Supplementary Appendix materials for

Breast cancer detection accuracy of AI in an entire screening population: a retrospective, multicentre study

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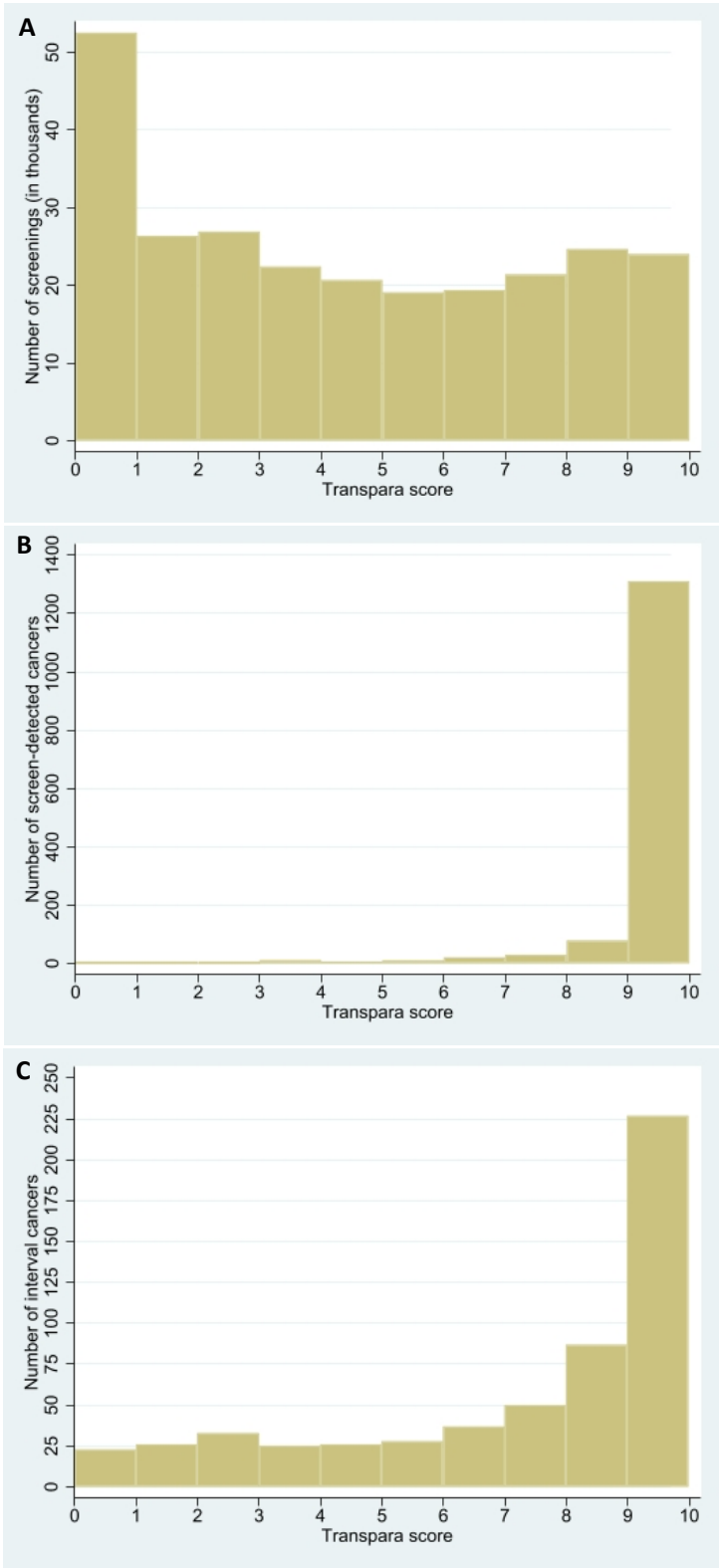
Supplementary eFigure 1: Distribution of Transpara exam scores across the study sample



(A) The Transpara exam score distributed across (A) all screening mammograms, (B) screen-detected cancers, and (C) interval cancers in the study sample. The Transpara exam score was precalibrated in such a way that the number of screening mammograms in each category should be almost equal, i.e., 10% of the mammograms would fall into each category of scores. When matching the AI score thresholds in the study to the mean sensitivity and mean specificity of the first reader, AI_{sens} and AI_{spec} used a Transpara exam score of 9.56858 and 9.70159, respectively.

Supplementary eTable 1: Detection accuracy analysis across radiologist position

	Sensitivity (95% CI); p value*	Specificity (95% CI); p value*	PPV (95% CI); p value†	NPV (95% CI); p value†	Recall rate (95% CI); p value†
First reader	63.7 (61.6-65.8); ref.	97.8 (97.7-97.8); ref.	18.7 (17.8-19.6); ref.	99.7 (99.7-99.7); ref.	2.7 (2.6-2.8); ref.
Second reader	68.3 (66.2-70.3); <0.0001	98.0 (98.0-98.1); <0.0001	21.7 (20.7-22.7); <0.0001	99.7 (99.7-99.8); 0.004	2.5 (2.4-2.6); <0.0001
Arbitrator	90.8 (87.5-93.5); <0.0001	53.0 (51.8-54.1); <0.0001	9.7 (8.7-10.7); <0.0001	99.0 (98.7-99.7); <0.0001	49.3 (48.2-50.5); <0.0001
Combined reading	73.9 (72.0-75.8); <0.0001	97.9 (97.9-98.0); <0.0001	22.0 (21.0-23.0); <0.0001	99.8 (99.8-99.8); <0.0001	2.7 (2.6-2.7); 0.18

Data are % (95% CI); p value. PPV=positive predictive value. NPV=negative predictive value. *p values were calculated using McNemar's test. †p values were calculated using exact binomial test.

Supplementary eTable 2: Detection agreements and discrepancies across cancer subgroups in the Standalone AI scenario

	Detected by both First reader and		Detected by First reader, missed by		Missed by First reader, detected by		Missed by both First reader and	
	Standalone AI_{sens}	Standalone AI_{spec}	Standalone AI_{sens}	Standalone AI_{spec}	Standalone AI_{sens}	Standalone AI_{spec}	Standalone AI_{sens}	Standalone AI_{spec}
All cancers (n=2041)	1043 (51.1)	981 (48.1)	258 (12.6)	320 (15.7)	258 (12.6)	216 (10.6)	482 (23.6)	254 (25.7)
Screen-detected cancers (n=1479)	1018 (68.8)	961 (65.0)	244 (16.5)	301 (20.4)	144 (9.7)	127 (8.6)	73 (4.9)	90 (6.1)
Interval cancers (n=562)	25 (4.4)	20 (3.6)	14 (2.5)	19 (3.4)	114 (20.3)	89 (15.8)	409 (72.8)	434 (77.2)
<12 months after screening (n=170)	7 (4.1)	6 (3.5)	6 (3.5)	7 (4.1)	36 (21.2)	30 (17.6)	121 (71.2)	127 (74.7)
≥12 months after screening (n=392)	18 (4.6)	14 (3.6)	8 (2.0)	12 (3.1)	78 (19.9)	59 (15.1)	288 (73.5)	307 (78.3)
Histological subtype								
Invasive ductal (n=1393)	733 (52.6)	689 (49.5)	172 (12.3)	216 (15.5)	174 (12.5)	144 (10.3)	314 (22.5)	344 (24.7)
Invasive lobular (n=222)	93 (41.9)	87 (39.2)	24 (10.8)	30 (13.5)	35 (15.8)	27 (12.2)	70 (31.5)	78 (35.1)
Other invasive (n=215)	65 (30.2)	60 (27.9)	38 (17.7)	43 (20.0)	22 (10.2)	19 (8.8)	90 (41.9)	93 (43.3)
Ductal carcinoma in situ (n=211)	152 (72.0)	145 (68.7)	24 (11.4)	31 (14.7)	27 (12.8)	26 (12.3)	8 (3.8)	9 (4.3)
Tumour size*								
0-10 mm (n=577)	302 (52.3)	277 (48.0)	97 (16.8)	122 (21.1)	77 (13.3)	65 (11.3)	101 (17.5)	113 (19.6)
11-20 mm (n=790)	431 (54.6)	409 (51.8)	90 (11.4)	112 (14.2)	82 (10.4)	66 (8.4)	187 (23.7)	203 (25.7)
21-50 mm (n=380)	136 (35.8)	129 (33.9)	38 (10.0)	45 (11.8)	58 (15.3)	48 (12.6)	148 (38.9)	158 (41.6)
51+ mm (n=49)	15 (30.6)	15 (30.6)	2 (4.1)	2 (4.1)	11 (22.4)	8 (16.3)	21 (42.9)	24 (49.0)
Unknown (n=34)	7 (20.6)	6 (17.6)	7 (20.6)	8 (23.5)	3 (8.8)	3 (8.8)	17 (50.0)	17 (50.0)
Malignancy grade*								
Grade 1 (n=507)	283 (55.8)	263 (51.9)	48 (9.5)	68 (13.4)	76 (15.0)	61 (12.0)	100 (19.7)	115 (22.7)
Grade 2 (n=815)	417 (51.2)	395 (48.5)	103 (12.6)	125 (15.3)	109 (13.4)	92 (11.3)	186 (22.8)	203 (24.9)
Grade 3 (n=358)	141 (39.4)	131 (36.6)	52 (14.5)	62 (17.3)	33 (9.2)	26 (7.3)	132 (36.9)	139 (38.8)
Unknown (n=150)	50 (33.3)	47 (31.3)	31 (20.7)	34 (22.7)	13 (8.7)	11 (7.3)	56 (37.3)	58 (38.7)
TNM stage*								
Local (I + II) (n=1761)	876 (49.7)	822 (46.7)	229 (13.0)	283 (16.1)	224 (12.7)	184 (10.4)	432 (24.5)	472 (26.8)
Locally advanced (III) (n=44)	10 (22.7)	10 (22.7)	5 (11.4)	5 (11.4)	4 (9.1)	3 (6.8)	25 (56.8)	26 (59.1)
Distant metastasis (IV) (n=20)	4 (20.0)	3 (15.0)	0 (0.0)	1 (5.0)	3 (15.0)	3 (15.0)	13 (65.0)	13 (65.0)
Unknown (n=5)	1 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)	4 (80.0)
Lymph node positivity*								
No (n=1340)	665 (49.6)	624 (46.6)	175 (13.1)	216 (16.1)	161 (12.0)	135 (10.1)	339 (25.3)	365 (27.2)
Yes (n=490)	226 (46.1)	212 (43.3)	59 (12.0)	73 (14.9)	70 (14.3)	55 (11.2)	135 (27.6)	150 (30.6)
ER positivity*								
0% (n=207)	62 (30.0)	57 (27.5)	34 (16.4)	39 (18.8)	13 (6.3)	10 (4.8)	98 (47.3)	101 (48.8)
1-9% (n=98)	26 (26.5)	22 (22.4)	20 (20.4)	24 (24.5)	12 (12.2)	11 (11.2)	40 (40.8)	41 (41.8)
10-100% (n=1514)	799 (52.8)	753 (49.7)	178 (11.8)	224 (14.8)	204 (13.5)	167 (11.0)	333 (22.0)	370 (24.4)
Unknown (n=11)	4 (36.4)	4 (35.4)	2 (18.2)	2 (18.2)	2 (18.2)	2 (18.2)	3 (27.3)	3 (27.3)
HER2 status*								
Negative (n=1581)	782 (49.5)	733 (46.4)	210 (13.3)	259 (16.4)	204 (12.9)	169 (10.7)	385 (24.4)	420 (26.6)
Positive (n=225)	103 (45.8)	97 (43.1)	20 (8.9)	26 (11.6)	25 (11.1)	19 (8.4)	77 (34.2)	83 (36.9)
Unknown (n=24)	6 (25.0)	5 (25.0)	4 (16.7)	4 (16.7)	2 (8.3)	2 (8.3)	12 (50.0)	12 (50.0)

Data are n (%). The cancer detection rate is reported as the number of detected cancers out of the number of true cancers for the subgroup in the same row.TNM=tumour, node, metastasis. ER=estrogen receptor. HER2=human epidermal growth factor receptor 2. AI_{sens}=artificial intelligence score cut-off point matched at mean first reader sensitivity. AI_{spec}=artificial intelligence score cut-off point matched at mean first reader specificity. *Reported for invasive cancers only.

Supplementary eTable 3: Detection agreements and discrepancies across cancer subgroups in the AI-integrated screening scenario

	Detected by both Combined reading and		Detected by Combined reading, missed by		Missed by Combined reading, detected by		Missed by both Combined reading and	
	Integrated AI_{sens}	Integrated AI_{spec}	Integrated AI_{sens}	Integrated AI_{spec}	Integrated AI_{sens}	Integrated AI_{spec}	Integrated AI_{sens}	Integrated AI_{spec}
All cancers (n=2041)	1450 (71.0)	1439 (70.5)	59 (2.9)	70 (3.4)	105 (5.1)	83 (4.1)	427 (20.9)	449 (22.0)
Screen-detected cancers (n=1479)	1425 (96.3)	1413 (95.5)	54 (3.7)	66 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interval cancers (n=562)	27 (4.8)	27 (4.8)	3 (0.5)	3 (0.5)	103 (18.3)	82 (14.6)	429 (76.3)	450 (80.1)
<12 months after screening (n=170)	13 (7.6)	13 (7.6)	1 (0.6)	1 (0.6)	34 (20.0)	28 (16.5)	122 (71.8)	128 (75.3)
≥12 months after screening (n=392)	14 (3.6)	14 (3.6)	2 (0.5)	2 (0.5)	69 (17.6)	54 (13.8)	307 (78.3)	322 (82.1)
Histological subtype								
Invasive ductal (n=1393)	996 (71.5)	990 (71.1)	38 (2.7)	44 (3.2)	76 (5.5)	63 (4.5)	283 (20.3)	296 (21.2)
Invasive lobular (n=222)	137 (61.7)	134 (60.4)	6 (2.7)	9 (4.1)	17 (7.7)	11 (5.0)	62 (27.9)	68 (30.6)
Other invasive (n=215)	110 (51.2)	113 (52.6)	11 (5.1)	8 (3.7)	12 (5.6)	9 (4.2)	82 (38.1)	85 (39.5)
Ductal carcinoma in situ (n=211)	207 (98.1)	202 (95.7)	4 (1.9)	9 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumour size*								
0-10 mm (n=577)	468 (81.1)	469 (81.3)	28 (4.9)	27 (4.7)	16 (2.8)	13 (2.3)	65 (11.3)	68 (11.8)
11-20 mm (n=790)	560 (70.9)	554 (70.1)	21 (2.7)	27 (3.4)	38 (4.8)	29 (3.7)	171 (21.6)	180 (22.8)
21-50 mm (n=380)	185 (48.7)	183 (48.2)	4 (1.1)	6 (1.6)	41 (10.8)	33 (8.7)	150 (39.5)	158 (41.6)
51+ mm (n=49)	17 (34.7)	17 (34.7)	1 (2.0)	1 (2.0)	7 (14.3)	5 (10.2)	24 (49.0)	26 (53.1)
Unknown (n=34)	13 (38.2)	14 (41.2)	1 (2.9)	0 (0.0)	3 (8.8)	3 (8.8)	17 (50.0)	17 (50.0)
Malignancy grade*								
Grade 1 (n=507)	91 (60.7)	94 (62.7)	8 (5.3)	5 (3.3)	5 (3.3)	3 (2.0)	46 (30.7)	48 (32.0)
Grade 2 (n=815)	397 (78.3)	391 (77.1)	13 (2.6)	19 (3.7)	21 (4.1)	19 (3.7)	76 (15.0)	78 (15.4)
Grade 3 (n=358)	561 (68.8)	560 (68.7)	26 (3.2)	27 (3.3)	56 (6.9)	45 (5.5)	172 (21.1)	183 (22.5)
Unknown (n=150)	194 (54.2)	192 (53.6)	8 (2.2)	10 (2.8)	23 (6.4)	16 (4.5)	133 (37.2)	140 (39.1)
TNM stage*								
Local (I + II) (n=1761)	1226 (69.6)	1219 (69.2)	54 (3.1)	61 (3.5)	98 (5.6)	77 (4.4)	383 (21.7)	404 (22.9)
Locally advanced (III) (n=44)	12 (27.3)	13 (29.5)	1 (2.3)	0 (0.0)	4 (9.1)	3 (6.8)	27 (61.4)	28 (63.6)
Distant metastasis (IV) (n=20)	4 (20.0)	4 (20.0)	0 (0.0)	0 (0.0)	3 (15.0)	3 (15.0)	13 (65.0)	13 (65.0)
Unknown (n=5)	1 (20.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (80.0)	4 (80.0)
Lymph node positivity*								
No (n=1340)	942 (70.3)	941 (70.2)	42 (3.1)	43 (3.2)	63 (4.7)	51 (3.8)	293 (21.9)	305 (22.8)
Yes (n=490)	301 (61.4)	296 (60.4)	13 (2.7)	18 (3.7)	42 (8.6)	32 (6.5)	134 (27.3)	144 (29.4)
ER positivity*								
0% (n=207)	91 (44.0)	94 (45.4)	11 (5.3)	8 (3.9)	9 (4.3)	7 (3.4)	96 (46.4)	98 (47.3)
1-9% (n=98)	48 (49.0)	45 (45.9)	1 (1.0)	4 (4.1)	9 (9.2)	6 (6.1)	40 (40.8)	43 (43.9)
10-100% (n=1514)	1097 (72.5)	1091 (72.1)	43 (2.8)	49 (3.2)	86 (5.7)	69 (4.6)	288 (19.0)	305 (20.1)
Unknown (n=11)	7 (63.6)	7 (63.6)	0 (0.0)	0 (0.0)	1 (9.1)	1 (9.1)	3 (27.3)	3 (27.3)
HER2 status*								
Negative (n=1581)	1105 (69.9)	1097 (69.4)	46 (2.9)	54 (3.4)	89 (5.6)	71 (4.5)	341 (21.6)	359 (22.7)
Positive (n=225)	127 (56.4)	129 (57.3)	8 (3.6)	6 (2.7)	15 (6.7)	11 (4.9)	75 (33.3)	79 (35.1)
Unknown (n=24)	11 (45.8)	11 (45.8)	1 (4.2)	1 (4.2)	1 (4.2)	1 (4.2)	11 (45.8)	11 (45.8)

Data are n (%). The cancer detection rate is reported as the number of detected cancers out of the number of true cancers for the subgroup in the same row.TNM=tumour, node, metastasis. ER=estrogen receptor. HER2=human epidermal growth factor receptor 2. AI_{sens}=artificial intelligence score cut-off point matched at mean first reader sensitivity. AI_{spec}=artificial intelligence score cut-off point matched at mean first reader specificity. *Reported for invasive cancers only.

Supplementary eTable 4: Comparison of screening outcome and results of the reference standard in both study scenarios with descriptive workload analysis.

	Standalone AI			AI-integrated screening		
	First reader	**Standalone AI_{sens}**	**Standalone AI_{spec}**	**Combined reading**	**Integrated AI_{sens}**	**Integrated AI_{spec}**
Number of episodes						
True positive	1301 (ref.)	1301 (0.0)	1197 (-7.9)	1509 (ref.)	1555 (+3.0)	1522 (+0.9)
True negative	249959 (ref.)	246590 (-1.3)	249952 (<-0.1)	250278 (ref.)	248616 (-0.7)	250234 (<-0.1)
False positive	5671 (ref.)	9040 (+59.4)	5678 (+0.1)	5352 (ref.)	7014 (+31.1)	5396 (+0.8)
False negative	740 (ref.)	740 (0.0)	844 (+14.1)	532 (ref.)	486 (-8.6)	519 (-2.4)
Workload						
Recalls	6972 (ref.)	10341 (+48.3)	6875 (-1.4)	6861 (ref.)	8569 (+24.9)	6918 (+0.8)
Human readings	257671 (ref.)	0 (-100)	0 (-100)	522105 (ref.)	270936 (-48.1)	267946 (-48.7)
Arbitrations	NA	NA	NA	7434 (ref.)	13265 (+74.4)	10275 (+38.2)

Data are n (Δ%). AI_{sens}=artificial intelligence score cut-off point matched at mean first reader sensitivity. AI_{spec}=artificial intelligence score cut-off point matched at mean first reader specificity.

Supplementary eTable 5: Detection accuracy analysis with inclusion of next-round screen-detected cancers and long-term cancers in both study scenarios

	Sensitivity (95% CI); p value*	Specificity (95% CI); p value*	PPV (95% CI); p value†	NPV (95% CI); p value†
Standalone AI				
First reader	30.5 (29.2-31.8); ref.	97.8 (97.7-97.9); ref.	20.2 (19.3-21.2); ref.	98.7 (98.7-98.8); ref.
Standalone AI_{sens}	37.7 (36.2-39.2); <0.0001	96.6 (96.5-96.7); <0.0001	16.9 (16.1-17.7); <0.0001	98.8 (98.8-98.9); <0.0001
Standalone AI_{spec}	33.3 (31.8-34.7); <0.0001	97.9 (97.8-98.0); 0.03	22.4 (21.3-23.4); <0.0001	98.8 (98.7-98.8); 0.02
AI-integrated screening				
Combined reading	34.5 (33.2-35.8); ref.	97.9 (97.9-98.0); ref.	23.2 (22.2-24.3); ref.	98.8 (98.7-98.8); ref.
Integrated AI_{sens}	39.1 (37.7-40.6); <0.0001	97.3 (97.3-97.4); <0.0001	21.1 (20.2-22.0); <0.0001	98.9 (98.8-98.9); 0.0004
Integrated AI_{spec}	37.3 (35.9-38.7); <0.0001	97.9 (97.9-98.0); 0.28	24.9 (23.9-26.0); 0.001	98.8 (98.8-98.9); 0.02

Data are % (95% CI); p value. Next-round screen-detected cancers (n=1232) and long-term cancers (n=2372) include ductal carcinoma in situ. Linear regression with the measure of performance was used to take the correlation between women and possible multiple cancers into account. PPV=positive predictive value. NPV=negative predictive value. AI_{sens}=artificial intelligence score cut-off point matched at mean first reader sensitivity from the primary analysis presented in study table 2. AI_{spec}=artificial intelligence score cut-off point matched at mean first reader specificity from the primary analysis presented in study table 2. *p values were calculated using McNemar's test. †p values were calculated using exact binomial test.