



PanPath: A Study to Assess Real-World Agreement in the Evaluation of HER2 Protein Expression in Non-Breast/Gastric Solid Tumour Tissue

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38th European Congress of Pathology
12 – 16 September 2026, Stockholm, Sweden



Disclosures

- G.V. has received consulting fees from Agilent, AstraZeneca, Daiichi Sankyo, Gilead, and Roche; received payment or honoraria from Agilent, AstraZeneca, Pfizer, and Roche; received support for attending meetings and/or travel from AstraZeneca and Roche; and has participated on a data safety monitoring board or advisory board for AstraZeneca and Daiichi Sankyo

Background

- HER2 expression has been identified across multiple tumour types, and T-DXd, a HER2-directed therapy, has demonstrated clinical benefit across HER2-expressing cancers¹⁻⁶
- Although tumour-specific HER2 IHC scoring algorithms have been developed for some tumour types (eg, breast, gastric, endometrial, and colorectal), HER2 testing and scoring guidelines remain limited in many non-breast/non-gastric solid tumours⁷⁻¹⁰
- As a result, pathologists may have limited experience assessing HER2 expression in these settings, and few data on HER2 IHC scoring concordance and impact of training are available in these tumour types^{7,10,11}
- Further evidence is needed to characterise baseline HER2 IHC scoring performance and evaluate the impact of educational interventions in non-breast/non-gastric solid tumours to improve identification of patients who may be eligible for HER2-directed therapies

HER2, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **T-DXd**, trastuzumab deruxtecan.

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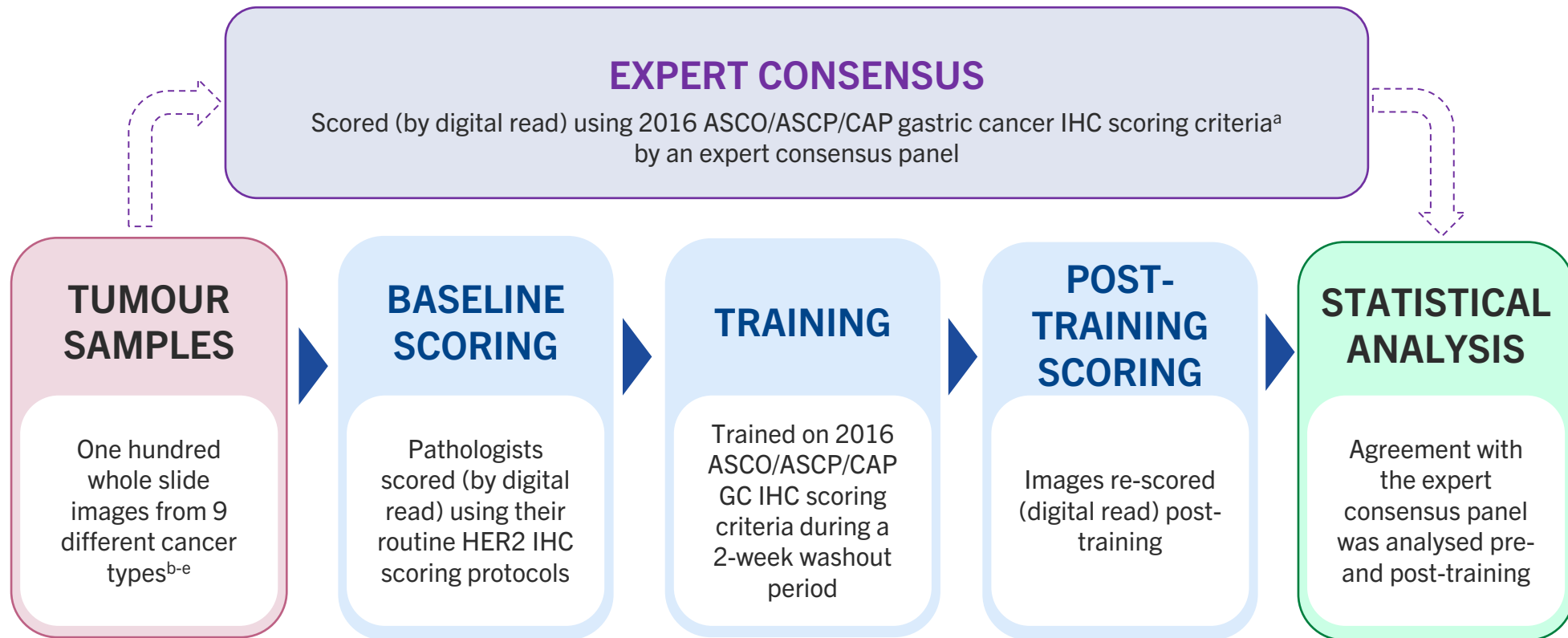
Objectives

- Assess the real-world agreement of pathologists in HER2 IHC scoring of 9 types of non-breast/non-gastric solid tumours and investigate the impact of training on scoring agreement in phase 2 of this study, which was conducted outside the US^a

HER2, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **US**, United States.

^aThe results of phase 1 (conducted in the US) will be presented at the International Congress of the International Academy of Pathology (IAP); Fukuoka, Japan; October 8-13, 2026.

Methods



ASCO, American Society of Clinical Oncology; ASCP, American Society for Clinical Pathology; CAP, College of American Pathologists; GC, gastric cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

^aIn situ hybridization was not performed. ^bInclude non-small cell lung cancer, bladder cancer, biliary tract cancer, cervical cancer, colorectal cancer, endometrial cancer, ovarian cancer, pancreatic cancer, and salivary gland cancer. ^cSamples include HER2 IHC 3+/2+/1+/0. ^dFluorescence in situ hybridization status not known for IHC 2+ samples. ^eHER2 IHC was performed using either 4B5 (Ventana) or HercepTest.

Tumour sample characteristics

- Samples were selected to provide a balance of tumour types and HER2 IHC scores, with enrichment of HER2 IHC 3+ cases
- Each tumour type included approximately 3-4 HER2 IHC 3+ cases

Characteristic	n (%)
Samples with consensus score	100 (100)
Tumour type	
NSCLC	12 (12.0)
Bladder	11 (11.0)
Biliary tract	10 (10.0)
Cervical	12 (12.0)
Colorectal	11 (11.0)
Endometrial	11 (11.0)
Ovarian	11 (11.0)
Pancreatic	11 (11.0)
Salivary gland	11 (11.0)
HER2 IHC consensus score	
0	27 (27.0)
1+	14 (14.0)
2+	24 (24.0)
3+	35 (35.0)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

Pathologists’ demographics and characteristics

- Forty-one pathologists who completed the demographic survey were from various geographic regions, with most practising in academic settings
- The majority had <10 years of prior experience interpreting HER2 IHC in non-breast/non-gastric settings
- Most pathologists had experience with the 4B5 (Ventana) HER2 testing assay
- 31.7% of pathologists received tumour-agnostic HER2 IHC training within the previous 3 months

Characteristic	n (%) ^a
Pathologists who completed the survey^b	41 (100)
Geographic region	
Europe	13 (31.7)
Asia	16 (39.0)
Rest of the world ^c	12 (29.3)
Practice setting^d	
Academic	29 (70.7)
Community	9 (22.0)
Reference laboratory	8 (19.5)
Other	2 (4.9)
Experience with HER2 testing in non-breast/non-gastric tumours	
0-4 years	17 (41.5)
5-9 years	20 (48.8)
≥10 years	4 (9.8)

Characteristic	n (%) ^a
Experience with HER2 assays^d	
HercepTest (Agilent Autostainer)	2 (4.9)
HercepTest (Omnis)	2 (4.9)
4B5 antibody (Ventana)	35 (85.4)
Leica	2 (4.9)
Other ^e	4 (9.8)
Tumour agnostic HER2 IHC training in last 3 months^f	
Yes	13 (31.7)
No	28 (68.3)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
^aPercentages are based on the number of pathologists who submitted the demographics data. ^bTen pathologists did not submit demographic data. ^cParticipants were from Australia, Brazil, and Canada. ^dRespondents could select more than one option. ^eIncludes Agilent/Dako platforms: HER2 (Dako, clone A0485), Nil, AO485, and Leica platform: EP3 CellMark. ^fPreceding the time at which the survey was taken.

Primary endpoint: agreement with expert consensus panel score for HER2 IHC 3+ versus non-3+ before and after training^a

- Agreement for HER2 IHC 3+ cases (PPA) was 84.3% pre-training and increased numerically after training
- Agreement for HER2 IHC non-3+ (NPA) cases remained consistent before and after training (>91%)
- Post-training OPA was 90%, and concordance with the expert consensus panel remained substantial (Cohen's κ = 0.78)

Measure of agreement	Pre-training (n = 4547)	Post-training (n = 4101)	Difference ^f
PPA, ^b % (95% CI)	84.3 (76.3, 91.0)	87.2 (79.9, 93.3)	+3.7 (−0.5, 8.6)
NPA, ^c % (95% CI)	92.5 (88.0, 96.2)	91.5 (86.3, 95.7)	−1.1 (−4.1, 1.2)
OPA, ^d % (95% CI)	89.6 (85.8, 93.1)	90.0 (86.1, 93.5)	+0.6 (−1.4, 2.4)
Cohen's κ , ^e (95% CI)	0.77 (0.68, 0.84)	0.78 (0.69, 0.86)	+0.02 (−0.03, 0.06)

CI, confidence interval; **HER2**, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **NPA**, negative percent agreement; **OPA**, overall percent agreement; **PPA**, positive percent agreement.

HER2 IHC non-3+ is defined as HER2 IHC 2+/1+/0, regardless of the in situ hybridization test result.

^aNo statistical hypothesis testing was performed. ^bPPA is the proportion of consensus HER2 IHC 3+ assessments in which individual pathologist results are assessed as HER2 IHC 3+. ^cNPA is the proportion of consensus HER2 IHC non-3+ assessments in which individual pathologist results are assessed as HER2 IHC non-3+. ^dOPA is the proportion of assessments in which the consensus and pathologist scores give the same outcome. ^eCohen's κ is a measure of the strength of agreement: <0: poor; 0-0.2: slight; 0.21-0.4: fair; 0.41-0.6: moderate; 0.61-0.8: substantial; 0.81-1: almost perfect. ^fDifferences of PPA, NPA, OPA, and Cohen's κ from pre-training to post-training are reported based on assessments that were available at both timepoints. The differences in total cases between pre- and post-training are due to the loss of participating pathologists and missing scores from pre- and post-training (<1%).

Exploratory analysis: agreement with expert consensus panel score by HER2 IHC scores before and after training^a

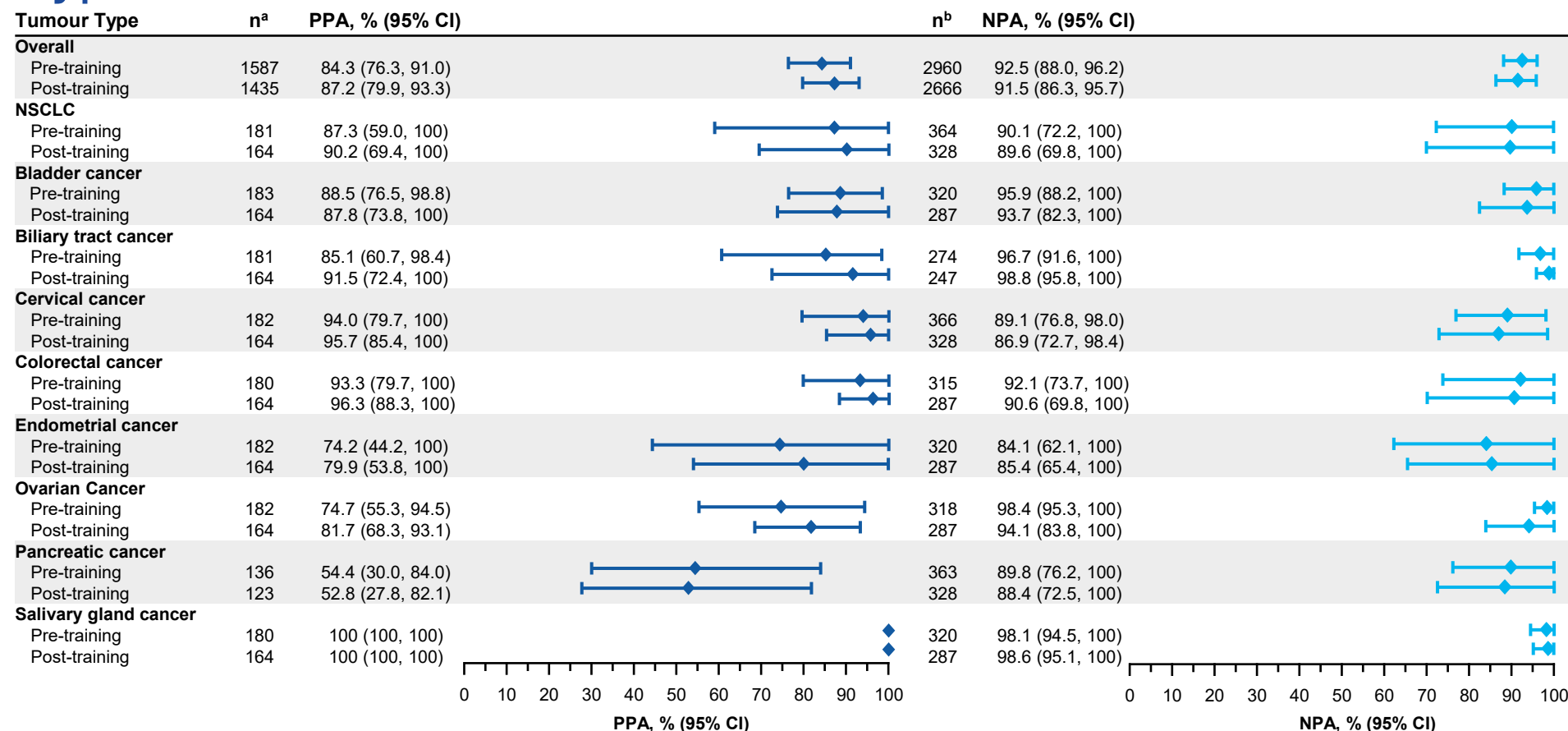
- Highest agreement was observed for HER2 IHC 3+ both before and after training
- Numerical improvements were observed for HER2 IHC scores 0 and 3+, with minimal changes for scores 1+ and 2+

	Score	Pre-training (n = 4547)	Post-training (n = 4101)
PA, % (95% CI)	0	67.7 (54.0, 80.7)	71.5 (57.3, 84.3)
	1+	57.1 (46.4, 68.2)	56.8 (45.2, 68.2)
	2+	55.4 (47.0, 63.9)	56.1 (46.5, 65.2)
	3+	84.3 (76.3, 91.0)	87.2 (79.9, 93.3)
OPA, % (95% CI)		69.1 (63.6, 74.4)	71.2 (65.3, 76.7)
Weighted linear κ^b (95% CI)		0.73 (0.67, 0.79)	0.75 (0.69, 0.81)

CI, confidence interval; **HER2**, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **OPA**, overall percent agreement; **PA**, percent agreement.
^aNo statistical hypothesis testing was performed. ^bWeighted linear κ summarizes agreement across all HER2 IHC scores (3+/2+/1+/0).

Exploratory analysis: agreement with expert consensus panel score by tumour type

- Agreement with the expert consensus panel is presented by tumour type for pre- and post-training assessments, demonstrating variability across tumour types^c
- Salivary gland, colorectal, and cervical had the highest PPA; endometrial, ovarian, and pancreatic had the lowest
- Salivary gland had the highest NPA; endometrial had the lowest



CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NPA, negative percent agreement; NSCLC, non-small cell lung cancer; PPA, positive percent agreement.

^aNumber of assessments for which the consensus score is HER2 IHC 3+. ^bNumber of assessments for which the consensus score is HER2 non-IHC 3+. ^cAll subgroup analyses are performed by repeating the main analyses using subgroup levels to subset the data and not adjusted for confounding factors.

Conclusions

- Substantial baseline agreement with the expert consensus panel was observed for HER2 IHC 3+ versus non-3+ (IHC 2+/1+/0) classification across multiple solid tumour types
- Training on HER2 IHC scoring was associated with a numerical increase in HER2 IHC 3+ classification (PPA +3.7%), suggesting that targeted educational initiatives may improve identification of patients eligible for HER2-directed therapies
- Agreement for HER2 IHC non-3+ remained consistently high before and after training, indicating that pathologists accurately identified HER2-negative cases across multiple solid tumour types
- Exploratory analyses showed generally consistent agreement across tumour types and geographic regions, with similar patterns observed before and after training

Limitation

- Although a washout period and randomised case sequence were implemented, use of the same images in the pre- and post-training assessments may have introduced bias

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PPA, positive percent agreement.

Acknowledgements

We thank:

All pathologists and laboratories who participated in this study;
Kristen Sarlo, PharmD, Christoph Lauer, PhD, and Alessia Sacco from
Daiichi Sankyo; Benjamin Chen, MD, PhD from PathAI; and Eun-Ang
Raiber-Moreau, PhD from AstraZeneca

This study was sponsored and designed by Daiichi Sankyo and AstraZeneca.
In March 2019, AstraZeneca entered into a global development and commercialization collaboration
agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

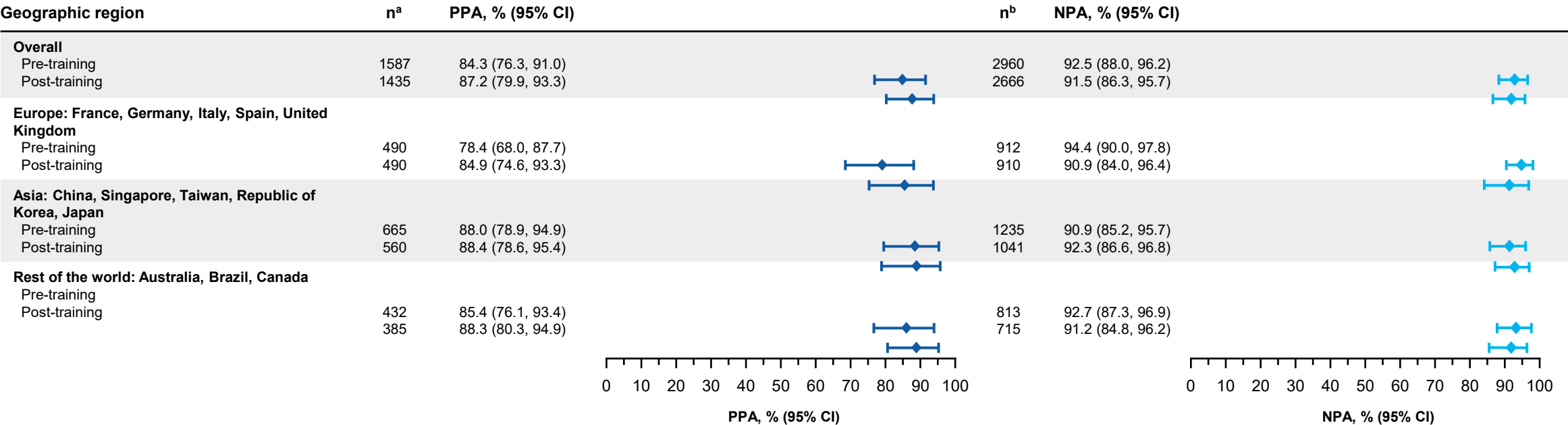
Supplemental materials can be
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Medical writing support, under the direction of the authors, was provided by
Agnieszka Looney, PhD, Jennifer Lau, PhD, and Katie Henderson, PhD, of
ApotheCom, and was funded by Daiichi Sankyo in accordance with Good
Publication Practice (GPP) guidelines (<http://www.ismpp.org/gpp-2022>).

<https://bit.ly/ESP2026DS>

Exploratory analysis: agreement with expert consensus panel score by pathologists' region



- Agreement with the expert consensus panel is presented by pathologists' geographic region for pre- and post-training assessments^c
- Asia had the highest pre- and post-training PPA; Europe had the lowest pre- and post-training PPA
- Europe had the highest pre-training NPA and Asia had the lowest; Asia had the highest post-training NPA and Europe had the lowest

CI, confidence interval; **HER2**, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **NPA**, negative percent agreement; **PPA**, positive percent agreement.
^aNumber of assessments for which the consensus score is HER2 IHC 3+. ^bNumber of assessments for which the consensus score is HER2 non-IHC 3+. ^cAll subgroup analyses are performed by repeating the main analyses using subgroup levels to subset the data and not adjusted for confounding factors.

Interrater reliability

- Pathologists demonstrated substantial agreement in distinguishing HER2 IHC 3+ from IHC 2+/1+/0 cases (Fleiss' κ = 0.72 pre-training; 0.73 post-training)
- Interrater reliability was maintained following training

Measure of reliability	n
Number of pathologists, n	
Pre-training	47
Post-training	42
Number of assessments, n	
Pre-training	4547
Post-training	4101
Fleiss' κ (95% CI)^a	
Pre-training	0.72 (0.64, 0.79)
Post-training	0.73 (0.66, 0.80)

HER2 IHC non-3+ is defined as HER2 IHC 2+/1+/0, regardless of the in situ hybridization test result.

CI, confidence interval; **HER2**, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry.

^aFleiss' κ agreement: <0: poor; 0-0.2: slight; 0.21-0.4: fair; 0.41-0.6: moderate; 0.61-0.8: substantial; 0.81-1: almost perfect.