SUPPLEMENTARY INFORMATION

SUPPLEMENTARY TABLES

Supplementary Table 1 Discrepancies between the study pathologists in the external validation set

Diagnosis	**Discrepancies N (%)**	**Discrepancies details - N**
Invasive vs. non-invasive	11 (7%)	Invasive vs. benign – 4 Invasive vs. DCIS/ADH – 7
IDC vs. ILC vs. other invasive	7 (4.5%)	IDC vs. ILC – 5 IDC vs. Metaplastic – 2
DCIS/ADH vs. benign	14 (10.4%)	DCIS IG/HG vs. Benign – 9 DCIS LG/ADH vs. Benign – 5
DCIS HG/IG vs. LG/ADH	25 (18.5%)	DCIS HG vs. LG/ADH – 10 DCIS IG vs. LG/ADH – 15

ADH – atypical ductal hyperplasia; DCIS – ductal carcinoma in-situ; HG/IG/LG – high- / intermediate-/low- grade; IC-NST– infiltrating/invasive carcinoma no special type (IDC); ILC – infiltrating/invasive lobular carcinoma.

Supplementary Table 2. AI algorithm performance on rare invasive subtypes detection in the external validation set

Set	**Analysis**	**Number of cases**	**AUC[a,b] [95% CI]**	**Specificity [95% CI]**	**Sensitivity [95% CI]**	**PPV NPV**
External validation set (IC + MHS)	**Rare Invasive vs. non-invasive**	314 34 rare invasive 280 non-invasive	0.992 [0.985;0.999]	94.12% [79.93%;99.35%]	95.71% [92.58%;97.61%]	72.7% 99.3%

[a]AUC = area under the ROC curve

[b]The AUC of the precision-recall curve is 0.9434 and the F1 score is 87.5%

Supplementary Table 3. AI algorithm performance on H&E- and HES- stained biopsies of the external validation set*

Set	Analysis	Number of cases	AUC [95% CI]	Specificity [95% CI]	Sensitivity [95% CI]	PPV NPV
H&E	**Invasive vs. non-invasive**	167 55 invasive 112 non-invasive	0.991 [0.981;1]	93.75% [87.10%;97.50%]	96.36% [86.40%;100%]	88.3% 98.1%
	DCIS vs. benign/other [a]	103 50 DCIS 53 benign/other	0.998 [0.994;1]	98.1% [88.62%;100%]	98% [87.99%;100%]	98% 98.1%
	IDC vs. ILC [b,c]	54 37 IDC 17 ILC	0.976 [0.944;1]	94.12% [69.24%;100%]	91.9% [76.98%;98.93%]	97.1% 84.2%
	DCIS HG/IG vs. LG/ADH[d]	58 41 DCIS HG/IG 17 DCIS LG/ADH	0.937 [0.879;0.995]	82.35% [55.80%;96.98%]	82.92% [67.40%;92.86%]	91.9% 66.7%
HES	**Invasive vs. non-invasive**	269 101 DCIS/ADH 168 benign/other	0.989 [0.980;1]	93.45% [88.29%;96.67%]	95.05% [88.28%;98.52%]	89.7% 96.9%
	DCIS vs. benign/other [a]	145 53 DCIS 93 benign/other	0.960 [0.931;0.988]	89.13% [80.50%;94.63%]	88.68% [76.28%;95.85%]	82.5%, 93.2%
	IDC vs. ILC [b,c]	99 61 IDC 38 ILC	0.971 [0.938;1]	92.11% [77.52%;98.96%]	91.8% [81.17%;97.48%]	94.9%, 87.5%
	DCIS HG/IG vs. LG/ADH [d]	76 47 DCIS HG/IG 29 DCIS LG/ADH	0.913 [0.852; 0.975]	82.75% [63.51%;94.34%]	82.98% [68.65%; 92.32%]	88.6% 75%

*The small differences between the two sets could stem from differences between the scanners and/or between the stains (H&E vs HES) and/or between the labs (different preprocessing of tissue).

[a] Includes only non-invasive cases; [b] Includes only IDC (IC-NST and rare subtypes) and ILC cases, exclude other invasive cases; [c]IDC was considered positive and ILC negative for these analyses; [d]DCIS HG/IG considered positive and DCIS LG/ADH negative for these analyses;

ADH – atypical ductal hyperplasia; AUC – area under the receiver operating characteristic curve; DCIS – ductal carcinoma in-situ; HG/IG/LG – high- / intermediate- /low- grade; IDC – invasive ductal carcinoma; ILC – infiltrating/invasive lobular carcinoma; NPV – negative predicting value; PPV – positive predicting value.

Supplementary Table 4. AI algorithm performance on TILs detection in the external validation set

Set	Analysis	Number of cases	AUC [95% CI]	Specificity [95% CI]	Sensitivity [95% CI]
External validation set (IC + MHS)	**TILs in Invasive+DCIS**	109 32 TILs positive 77 TILs negative	0.965 [0.934;0.996]	85.7% [76.3%;92%]	93.8% [78.8%;99.3%]
	TILs in Invasive	47 19 TILs positive 28 TILs negative	0.953 [0.892;1]	85.7% [67.9%;94.9%]	94.7% [73.5%;99.9%]
	TILs in DCIS	62 13 TILs positive 49 TILs negative	0.962 [0.920;1]	85.7% [73%;93.2%]	92.3% [64.6%;100%]

Supplementary Table 5. Algorithm optimization process

Architecture	Inception V1		Inception V3		ResNet 101	
Magnification	10x	2.5x	40x	5x	20x	10x
Log loss	1.901	2.223	2.059	1.801	1.862	1.762
Log loss of combination	1.703		1.6		1.651	
Ensemble log loss	1.476					

Supplementary Table 6. Distribution of cases used for algorithm training

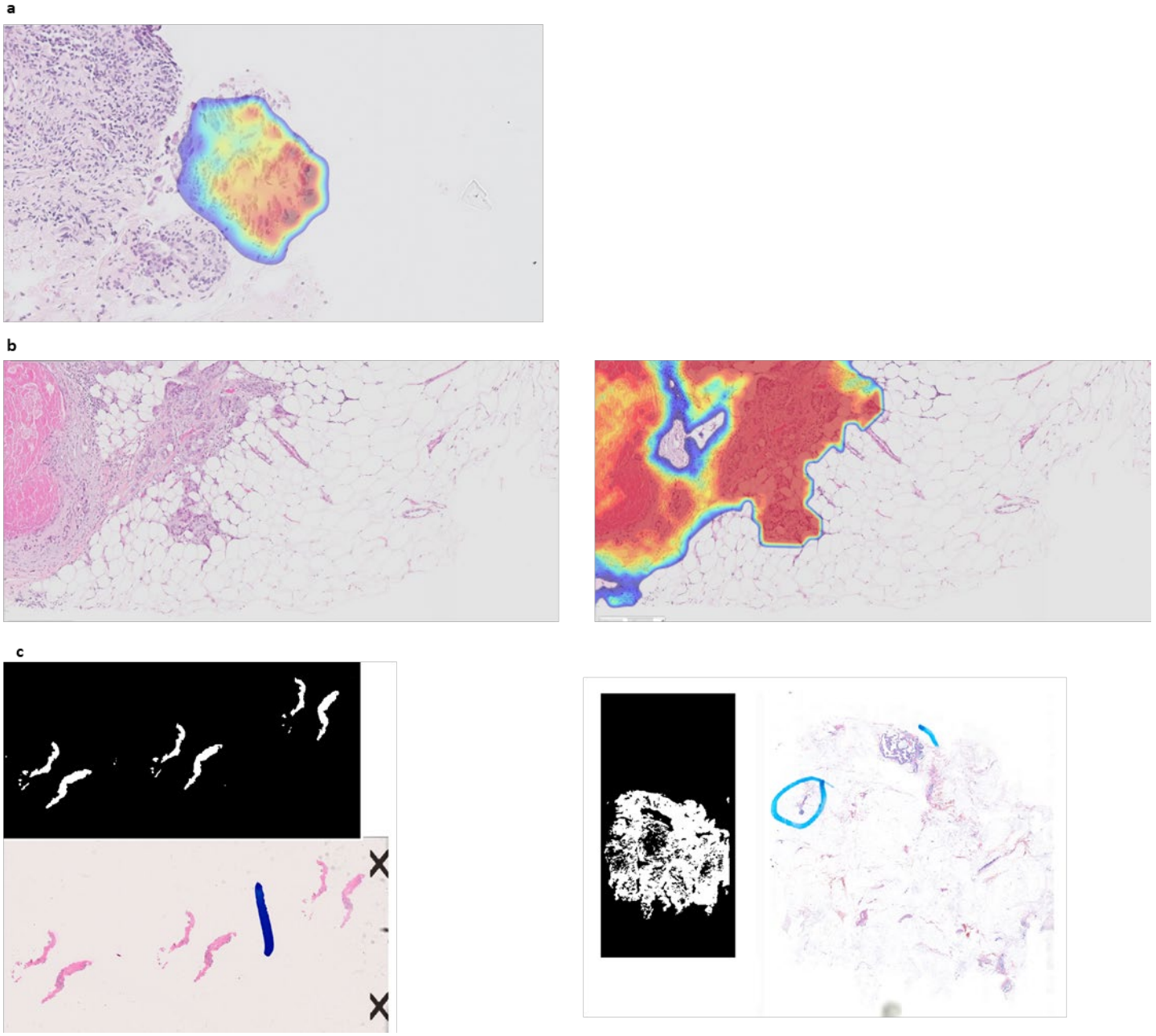
Diagnosis	**Sub-type**	**Total Cases (Training set)**
Benign/Other		935
Invasive	IDC	391
	ILC	109
	IDC+ILC	35
	Invasive Other	42
DCIS/ADH	DCIS	266
	ADH	214
Total		**1992**

DCIS – ductal carcinoma in-situ; ADH – atypical ductal hyperplasia; IDC - includes invasive ductal carcinoma (IC-NST and rare subtypes); ILC – infiltrating/invasive lobular carcinoma.

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Pathology workflow with the integrated AI-based Second Read solution.

a. The AI algorithm analyzed WSIs that had been diagnosed by pathologists in their routine workflow. The system raised alerts for cases with a potential discrepancy between the pathologist's diagnosis and the algorithmic results on the existence of invasive or in-situ breast cancer. Pathologists used the system's web-based user interface to review the cases; **b.** Example of a case list with pink-labeled alerts; **c.** Example of a resolved alert after the pathologist performed a second review, specifically focused on the region that triggered the alert, as highlighted by heatmap in the slide viewer.



Supplementary Figure 2 Examples of algorithm detection for problematic areas.

a. An image of a macrocalcification area correctly identified on the edge of a biopsy; **b.** An image of an invasive tumor area correctly detected inside a region of fat tissue (H&E --left, with invasive cancer heatmap -right, x8 magnification); **c.** Images of slides containing artifacts such as pen and bubbles and the respective tissue detection mask that indicates that these artifacts were correctly ignored by the algorithm.