* tests.

**Results:** AI-Assistance significantly improved the inter-rater agreement (linear kappa 0.73 with assistance versus 0.675 without assistance,  $p < 0.001$ ) Moreover, the agreement was even better on high confidence predictions (linear kappa 0.8 vs 0.73,  $p < 0.001$ ). This improvement was particularly strong for non-HN specialised pathologists and younger pathologists. Hence, the AI-Assistance enabled the pathologists' panel to perform on par with the expert panel described in the literature.

**Conclusions and Relevance:** Our AI-Assistance is of great value for helping pathologists in the difficult task of diagnosing squamous dysplasias and carcinomas, improving for the first time the inter-rater agreement. It demonstrates the possibility of a truly Augmented Pathology in complex tasks such as the classification of head and neck squamous lesions.

## **Introduction**

Head and Neck Squamous cell carcinomas (HNSCC) are a significant global health concern, ranking sixth worldwide in both incidence and mortality rates<sup>1</sup>. These cancers are notoriously associated with poor prognosis and high morbidity in the laryngeal and pharyngeal regions<sup>2,3</sup>. One reason for these figures is the late diagnosis of invasive lesions and their dysplastic counterparts. Early detection of dysplasia is essential in preventing invasive carcinomas<sup>4</sup>, and accurate grading is decisive as the grade remains the most important prognostic factor for the biological behaviour of disease, guiding the physicians in their care strategy<sup>5</sup>. Pathological examination is the gold standard diagnostic method<sup>6</sup> but poses many challenges. The small size of the samples impairs their optimal embedding orientation, often resulting in difficult-to-analyse tangent cuts. Changes in epithelium thickness between anatomical locations<sup>7</sup> and within a lesion itself<sup>8</sup> can make it challenging to differentiate reactive epithelial changes such as basal hyperplasia, from true dysplastic lesions. Moreover, dysplasia grading is a complex task that requires simultaneous consideration of multiple cytological and architectural features<sup>8,9</sup>. Unlike most anatomical locations such as the uterine cervix or the digestive tract, the grading of head and neck dysplasia lacks immunohistochemical markers for guidance, thereby exclusively relying on Haematoxylin and Eosin (HE) staining and morphological assessment<sup>8,10,11</sup>. The complexity of grading is evident from the multiple classifications proposed since the 1960s each with its own terminology (squamous intraepithelial neoplasia (SIN) by Friedmann and Osborn in 1976, intraepithelial neoplasia of the larynx by Crissman and Fu in 1986, laryngeal intraepithelial neoplasia (LIN) by Friedmann and Ferlito in 1988, squamous intraepithelial lesion (SIL) by Gale *et al* in 2014) and number of dysplasia categories<sup>11,12</sup>. This multitude of options has led to ambiguity and dissonance without a single approach standing out as superior. Additionally, dysplastic lesions of the oral cavity are graded using a different system without a solid explanation for the rationale behind this distinction.

Numerous studies have highlighted the mediocre inter-rater agreement among pathologists, reflecting the significant challenges of pathological examination<sup>13,14</sup>. In an attempt to address this issue, the WHO proposed in 2017 to simplify dysplasia grading by combining moderate and severe dysplastic lesions into a larger “high grade dysplasia” category<sup>10,12</sup>. However, despite this simplification, reproducibility between pathologists remained unsatisfactory<sup>15</sup>. Notably, the latest study on this topic by Mehlum *et al*<sup>16</sup> compared all reproducibility studies on head and neck squamous lesions in the literature, reported mediocre inter-rater agreement, demonstrating difficulties in providing reliable diagnosis even with the simplified binary system. Moreover, the scarcity of head and neck pathology specialists exacerbates the difficulties in getting optimal patient care. Therefore, the development of new tools to assist pathologists in their diagnoses is critical.

Recently, several studies have shown the benefits of AI models for improved diagnostic accuracy and reproducibility among pathologists, leading to what could be called an “augmented pathology”. However, most of these works have focused on classification between different cancer subtypes or carcinoma gradings<sup>17-21</sup>. In a previous work<sup>22</sup>, we proposed a deep learning model for classifying head and neck squamous lesions with an indication of the model’s confidence. However, we didn’t assess its effectiveness in a real-life setting.

The objective of the present study was to assess whether AI-Assistance could increase accuracy and reproducibility among pathologists, ultimately leading to more effective and efficient management of patients, in the challenging task of detecting and grading laryngeal and pharyngeal (oropharynx and nasopharynx excluded) squamous dysplastic and invasive lesions.

## **Materials and Methods**

### **Deep Learning Model Implementation and Evaluation**

Based on the widely used Attention-MIL architecture<sup>23</sup>, we developed, trained and validated a model for automatic grading of head and neck squamous lesions<sup>22</sup>. For each slide, it generates two outputs: the predicted lesion (ranging from non-dysplastic, low grade dysplasia, high grade dysplasia, to carcinoma) and an associated confidence score. The confidence score is specifically designed to measure the model's level of confidence for lesions on the same spectrum: it measures the extent to which the model hesitated with the second most probable (adjacent) class, as described in a previous work<sup>24</sup>. The confidence threshold is optimised to reach an overall AUC > 0.9 on the validation set (thus settled at 0.5).

The model was trained using a dataset of 1949 digitised Haematoxylin, Eosin and Saffron-stained slides obtained from 456 patients who underwent either biopsies or surgical resection at Hôpital Européen Georges Pompidou (AP-HP, Paris, France). Each slide was associated with one class based on the most severe lesion present in the sample. The slides were digitised at 20X magnification using a Hamamatsu NanoZoomer® s360 scanner, resulting in a pixel resolution of 0.45 µm. To properly evaluate the model's performance, an independent subsample of 115 biopsies was used as the test set. The classes for these slides were determined using a dual-blind review by two pathologists with expertise in head and neck squamous lesions, followed by a consensus meeting to thoroughly discuss any slides on which they disagreed. This dataset was used to evaluate the performance of the AI model and to assess the effectiveness of AI-assisted reviews in terms of reproducibility between pathologists and their diagnostic performances. Finally, the model was validated on an external dataset from another centre (Hôpital Tenon, AP-HP, Paris, France) including 87 slides from 67 patients<sup>22</sup>. Details about the datasets are shown in **Supplementary Table A**.

### **Randomized Protocol and Pathologists Panel**

The panel consisted of eight pathologists with varying experience levels and practice backgrounds: two residents in their last year of residency, three pathologists specialised in head and neck pathology, and three pathologists with no routine practice in head and neck pathology (details in **Supplementary Figure A**). The two expert pathologists who labelled the 115 slides of the reference test set were not included in the panel. All panel members were tasked with reviewing the slides from the reference standard test set with and without AI-Assistance. Residents and non-specialized pathologists were provided with the references of the latest WHO grading system beforehand to update their knowledge. The study was designed as a randomised crossover trial, where each participant was randomly assigned to start with either the AI-assisted review or the non-assisted review, following protocols used in other studies<sup>19,25,26</sup>. The pathologists independently reviewed the 115 slides and assigned a diagnosis to each of them without external input, in one uninterrupted session. A mandatory

washout period of at least two weeks was required between the two reviews to avoid potential carryover effects.

## Digital Platform and Review Process

The reviews were conducted using the EyeDo© digital platform (Tribun Health), a web-based viewer allowing for simultaneous visualisation of the slides, the model's prediction, and the confidence score. A user guide was provided to the participants. Both the assisted and non-assisted reviews were performed on the same platform, but the slide names were changed between the two reviews to ensure blinding. During the non-assisted review, the pathologists had access only to the slides and were blind to any other information related to the case. For the assisted reviews, they were provided with the model's prediction, the confidence score expressed as a percentage, a categorization of the confidence (high or low, following the threshold established beforehand) and a heatmap that could be toggled on and off, highlighting regions of the slide that contributed to the prediction, as shown in **Figure 1** and **Supplementary Figure B**. For each slide, the reviewers were asked to fill in a table with their diagnosis, with the slide names pre-filled in the order of appearance on the platform.

## Statistical Analysis

After all the panel members completed the assisted and unassisted reviews, their diagnoses were compared to the reference internal test set. Cohen's kappa with linear weights was used as the primary metric to measure the reproducibility, to compare it with the other studies published in the literature. Other standard classification metrics (accuracy, sensibility, specificity, negative and positive predictive values) were computed per class in a one-versus-rest manner. Confidence intervals of the AI algorithm model were computed using 10000 bootstraps. Statistical differences of the metrics between the AI-Assisted and the non-assisted reviews were assessed with a paired t-test testing the null hypothesis that the two reviews by the panel have identical average. To account for possible bias in the reference standard of the internal test set, the pairwise agreement between all panel members individually were computed for the two reviews. All statistical analyses were performed using python (v3.6.9), pandas (v1.1.5), scikit learn (v1.2.0) and scipy (v1.6.0).

## Results

### Standalone Model's Performances

On the internal test set, the standalone AI model achieved an average AUC of 0.878 (95% CI: [0.801-0.937]) across the four classes, with an AUC > 0.9 for the detection of carcinoma, and an average linear kappa of 0.675 (95%CI: [0.575-0.760]). For the correct predictions, the confidence score had an average value of 0.846 +/- 0.153, compared to 0.288 +/- 0.150 for incorrect predictions, showing a good correlation between high model's confidence and correct predictions. The overall AUC improved by 5.3% (0.931 [0.888-0.968]) when removing slides with low confidence. Conversely, overall AUC computed on the uncertain slides was 0.694 [0.580-0.797]. The linear kappa was 0.833 [0.737-0.905] on high confidence slides and 0.275 [0.077-0.449] on low confidence slides (+55.8%). Similar performances were observed on the external test set, where the model achieved an average AUC of 0.886 (95% CI: [0.813-0.947]). All metrics are detailed in **Supplementary Table B**.

## **Agreement of the Pathologists' Panel with and without AI-Assistance**

Agreement comparisons are presented in **Figure 2**. The results demonstrate that AI-Assistance significantly improved inter-rater agreement, as indicated by the reduced range of kappa range values (as shown in **Fig 2A**). Furthermore, the combined analysis of pathologist and AI showed greater efficiency compared to the standalone AI model (0.73 vs 0.675,  $p < 0.001$ ). When considering pairwise agreement within the panel without taking the reference standard labels into account, the median agreement was 0.619 in the non-assisted review and 0.734 in the assisted review. These results show that AI-Assistance led to increased consistency in grading among the pathologists (as shown in **Fig 2B**).

## **Pathologists' Performances Improvement with AI-Assistance depending on their Experience**

The overall performances of pathologists depending on their category (resident, non-HN specialist, HN specialist) are presented in **Figure 3**. The results show that the assisted residents and non-HN specialists outperformed the standalone AI model and demonstrated significant improvement across all metrics. These findings highlight the powerful impact of the AI-Assistance for non-HN specialists and young pathologists, suggesting its promising benefits in routine practice. However, it is worth noting that the HN specialists, who already achieved better performances than the standalone model, did not benefit from much improvement from the AI-Assistance. Detailed results are shown in **Supplementary Table C**.

## **Pathologists' Performances depending on the Confidence Score**

When considering the model's confidence scores, the results indicate that there was no improvement in pathologist's agreement on low confidence predictions, and a significant improvement when the confidence score was high (as shown in **Figure 4**). There was no difference in the kappa values between assisted and non-assisted reviews when the confidence score was below the threshold, suggesting that the pathologists did not take the model's predictions into account in these cases. Conversely, on high confidence predictions, reproducibility was significantly higher and with a reduced distribution of kappa values (high confidence slides: linear kappa 0.8 assisted vs 0.73 non-assisted,  $p < 0.001$ ). This indicates that pathologists were more inclined to consider the predictions and that it facilitated higher diagnostic performances.

## **Metrics Improvement with AI-Assistance depending on the Type of Lesion**

Pathologists' performances per diagnostic class are shown in **Table 1**. Globally, the pathologists were more performant with the AI-Assistance. Specificity improved significantly for low grade dysplasia, indicating better discrimination of this subtle lesion (non-assisted pathologists: 0.814 vs assisted pathologists: 0.855,  $p = 0.021$ ). Moreover, performances showed drastic improvements for high grade dysplasia and carcinoma, the pathologists becoming more efficient than the standalone model (for instance, accuracy for high grade dysplasia: 0.774 for the standalone model vs 0.806 for the Augmented Pathologist,  $p = 0.003$ ). These results show that the AI tool assisted pathologists in identifying these harmful lesions with the highest therapeutic impact, and the combination of the pathologist's expertise and the AI analysis proved to be complementary and more powerful when used together.

## **Discussion**

To the best of our knowledge, the benefit of an AI-Assistance in the difficult task of detecting and grading dysplasia in the laryngeal and pharyngeal regions wasn't assessed before. Due to their limited number, studies on dysplasia detection and classification by AI models have not assessed whether these models enhance the performance of pathologists. Furthermore, almost all of them didn't follow any official classification system. For instance, Tomita *et al*<sup>27</sup> combined low and high grade dysplasias as well as true invasive adenocarcinoma and high grade suggestive of invasion due to their dataset's limited size. Other works on Barrett's esophagus<sup>28,29</sup> didn't grade dysplasia either. One major limitation of these studies is the scarcity of the datasets, which results in inadequate training sets to learn such nuanced pathological aspects. Benefiting from a substantial training set of nearly 2000 slides, our model was subsequently validated on two different test sets. To our knowledge, only one previous work on gastric dysplasia successfully differentiated between epithelial regeneration change and dysplasia and graded the latter in a large cohort<sup>30</sup>. However, this study did also not assess if the AI tool could improve pathologist performance in a real-world setting.

Indeed, it is imperative to remember that even if an efficient standalone AI model is developed, the use of such a tool without medical control is currently impossible due to possible errors, with potential harmful patient outcomes. Thus, pathologist validation of the AI predictions is mandatory. Our findings demonstrate that pathologists supplemented with AI were more efficient than the standalone deep learning model. Notably, AI-Assistance significantly improved the panel's accuracy and reproducibility, especially for non-HN specialists and less experienced pathologists. These results show that our solution combining an efficient model with a confidence score is a helpful tool for the diagnosis of laryngeal and pharyngeal squamous lesions for non-specialists and younger pathologists.

Our AI-assisted method enabled our pathologist panel to surpass the performances reported in earlier studies<sup>16</sup> and to perform equivalently to the expert panel of Gale *et al*<sup>12</sup> which achieved a weighted kappa of 0.80 among ten globally recognized expert pathologists. The agreement was even greater on high confidence predictions, showing that the confidence score is efficient in guiding pathologists in their diagnosis, emphasising the need to integrate model confidence indicators in AI-assisted workflows.

The implications of our study are significant for clinical practice, since the use of our AI model by pathologists across varied backgrounds could lead to more precise and uniformed diagnoses, and improved patient care management. Additionally, the tool's explanatory features, such as reliability scores and heatmap regions that influenced the prediction, provide the opportunity for pathologists to improve their own knowledge in the field. The educational potential of our confidence-based model could be explored in future work.

## **Limitations**

This study does have several limitations. Primarily, the model was trained using a single slide per sample, which was selected by a pathologist as the best representative of the lesion. In routine practice, a pathologist would examine multiple slides for the same sample, with a variation of the difficulty depending on the cut level. This selection of the best slide could have helped in the training of the model. However, all cuts on the selected slide were scanned and incorporated into the training and validation processes. Another limitation is the absence of

clinical information, which is provided to the pathologist in a real-life setting. Finally, the relatively small size of the pathologist panel could have potentially restrained the statistical power of our tests. Despite these limitations, our results still highlight the great potential of AI-assisted pathology in the diagnosis of laryngeal and pharyngeal squamous lesions.

## **Conclusions**

In this study, we demonstrate the feasibility and effectiveness of authentic Augmented Pathology in the challenging task of diagnosing laryngeal and pharyngeal squamous lesions. For the first time, we describe a methodology that truly improves inter-rater agreement such as no classification system alone achieved before. By providing a reliable diagnosis and an efficient confidence score, we believe that our AI model has the potential for broad acceptance in clinical practice, thereby greatly improving patient care and management.

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### **Conflict of interest**

The authors declare no competing interests.

### **Ethics Approval and Consent to Participate**

Our study was approved by the ethics committee of Assistance Publique - Hôpitaux de Paris Centre (CERAPHP. Centre - Institutional Review Board registration #00011928). All the patients were informed by a notification letter of the study and the possibility to refuse the use of their medical data, in line with current legislation. The study was performed in accordance with the Declaration of Helsinki.

### **Funding**

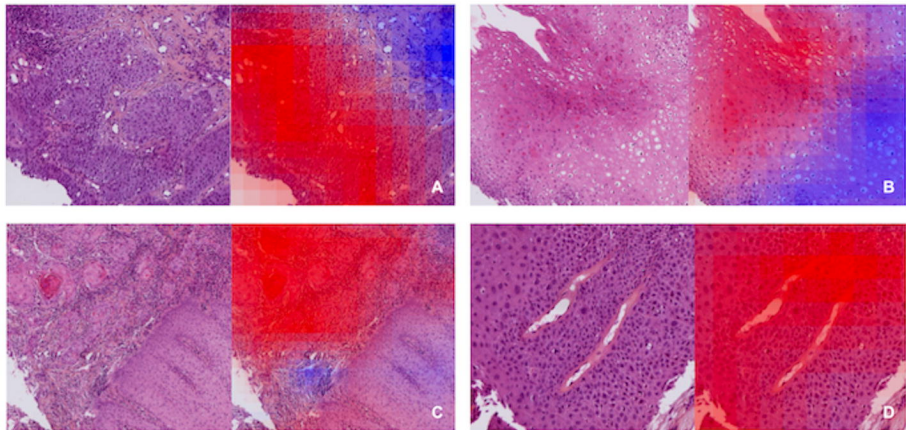
ML was supported by a CIFRE PhD fellowship founded by Keen Eye, Paris, France and ANRT (CIFRE 2019/1905). Furthermore, this work was supported by the French government under management of Agence Nationale de la Recherche as part of the “Investissements d’avenir” program, reference ANR-19-P3IA-0001 (PRAIRIE 3IA Institute).

### **Data Availability Statement**

The WSI dataset described in the manuscript were subject to hospital regulations and could not be publicly released. Data sharing with other research teams is possible under formal agreement with Assistance Publique - Hôpitaux de Paris (contact first and last authors for more information).

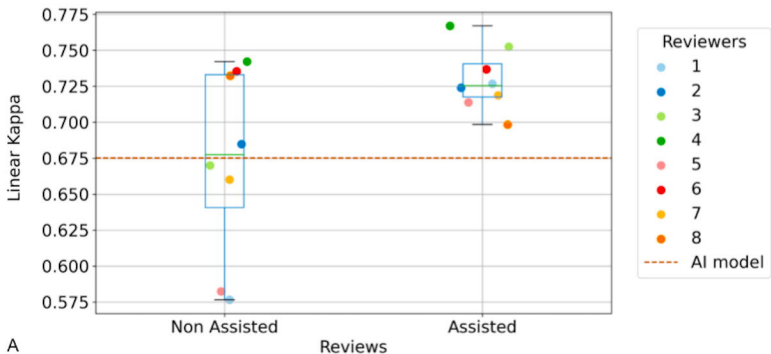
### **Author contributions**

Concept and design: CB, SB, TW. Ethical approvals processes: CB, SB. Creation of the clinical and pathology database, slides selection and labelling: YBH. Reference standard test set review: CB, YBH. Data management and processing, software implementation and statistical analyses: ML. Pathologists panel: CL, AB, CB, AB, ED, FEL, AM, CT. Results analysis: YBH and ML. Discussion of results: YBH, ML, CB, TW. Manuscript writing and review: all authors. All authors read and approved the final paper.

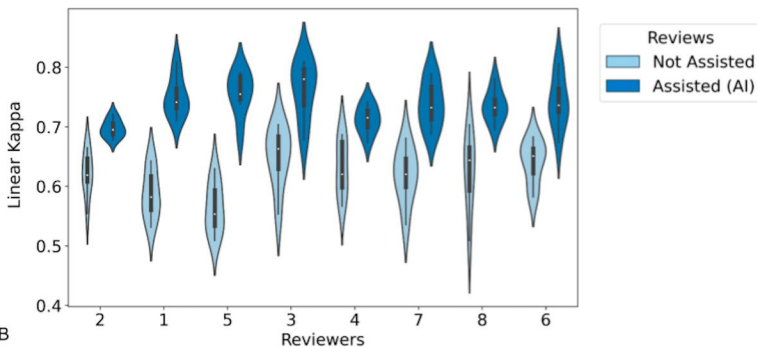


**Figure 1. Examples of Assisted Reviews on the Digital Platform**

- A. Prediction: High grade dysplasia; Confidence score: 70%; Confidence level: high
  - B. Prediction: Low grade dysplasia ; Confidence score: 70% ; Confidence level: high
  - C. Prediction: Invasive carcinoma; Confidence score : 100% ; Confidence level: high
  - D. Prediction: Non dysplastic; Confidence score: 40%; Confidence level: low (ground truth: High grade dysplasia)
- HES staining, magnification 10X (A-B-C) - 20X (D)



A

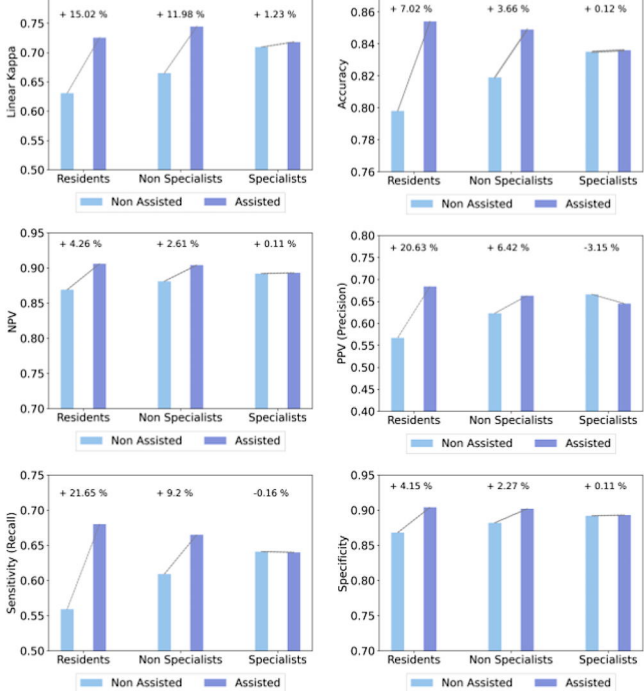


B

**Figure 2. Agreement between Pathologists with and without AI-Assistance**

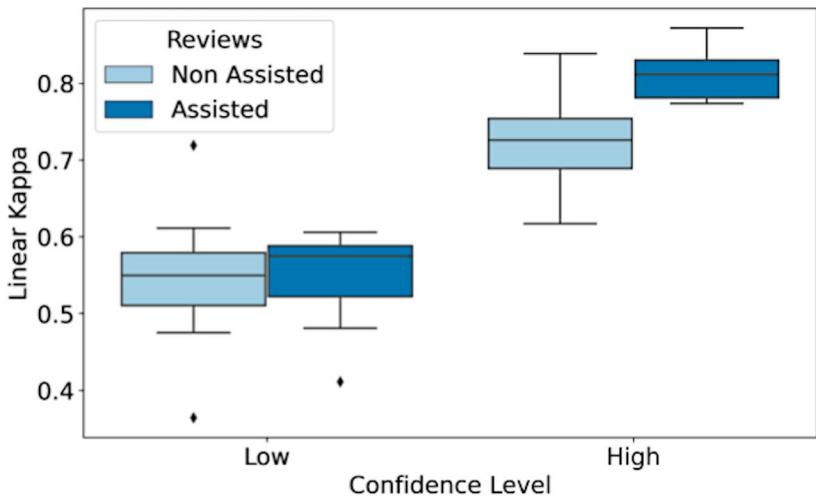
A. Linear kappa values for each pathologist with and without the AI-assistance, compared to the standalone AI-model. The assisted review significantly improved the inter-rater agreement and drastically reduced the kappa's range between pathologists.

B. Pairwise agreement showing an increase in the inter-rater agreement without considering the reference standard labels (linear kappa 0.734 assisted vs 0.619 non-assisted).



**Figure 3. Performances Improvements with AI-Assistance per Pathologist Category**

The assisted residents and non-HN specialists outperformed the standalone AI model and demonstrated significant improvement across all metrics. However, HN specialists didn't benefit from much improvement.



**Figure 4. Pathologists' Performances depending on the Confidence Threshold**

The impact of the model's confidence on the inter-rater agreement (high confidence slides: linear kappa 0.8 assisted vs 0.73 non-assisted,  $p < 0.001$ ).

**Table 1. Classification Metrics per Type of Lesion**

Metric	Status	Type of Lesion			
		Non-dysplastic	Low grade dysplasia	High grade dysplasia	Carcinoma
Accuracy	Non assisted vs Assisted (p-value*)	<b>0.834 vs 0.862 (0.039)</b>	0.749 vs 0.779 (0.076)	0.787 vs 0.806 (0.084)	<b>0.911 vs 0.934 (0.041)</b>
	Standalone model vs Augmented Pathologist (p-value*)	0.861 vs 0.862 (0.224)	0.757 vs 0.779 (0.986)	<b>0.774 vs 0.806 (0.003)</b>	<b>0.896 vs 0.934 (0.004)</b>
NPV	Non assisted vs Assisted (p-value*)	<b>0.879 vs 0.912 (0.031)</b>	0.872 vs 0.874 (0.433)	0.855 vs 0.864 (0.256)	<b>0.924 vs 0.95 (0.027)</b>
	Standalone model vs Augmented Pathologist (p-value*)	0.911 vs 0.912 (0.193)	0.882 vs 0.874 (0.942)	<b>0.819 vs 0.864 (0.000)</b>	<b>0.921 vs 0.95 (0.048)</b>
PPV (Precision)	Non assisted vs Assisted (p-value*)	0.663 vs 0.706 (0.135)	0.349 vs 0.393 (0.179)	<b>0.606 vs 0.645 (0.049)</b>	0.888 vs 0.904 (0.173)
	Standalone model vs Augmented Pathologist (p-value*)	0.68 vs 0.706 (0.406)	0.4 vs 0.393 (0.071)	<b>0.571 vs 0.645 (0.001)</b>	<b>0.846 vs 0.904 (0.003)</b>
Sensitivity (Recall)	Non assisted vs Assisted (p-value*)	<b>0.565 vs 0.69 (0.034)</b>	0.451 vs 0.435 (0.632)	0.592 vs 0.61 (0.350)	<b>0.836 vs 0.896 (0.027)</b>
	Standalone model vs Augmented Pathologist (p-value*)	0.68 vs 0.69 (0.193)	0.545 vs 0.435 (0.527)	0.414 vs 0.61 (0.969)	<b>0.846 vs 0.896 (0.004)</b>
Specificity	Non assisted vs Assisted (p-value*)	0.913 vs 0.913 (0.500)	<b>0.814 vs 0.855 (0.021)</b>	0.858 vs 0.858 (0.075)	0.948 vs 0.952 (0.306)
	Standalone model vs Augmented Pathologist (p-value*)	0.911 vs 0.913 (0.383)	0.806 vs 0.855 (0.071)	<b>0.895 vs 0.858 (0.000)</b>	<b>0.921 vs 0.952 (0.011)</b>

\* One sided paired *t* tests. Results with statistical significance are in bold.