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Nationwide real-world implementation of AI for cancer detection in population-based mammography screening

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Artificial intelligence (AI) in mammography screening has shown promise in retrospective evaluations, but few prospective studies exist. PRAIM is an observational, multicenter, real-world, noninferiority, implementation study comparing the performance of AI-supported double reading to standard double reading (without AI) among women (50–69 years old) undergoing organized mammography screening at 12 sites in Germany. Radiologists in this study voluntarily chose whether to use the AI system. From July 2021 to February 2023, a total of 463,094 women were screened (260,739 with AI support) by 119 radiologists. Radiologists in the AI-supported screening group achieved a breast cancer detection rate of 6.7 per 1,000, which was 17.6% (95% confidence interval: +5.7%, +30.8%) higher than and statistically superior to the rate (5.7 per 1,000) achieved in the control group. The recall rate in the AI group was 37.4 per 1,000, which was lower than and noninferior to that (38.3 per 1,000) in the control group (percentage difference: −2.5% (−6.5%, +1.7%)). The positive predictive value (PPV) of recall was 17.9% in the AI group compared to 14.9% in the control group. The PPV of biopsy was 64.5% in the AI group versus 59.2% in the control group. Compared to standard double reading, AI-supported double reading was associated with a higher breast cancer detection rate without negatively affecting the recall rate, strongly indicating that AI can improve mammography screening metrics.

Mammography screening programs contribute to reducing mortality associated with breast cancer[1,2]. However, there is still room for improvement in breast cancer screening. On the one hand, the sensitivity of screening could be improved to lead to lower interval cancer rates and more effective treatment of patients with breast cancer. On the other hand, the specificity of screening could be increased to reduce the recall rate by minimizing false-positive results, which can cause anxiety and uncertainty among the screened women. Thus, a higher specificity would lessen the burden on the screening participants and the healthcare system by minimizing unnecessary, invasive and costly medical procedures.

Furthermore, the programs generate substantial volumes of mammograms, which, in many programs (including the German mammography screening program), require interpretation by two independent radiologists; a consensus conference or arbitration may also be necessary to achieve high sensitivity and specificity[3,4]. Thus, the radiologists'

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work involves the repetitive task of interpreting hundreds of images per week, most of which have no signs of breast cancer. This approach heavily relies on human expertise, yet screening programs are experiencing a lack of radiologists[5]. With national and international guidelines recently recommending mammography screening also for the age groups 40/45–49 and 70–74 years, the workload is expected to increase[6–8].

Integrating artificial intelligence (AI) into breast cancer screening workflows could alleviate some of the problems that screening programs face. Retrospective studies have shown that AI has comparable and sometimes superior accuracy to radiologists, suggesting that the technology can support radiologists in interpreting mammograms by improving the identification of subtle abnormalities that might otherwise elude human readers and by reducing the reading workload[9–11]. Growing evidence indicates that AI detects 20–40% of interval cancers that can retrospectively be seen or suspected on prior screening mammograms but were missed by radiologists[12–14]. Using retrospective data in studies evaluating the impact of AI on screening metrics is limited by the uncertainty of outcomes in women whose mammography findings were flagged as suspicious by AI only and were, therefore, not referred for consensus conferences or further assessments. A growing body of prospective evidence demonstrates the potential of AI to improve screening metrics and additionally reduce reading workload. The MASAI (MAmmography Screening with AI) trial[15], the ScreenTrustCAD study[16] and a study by Ng et al.[17] all reported increased cancer detection for workflows incorporating AI, but the results on recall rates were inconsistent. However, these studies are limited by small sample sizes (which restrict the analysis of subgroups) and by the lack of heterogeneity in terms of screening sites, mammography equipment vendors and the radiologists involved, thereby reducing their generalizability to real-world settings.

In a retrospective analysis, Leibig et al.[18] demonstrated that the use of AI in a decision referral approach, in which AI confidently predicts normal or highly suspicious examination results and refers uncertain results to the radiologists' expertise, yielded superior metrics than AI or radiologists alone. In the PRAIM (PRospective multicenter observational study of an integrated AI system with live Monitoring) implementation study embedded in the German mammography screening program, we investigated whether the performance metrics achieved by double reading using an AI-supported CE (Conformité Européenne)-certified medical device with a decision referral approach were noninferior to those achieved by double reading without AI support in a real-world setting. Here, we report the impact of AI on cancer detection and recall rates.

Results

The study was conducted within Germany's organized breast cancer screening program targeting asymptomatic women aged 50–69 years (Fig. 1). All women participating in the screening program were eligible for study inclusion. Between July 1, 2021, and February 23, 2023, data from screening participants were collected from 12 screening sites that used the AI system (Extended Data Table 1). In the German mammography screening program, which is based on a binding national guideline, four two-dimensional mammograms (craniocaudal and mediolateral oblique views of each breast) are taken for each participating woman. These mammograms are initially read independently by two radiologists (sometimes, a third radiologist supervises). If at least one radiologist deems the case suspicious, a consensus conference is held. The participants of the consensus conference are at least the two initial readers and one head radiologist, but more radiologists of the screening site can participate. If the suspicious finding persists in the consensus conference, the woman is recalled for further diagnostic assessments, which can include, among others, ultrasonography, digital breast tomosynthesis, magnification views, contrast-enhanced mammography or magnetic resonance imaging.

For the study, examinations were assigned to the AI group when at least one of the two radiologists read and submitted the report with the AI-supported viewer. All examinations for which neither radiologist submitted the report using the AI-supported viewer formed the control group. The study group assignment was unknown to the women and radiographers as it was not yet assigned at the time of image acquisition. After image acquisition, AI predictions were computed for all women but were displayed only to radiologists using the AI-supported viewer. The radiologists performing the first and second reads were free to use either their existing reporting and viewer software without AI support or the AI-supported viewer. The decision to use the AI-supported viewer was made on a per-examination basis (that is, one radiologist typically delivered examinations for both the AI and control groups). Radiologists in a reader set independently chose whether to use the AI-supported viewer. The AI results were not disclosed to the other radiologist if they did not also choose to use the AI viewer.

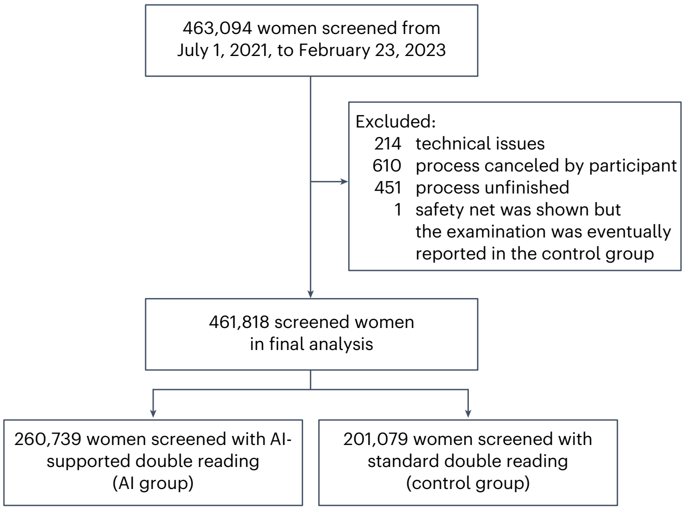
463,094 women screened from
July 1, 2021, to February 23, 2023
Excluded:
214 technical issues
610 process canceled by participant
451 process unfinished
1 safety net was shown but the examination was eventually reported in the control group
461,818 screened women in final analysis
260,739 women screened with AI-supported double reading (AI group)
201,079 women screened with standard double reading (control group)

Fig. 1 | Study profile. The flowchart shows the inclusion of study participants and their assignment into groups.

The AI system used was Vara MG (from the German company Vara), a CE-certified medical device designed to display mammograms (viewer software) and preclassify screening examinations to assist radiologists in their reporting routine. The performance of previous versions of the AI software has been previously reported[12,18]. When using the AI-supported viewer, radiologists were supported by two AI-based features (Extended Data Fig. 1):

1. Normal triaging. The software selects a subset of all examinations deemed highly unsuspicious by the AI model. These examinations are tagged 'normal' in the worklist.
2. Safety net. The software selects a subset of all examinations deemed highly suspicious by the AI model. Radiologists first read the screening examination without any further AI support. When the radiologists interpret an examination as unsuspicious, the safety net is activated with an alert and a suggested localization of the suspicious region(s) in the images. The radiologists are then prompted to review their decision and either accept or reject the safety net's suggestion.

Characteristics of the study population

Overall, 461,818 women who attended mammography screening at the 12 screening sites participated in the study. A total of 119 radiologists constituting 547 reader sets interpreted the examinations. Mammography hardware systems from five different vendors were used (Extended Data Table 2). Of all the participating women, 260,739 were screened in the AI group (with the AI-supported viewer being used by only one reader for 152,970 women and by both readers for 107,769 women) and 201,079 were screened in the control group. Table 1 presents the characteristics of the screened women and the detected breast cancers

Table 1 | Characteristics of the study population overall and by study group

Characteristics	AI group (*n*=260,739)	Control group (*n*=201,079)	Overall (*n*=461,818)
Age (years)			
Median (IQR)	58 (54–63)	58 (54–63)	58 (54–63)
Missing, *n* (%)	2 (<0.1%)	0 (0%)	2 (<0.1%)
50–59 years, *n* (%)	114,365 (43.9%)	87,781 (43.7%)	202,146 (43.8%)
Breast density, *n* (%)			
Nondense	165,332 (63.4%)	137,889 (68.6%)	303,221 (65.7%)
Dense	94,955 (36.4%)	63,125 (31.4%)	158,080 (34.2%)
Missing	452 (0.2%)	65 (<0.1%)	517 (0.1%)
Screening round, *n* (%)			
First	43,449 (16.7%)	35,680 (17.7%)	79,129 (17.1%)
Follow-up	217,290 (83.3%)	165,399 (82.3%)	382,689 (82.9%)
Screening sites			
Number of sites	11	12	12
Screened women per unit, median (IQR)	18,503 (15,703–29,466)	13,341 (4,860–21,980)	40,101 (27,060–47,858)
Radiologists			
Number	110	117	119
Number of reader sets	387	485	547
Screened women per reader set, mean (s.d.)	477 (1,069)	368 (637)	844 (1,326)
Minimum/maximum	0/8,664	0/5,940	1/8,939
Consensus conference			
Consensus conferences, *n* (%)	32,341 (12.4%)	21,996 (10.9%)	54,337 (11.8%)
Recall			
Recalls, *n* (per 1,000)	11,603 (44.5)	7,727 (38.4)	19,330 (41.9)
PPV of recall (%)	14.5	15.6	14.9
Preoperative biopsy			
Biopsy recommended, *n* (per 1,000)	2,843 (10.9)	1,981 (9.9)	4,824 (10.4)
PPV of biopsy (%)	59.0	60.5	59.6
Detected breast cancers			
Breast cancers, *n* (per 1,000)	1,679 (6.4)	1,202 (6.0)	2,881 (6.2)
Invasiveness, *n* (% of cancer detected)			
DCIS	341 (20.3%)	203 (16.9%)	544 (18.9%)
Invasive	1,308 (77.9%)	981 (81.6%)	2,289 (79.4%)
Other	30 (1.8%)	18 (1.5%)	48 (1.7%)
Breast cancer stage (UICC), *n* (% of cancer detected)			
0	341 (20.3%)	203 (16.9%)	544 (18.9%)
1	881 (52.5%)	588 (48.9%)	1,469 (51.0%)
2	327 (19.5%)	281 (23.4%)	608 (21.1%)
3	30 (1.8%)	24 (2.0%)	54 (1.9%)
4	2 (0.1%)	0 (0.0%)	2 (0.1%)
X	53 (3.2%)	34 (2.8%)	87 (3.0%)
Missing	45 (2.7%)	72 (6.0%)	117 (4.1%)
Invasive cancer grade, *n* (% of invasive cancer)			
G1	288 (22.0%)	230 (23.4%)	518 (22.6%)
G2	771 (58.9%)	551 (56.2%)	1,322 (57.7%)
G3	135 (10.3%)	155 (15.8%)	290 (12.7%)
X	48 (3.7%)	27 (2.8%)	75 (3.3%)
Missing	66 (5.1%)	18 (1.8%)	84 (3.7%)

Table 1 (continued) | Characteristics of the study population overall and by study group

Characteristics	AI group (*n*=260,739)	Control group (*n*=201,079)	Overall (*n*=461,818)
Invasive cancer size, *n* (% of invasive cancer)			
≤10 mm	475 (36.3%)	350 (35.7%)	825 (36.0%)
10–20 mm	572 (43.7%)	418 (42.6%)	990 (43.3%)
>20 mm	253 (19.4%)	210 (21.4%)	463 (20.2%)
Missing	8 (0.6%)	3 (0.3%)	11 (0.5%)

'Missing' means that the corresponding data entry is empty in the official screening documentation. 'X' indicates that physicians tried to determine a value but failed to do so. 'Other' invasiveness means that it was unclear whether the cancer was DCIS or invasive and other malignant neoplasms. IQR, interquartile range; UICC, Union for International Cancer Control.

by study group. Of the screened women, 41.9 per 1,000 had suspicious findings and were recalled for further assessment. A quarter of them (10.4 per 1,000) underwent biopsy procedures, and 6.2 per 1,000 were finally diagnosed with breast cancer. Most (79.4%) of the cancers were classified as invasive, and 18.9% were ductal carcinoma in situ (DCIS).

AI normal triaging, safety net trigger and acceptance rates

AI tagged 56.7% (262,055 of 461,818) of the examinations as normal. This proportion was higher in the AI group (59.4%) than in the control group (53.3%; Table 2) due to an observed reading behavior bias. In the AI group (*n* = 260,739), the safety net was triggered for 3,959 (1.5%) examinations, shown in 2,233 (0.9%) examinations and accepted in 1,077 (0.4%) examinations, leading to 541 (0.2%) recalls and 204 (0.08%) breast cancer diagnoses. Conversely, 8,032 (3.1%) examinations in the AI group underwent further evaluation by the consensus group despite being tagged as normal by AI, resulting in 1,905 (0.7%) recalls, 82 (0.03%) biopsies and 20 (0.008%) subsequent breast cancer diagnoses.

Table 2 | AI predictions and contributions to the radiologists' decisions

Conditions	AI group (*n*=260,739)	Control group (*n*=201,079)	Overall (*n*=461,818)
AI prediction			
Normal	154,891 (59.4%)	107,164 (53.3%)	262,055 (56.7%)
Not normal	105,848 (40.6%)	93,915 (46.7%)	199,763 (43.3%)
AI prediction normal and…[a]			
… consensus conference	8,032 (3.1%)	5,454 (2.7%)	13,486 (2.9%)
… recall	1,905 (0.7%)	1,162 (0.6%)	3,067 (0.7%)
… preoperative biopsy	82 (0.03%)	86 (0.04%)	168 (0.04%)
… confirmed cancer	20 (0.008%)	25 (0.012%)	45 (0.010%)
Safety net			
Triggered	3,959 (1.5%)	3,140 (1.6%)	7,099 (1.5%)
Shown	2,233 (0.9%)	NA	NA
Accepted	1,077 (0.4%)	NA	NA
Accepted and had a recall	541 (0.2%)	NA	NA
Accepted and confirmed cancer	204 (0.1%)	NA	NA

NA, not applicable. [a]The percentages relate the absolute numbers to the total number in the study group (or in the whole study sample for 'overall'), not the subgroup of mammograms tagged 'normal'.

Recall, cancer detection rate and positive predictive values

We controlled for the identified confounders (reader set and AI prediction; causal graph presented in Extended Data Fig. 2) through overlap weighting based on propensity scores (Extended Data Fig. 3). The model-based breast cancer detection rate (BCDR) per 1,000 women screened was 6.70 for the AI group and 5.70 for the control group. This represents a model-based absolute difference of one additional cancer per 1,000 screened women and a relative increase of 17.6% (95% confidence interval (CI): +5.7%, +30.8%). The BCDR in the AI group was considered noninferior and even statistically superior to that in the control group. The AI group had a lower model-based recall rate (37.4 per 1,000) than the control group (38.3 per 1,000), showing a −2.5% reduction (−6.5%, +1.7%) (Table 3). The positive predictive value (PPV) of recall was 17.9% in the AI group and 14.9% in the control group. The biopsy rate in the AI group was 8.2% higher (−0.4%, +17.6%) than in the control group. Despite this, the AI group demonstrated a statistically significantly higher PPV of biopsy (+9.0% (+2.0%, +16.4%)).

Subgroup analyses

Subgroup analyses showed that the BCDR increased in all subgroups by screening round, breast density and age, ranging between +12% and +23% (Table 4). The 95% CIs were completely positive for the subgroups of follow-up screening round, nondense breasts and age 60–69 years.

The relative differences in recall rates in the subgroups varied between −5% (age 50–59 years) and +4% (age 60–69 years), but all CIs except for women aged 50–59 years contained zero.

Sensitivity analyses

We conducted various sensitivity analyses, all of which showed that our analyses were robust to different analytical decisions.

In a model that, in addition to AI prediction and reader set, further adjusted for age, screening round, breast density and supervision in the propensity score model, the BCDR remained unchanged at 17.6% (5.7%, 30.8%). Similarly, in the additionally adjusted model, the PPV of recall and biopsy was 18.3% (−7.3%, 30.5%) and 9.3% (0.5%, 18.8%) higher, respectively, for the AI group than the control group (Extended Data Table 3). The results of the subgroup analyses by age group, screening round and breast density did not change meaningfully following additional adjustments.

Sensitivity analyses in which we adjusted for each reader individually instead of the reader set also provided data similar to the main results: in the AI group, the BCDR was 19.0% (7.4%, 31.8%) higher and the recall rate was −1.5% (−5.4%, 2.6%) lower, indicating that the results were robust to the different parameterization of the reader set variable.

The results were robust toward sampling error, as they remained nearly unchanged when the study sample was varied (bootstrapping and 80% random subset selection, each done 1,000 times): the mean BCDR was 17.6% (5.7%, 30.8%) for bootstrapping and 17.4% (11.4%, 23.8%) for the subset selection.

A propensity score-based alternative to overlap weighting is inverse propensity score weighting with trimming. After applying various trimming thresholds (Extended Data Table 4), the results remained similar.

Table 3 | Model-predicted BCDRs, recall rates, biopsy rates and consensus rates and corresponding differences in the AI and control groups

Variables	Model-based prediction		Model-based difference (95% CI)	
	AI group	Control group	Absolute difference	Percentage difference
BCDR (per 1,000 women screened)	6.7	5.7	1.0 (0.3, 1.7)	17.6% (5.7%, 30.8%)
By invasiveness				
Invasive	5.2	4.8	0.4 (−0.2, 1.0)	7.8% (−4.3%, 21.3%)
DCIS	1.4	0.8	0.6 (0.3, 0.8)	67.6% (29.6%, 116.8%)
Other	0.1	0.04	0.1 (−0.0005, 0.1)	189.6% (−6.6%, 797.7%)
By stage (UICC)				
0	1.4	0.8	0.6 (0.3, 0.8)	67.6% (29.6%, 116.8%)
1	3.3	2.8	0.4 (−0.02, 0.9)	15.4% (−0.9%, 34.4%)
2	1.4	1.5	−0.1 (−0.4, 0.2)	−7.5% (−25.7%, 15.3%)
3	0.1	0.1	−0.04 (−0.1, 0.04)	−34.4% (−71.9%, 53.0%)
4	0.02	≪0.01	0.02 (−0.01, 0.04)	NA
Missing + X	0.5	0.4	0.2 (−0.03, 0.3)	37.8% (−6.4%, 102.9%)
By grade (invasive cancers only)				
1	1.2	0.9	0.3 (0.01, 0.5)	30.0% (0.7%, 67.9%)
2	3.1	2.8	0.3 (−0.2, 0.7)	9.8% (−6.0%, 28.2%)
3	0.6	0.8	−0.2 (−0.5, −0.01)	−28.7% (−48.4%, −1.4%)
Missing + X	0.3	0.3	0.1 (−0.1, 0.2)	24.2% (−23.3%, 101.2%)
By tumor size (invasive cancers only)				
≤10 mm	1.8	1.6	−0.1 (−0.4, 0.2)	8.2% (−11.7%, 32.6%)
10–20 mm	2.4	2.0	0.3 (−0.1, 0.7)	16.1% (−3.0%, 39.1%)
>20 mm	1.1	1.2	−0.1 (−0.4, 0.2)	−9.0% (−29.2%, 17.0%)
Missing	0	0	0.02 (−0.004, 0.04)	NA
Consensus rate (per 1,000 women screened)	112.7	111.1	1.6 (−1.0, 4.2)	1.4% (−0.9%, 3.9%)
Recall rate (per 1,000 women screened)	37.4	38.3	−1.0 (−2.6, 0.6)	−2.5% (−6.5%, 1.7%)
PPV of recall	17.9%	14.9%	3.0 (1.5, 4.6) percentage points	20.5% (6.2%, 32.9%)
Biopsy rate (per 1,000 women screened)	10.4	9.6	0.8 (−0.0, 1.6)	8.2% (−0.4%, 17.6%)
PPV of biopsy	64.5%	59.2%	5.3 (1.3, 9.4) percentage points	9.0% (2.0%, 16.4%)

'Missing' means that the corresponding data entry is empty in the official screening documentation. 'X' indicates that physicians tried to determine a value but failed to do so. 'Other' invasiveness means that it was unclear whether the cancer was DCIS or invasive and other malignant neoplasms.

Another alternative to propensity score weighting as a method for confounder adjustment is stratification. Again, the results of sensitivity analyses including all confounder strata containing a certain minimum sample size (between 0 and 200) in each study group were in line with the main results.

We conducted a placebo intervention analysis to check whether the AI effect observed in the main analysis would vanish (as it should) when there is only a placebo intervention while all assumptions of the model are kept (that is, in the presence of residual confounding due to the reading behavior). As expected, the average model-based difference was minimal (0.8% (−9.9%, 11.6%)), indicating no residual confounding.

Reading times and workload reduction

The average reading time per screening examination was measured in the AI group only as it was technically not possible to measure this in the control group. On average, examinations tagged as normal were read more quickly (median reading time, 16 s) than unclassified examinations (median reading time, 30 s) and safety net examinations (median reading time, 99 s). Overall, radiologists spent 43% less time interpreting examinations tagged as normal, with a mean reading time of 39 s for normal examinations compared to 67 s for examinations not tagged as normal (Extended Data Fig. 4).

To evaluate the potential of AI integration to reduce reading workload through automation, we analyzed a fictitious scenario in which the screening examinations triaged as normal by AI were not read by radiologists. Rather, after an AI prediction of 'normal', the examination directly received the final classification 'normal', and thus, it would not be possible that any breast cancer signs missed by AI were detected by the radiologists, that a recall was made or that a cancer was detected. The analysis of this scenario showed that, when all normal-tagged examinations (56.7%) were automatically classified as normal, the BCDR was still higher and statistically superior by 16.7% (4.9%, 29.9%), the consensus rate was lower by −19.4% (−21.5%, −17.4%), the recall rate was statistically superior and lower by −15.0% (−18.6%, −11.2%), whereas the biopsy rate was higher by 5.8% (−2.7%, 15.0%) in the AI group than in the control group (Table 5).

Discussion

The PRAIM study was embedded within the German breast cancer screening program. To our knowledge, it is the largest study on the

Table 4 | Model-predicted BCDRs and recall rates and corresponding differences in the AI and control groups by screening round, breast density and age group

Variables	Model-based BCDR (per 1,000 women screened)			Model-based recall rate (per 1,000 women screened)		
	AI group	Control group	Percentage difference (95% CI)	AI group	Control group	Percentage difference (95% CI)
Screening round						
First	9.3	7.8	19.0% (−4.6%, 48.5%)	94.9	96.5	−1.7% (−7.7%, 4.6%)
Follow-up	6.2	5.2	17.9% (4.4%, 33.1%)	25.8	25.7	0.3% (−5.2%, 6.1%)
Breast density						
Nondense	6.3	5.4	16.6% (1.9%, 33.4%)	32.1	32.9	−2.7% (−7.9%, 2.9%)
Dense	7.4	6.2	18.7% (−0.5%, 41.4%)	47.1	49.0	−3.9% (−9.9%, 2.5%)
Age group						
50–59 years	5.7	5.1	12.1% (−3.6%, 30.5%)	44.3	46.7	−5.0% (−9.8%, −0.2%)
60–69 years	7.9	6.5	22.6% (5.5%, 42.4%)	28.5	27.4	4.1% (−3.6%, 11.9%)

effect of integrating AI into mammography screening on the BCDR and recall rate. This study extensively reports AI's performance in clinically relevant subgroups by screening round, breast density, age, cancer invasiveness, stage, grade and size, with important implications for policy-making. PRAIM included more than 460,000 women, 119 radiologists, 5 different machine vendors and 12 screening sites across Germany. The study did not exclude screening sites, machine vendors, radiologists (for example, based on years of professional experience) or subpopulations of women and allowed for updating the AI algorithms throughout the study, as would occur in a wider rollout. This real-world setting of PRAIM enhances the generalizability of the findings to similar double-reading mammography screening programs. The controlled implementation of AI into the screening process used in the PRAIM study—including onboarding of radiologists on the interpretation of AI recommendations before turning on AI predictions and live monitoring of the AI predictions by the vendor, compliant with postmarketing surveillance regulations—facilitated a safe and responsible rollout of AI[19].

Our AI approach for mammography screening provided confident normal and confident suspicious predictions (safety net) but no predictions in which it was not confident. The BCDR in the AI group, in which one or both radiologists used the AI-supported viewer to interpret examinations, was 17.6% (5.7%, 30.8%) higher (one additional breast cancer per 1,000 screened women) than in the control group, in which independent standard (human) double reading was done. AI use was also accompanied by a slightly but not statistically significant lower recall rate (−2.5% (−6.5%, 1.7%)).

Our results are in line with earlier published studies. Retrospective studies found a similar or higher BCDR for AI-supported breast cancer screening, suggesting that AI could improve cancer detection by reducing the interval cancer rate and through earlier detection of next-round screen-detected cancers, some of which are retrospectively visible on mammograms from a preceding screening round[12,14,20–22]. Three prospective studies have also reported higher BCDRs with AI-supported screening[15–17]. The MASAI study, a randomized controlled trial, deployed AI to triage examinations for single or double reading in the intervention group and reported a 20% (−0%, 50%) higher BCDR but also increased recall rates from 2.0% (1.9%, 2.2%) to 2.2% (2.0%, 2.3%)[15]. The ScreenTrustCAD study, which had a paired-reader design, showed that the reader replacement approach (AI plus one radiologist) achieved a higher BCDR (4% (0%, 9%)) and a lower recall rate (−4% (−6%, −3%)) than standard independent double reading[16]. Ng et al.[17] used AI as a third reader to refer examinations for arbitration, which resulted in the detection of additional cancers, most of which were aggressive[17].

The decision referral approach used in our study allowed for improving the BCDR without increasing the recall rate through a combination of a 'safety net' system and 'normal triaging'. Radiologists using the AI-supported viewer were only alerted and shown suspicious computer-assisted diagnosis marks after they interpreted examinations deemed suspicious by the AI as normal. This approach limits automation bias and reduces false-positive recall rates while leaving the final recall decision to the radiologists (see example cases in Extended Data Fig. 5)[18]. In the AI-supported group, the safety net was triggered 3,959 times and accepted 1,077 times, and 204 breast cancers (61 DCIS, 142 invasive, 1 other) were diagnosed among these safety net-induced reassessments. These breast cancers would have been missed otherwise. Labeling confident negative predictions may exploit automation bias and contribute to reducing the recall rate as radiologists may be less likely to falsely recall examinations tagged as normal by AI. However, radiologists in the AI group also detected 20 cancers among the examinations AI classified as normal.

Although our study and others have shown that the use of AI in breast cancer screening leads to higher BCDRs with comparable recall rates, there are still open questions. First, our study and others suggest that integrating AI into mammography screening might further increase DCIS detection, raising concerns about potential overdiagnosis and subsequent overtreatment. This increase might partially result from the earlier detection of cancers that would otherwise be diagnosed as invasive interval or next-round cancers. It is unclear whether or to what extent the increased BCDR, including the higher detection of DCIS, of AI-supported screening will lead to a lower incidence of interval cancers, better stage distribution of invasive disease and reduced incidence of next-round screen-detected cancers. Knowledge about the importance of higher detection of DCIS and grade 1 cancers on interval cancer rate and stage distribution is crucial but will only become clear after 2–3 years of follow-up. Among others, rejected safety net cases would be an interesting subgroup to help understand the ratio between overdiagnosis and interval or next-round cancers. In the present study, the DCIS detection rate was 0.8 per 1,000 women without AI and 1.4 per 1,000 women with AI, whereas invasive disease was detected in 4.8 per 1,000 women without AI compared to 5.2 per 1,000 women with AI. Once the true extent of overdiagnosis is established in future studies, the potential of AI to detect more DCIS cases that would otherwise not progress to invasive disease should be weighed against the benefit of increased detection of invasive tumors.

Second, it is unknown whether examinations for which the safety net was triggered but rejected by the radiologists represent a correct decision by the reader and thus a critical safety measure to reduce recall and overdiagnosis. Possibly, these cases were missed opportunities to detect even more cancers early and to improve overall program performance further. These questions will be investigated in the 2- to 3-year follow-up analyses. Last, a setting should be defined (for example, by guidelines) and evaluated in which human double reading can be replaced by AI-supported interpretation. This should include a risk–benefit assessment of AI use as well as legal implications.

Table 5 | Model-predicted BCDRs and recall rates and corresponding differences in the AI and control groups for a fictitious AI automation scenario

Variables	Model-based prediction		Model-based difference (95% CI)	
	AI group	Control group	Absolute difference	Percentage difference
BCDR (per 1,000 women screened)	6.7	5.7	1.0 (0.3, 1.6)	16.7% (4.9%, 29.9%)
Consensus rate (per 1,000 women screened)	89.5	111.1	−21.6 (−24.2, −19.1)	−19.4% (−21.5%, −17.4%)
Recall rate (per 1,000 women screened)	32.6	38.3	−5.7 (−7.3, −4.2)	−15.0% (−18.6%, −11.2%)
Biopsy rate (per 1,000 women screened)	10.1	9.6	0.553 (−0.271, 1.376)	5.8% (−2.7%, 15.0%)

In this fictitious AI automation scenario, screening examinations triaged as normal by AI were not read by radiologists but rather directly classified as normal, resulting in a 56.7% workload reduction for the double-reading system. This analysis used the same model as for the main analysis.

The integration of AI into screening workflows is expected to alleviate some of the labor shortages experienced by many screening programs. We compared the performance of one or both readers in a double-reading system using AI (deployed in a decision referral approach) to that of both readers not using AI. Therefore, we did not directly assess the extent of reading workload reduction that could be achieved by integrating AI. However, we observed that radiologists in the AI group spent less time interpreting examinations tagged as normal by AI compared to examinations with no confident predictions and examinations with the safety net (Extended Data Fig. 4), thus enabling the radiologists to allocate their time better. In a post hoc analysis assuming that all examinations tagged normal were not read by radiologists and were not forwarded to a consensus conference, we observed a 56.7% reduction in the reading workload. Interestingly, this resulted in a significantly lower recall rate (−15.0% (−18.6%, −11.2%)) while still improving the BCDR by 16.7% (4.9%, 29.9%) (Table 5). This potential workload reduction is comparable to that achieved through the reader replacement strategy used in ScreenTrustCAD and the risk-based triage in MASAI[15,16].

Our study has some limitations. PRAIM is an observational study with no random assignment of screening examinations to the AI-supported and standard-of-care groups. Thus, there was a risk that confounding factors influenced radiologists' decision to use AI to interpret examinations, which could bias the findings. Indeed, a reader behavior was observed in which some radiologists preferred to read normal-tagged examinations with the AI-supported viewer and to interpret examinations not tagged normal, including those in the safety net, with a standard viewer. Part of this behavior could be due to differences in the functionalities of the available viewers. For example, synchronized zoom (the ability to simultaneously enlarge all four views) is a feature introduced in the AI-supported viewer only during the study, whereas other viewers without AI support typically already have this feature. This reader behavior created a bias (Extended Data Fig. 6) toward a higher breast cancer prevalence within examinations interpreted without AI support. By using propensity scores with overlap weighting (Extended Data Fig. 3), we could overcome this bias on the BCDR as shown in a simulation analysis ('Statistical methods' in Methods). Alternative statistical approaches and sensitivity analyses, including additional adjustments for potential confounders, different parameterizations of the reader set variable, placebo intervention analysis, resampling methods and alternative statistical approaches to correct for confounding, consistently demonstrated that our findings are both unbiased and robust.

Our study has several strengths. Besides the high number of participants and the real-world setting, likely leading to more conservative effects, a strength of the study is its prospective design. Retrospective analyses are limited by information bias as the final outcomes for examinations identified as suggestive of cancer only by AI are usually unknown. Our study overcomes this limitation as the AI predictions in the study group were considered by radiologists while making clinical decisions. Another strength of PRAIM is the extensive reporting of subgroup results. They showed noninferior or even statistically superior BCDRs in AI-supported screening across screening rounds, breast densities and ages. Thus, AI can be considered for the full screening population and does not need stratified use. Although not a limitation or a strength, it is worth noting that the data used for this study were collected in the early stages of AI use by radiologists (a learning phase). The interaction behavior between radiologists and AI, and hence the screening program metrics achieved, might change as radiologists become more familiar with using the technology.

In conclusion, our findings substantially add to the growing body of evidence suggesting that AI-supported mammography screening is feasible and safe and can reduce workload. Our study also demonstrates that integrating AI into the screening workflow can improve the BCDR with a similar or even lower recall rate. The important downstream effects of AI-supported screening on overall program performance metrics, including interval cancer rate and stage-at-diagnosis distribution at subsequent screening rounds, are subject to follow-up investigations. Nevertheless, based on the now available evidence on breast cancer detection, recall rates, PPV of biopsy and time savings, urgent efforts should be made to integrate AI-supported mammography into screening guidelines and to promote the widespread adoption of AI in mammography screening programs.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03408-6.

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Methods

Ethics and data privacy

This research complies with all relevant ethical regulations. Women were informed about the use of AI software at each screening site, and their data were processed according to applicable data privacy rules, including the General Data Protection Regulation. The study protocol was registered in the German Clinical Trials Register (DRKS00027322) and was approved by the ethics committee of the University of Lübeck (22-043), which waived the need for informed consent.

Procedures

The AI models used in the study are part of a commercially available AI system (Vara). Different deep learning-based AI models were used for normal triaging and the safety net. These models were constructed from a combination of deep convolutional neural networks trained on mammography images. The labels (normal, benign, malignant) for these images were sourced from radiological reports, annotations of findings and biopsy data. The outcomes of ensuing screenings were used to confirm samples labeled 'normal'. The AI system evaluates the suspiciousness of mammography examination findings by combining per-image scores of incident images and their priors (if available) in an aggregation model. The final score represents the model's confidence estimate of suspiciousness for a specific case. The models underwent two optimization processes, one aimed at high sensitivity (normal triaging) and the other at high specificity (safety net). Example examinations for AI misclassifying a cancerous case as normal as well as correctly catching a cancer that both radiologists missed through the safety net are shown in Extended Data Fig. 5. The models were trained and validated on a dataset comprising more than 2 million images to identify malignant breast tissue in mammograms. To facilitate the training of the AI models, the radiologists annotated more than 200,000 images with polygons. The models internally output a score between 0 and 1 for each examination, in which 0 means maximally unsuspicious and 1 means maximally suspicious. Thresholds were calibrated based on separate retrospective datasets representative of German screening[18] and then applied to derive binary decisions (normal versus not normal, safety net versus no safety net) at an average of 60% normal triaging rate and 1.5% safety net trigger rate. For the remaining examinations, neither the 'normal' tag shown nor the 'safety net' is active. All radiologists who contributed examinations to the AI group were trained as part of the standard medical device onboarding process before they started using the AI-supported viewer. The training covered the functionality of the software, including the interpretation of normal triage flags and safety net alerts.

During the study, the medical device being examined underwent a series of updates, transitioning from version 1.0.5 to 2.6.2 (a total of ten updates). The AI models, which form the basis of the medical device, were updated three times, none of them using data from the study.

Data on the procedure, outcomes, participants and detected cancers were retrieved from the standardized documentation of the official mammography screening program (linked to the data of the AI system) and then transferred in anonymized form to an evaluation database. For analysis, women with missing outcome data (666 women, 0.1%; Fig. 1) or cancellations (610 women, 0.1%) were excluded.

Outcomes

The primary outcomes were the BCDR and recall rate. A suspicion of breast cancer after mammography was histopathologically confirmed either through preoperative biopsy or surgical biopsy. Examinations of women without detected breast cancer are typically completed within 2 weeks, but the final documentation of a cancer diagnosis and treatment can take several months. Therefore, follow-up time was set to a minimum of 200 days from the date of screening. A recall was defined as a woman being reinvited for further diagnostic examinations. The BCDR and recall rate were further stratified across screening round (first versus follow-up), breast density (American College of Radiology density levels I/II ('nondense') versus III/IV ('dense')) and age group (50–59 versus 60–69 years).

The secondary outcome measures were the AI predictions (normal or not normal, safety net) and their role in diagnosis. The safety net was considered 'triggered' when the score of the AI model exceeded the calibrated threshold for the safety net, 'shown' when the reader initially deemed the examination unsuspicious and was shown the warning and localization of the safety net in the AI-supported viewer, and 'accepted' when the radiologist consequently changed their assessment. Lastly, the time radiologists spent per examination was assessed in the AI group, stratified by AI prediction.

Change of analysis plan due to radiologist self-selection

During the data collection period, it was learned through user feedback sessions with radiologists and the AI vendor that the radiologists' choice to use the AI-supported viewer for the final mammogram report sometimes depended on the initial AI prediction (normal versus not normal), which was already visible in the worklist (Extended Data Fig. 1). The AI-supported viewer also offers a sorted worklist tab where only 'normal' examinations are presented one after another for expedited reading.

A common scenario described was that some radiologists tended to read all current examinations tagged as 'normal' in the AI-supported viewer, switched their software afterward and then read the remaining examinations in the control group without AI software. A reason for this behavior is that a consensus conference is more convenient when all participating readers used the same viewer for annotations during the initial reads, as this allows the annotations of all readers to be displayed easily during the consensus conference. In contrast, displaying annotations across different viewers does not work flawlessly owing to a lack of software interoperability. Therefore, when a screening examination was not flagged as normal, some readers tended to switch to the other viewer software to ease work with colleagues not using the AI-supported viewer. Additionally, the AI-supported viewer did not support some features helpful for diagnosing suspicious cases (which are more likely among non-normal examinations), such as synchronized zoom (the ability to simultaneously enlarge all four views). We call this observed behavior 'reading behavior bias'. This practice was not anticipated in the original study setup and introduced severe selection bias (Extended Data Fig. 6). Data illustrating this bias are shared (Code availability statement).

Thus, the original analysis plan had to be adapted.

Statistical methods

A sample size of 200,000 women per study group was targeted for assessing the noninferiority of AI in terms of the BCDR with the originally planned analysis. Because of the reading behavior bias described above, which was introduced by real-world actions and not anticipated in the original study setup, a severe bias could be present. A simulation study was conducted to (1) identify a statistical method that can successfully correct for this bias when estimating the effect of AI and (2) estimate the expected power for each considered statistical method. Only one of the considered methods—a simple regression model with cancer detection (yes versus no) as the outcome variable, intervention (AI versus control group) as the predictor, a quasi-binomial error distribution, and overlap weighting using propensity scores[23,24]—provided unbiased results and sufficiently high power in the simulation study. The empirical sandwich variance for propensity score weighting estimators was used[23,24]. Propensity scores depended on the reader set assessing the examination and on the AI prediction (normal versus not normal), which were identified as a minimal adjustment set in a causal graph analysis (see below) and were computed using logistic regression. Overlap weighting was used as some propensity scores were rather extreme (Extended Data Fig. 3a), indicating that some reader sets rarely used the AI-supported viewer, whereas some other reader sets usually did. The objective of overlap weighting is to place the highest weight on data in which the propensity for an examination being read with AI (AI group) and without AI (control group) is quite similar and place less weight on data with extreme propensity scores. Extended Data Fig. 3b shows that, after overlap weighting, the largest proportion of the weights was placed on areas of medium propensity scores (that is, readers who contributed reads to both the AI and control groups) and the distribution of the propensity to be in the AI group was the same in both study groups, indicating a balance in the confounders between the groups[23,24].

For breast cancer detection, AI-supported reading was considered noninferior if the detection rate in the AI group was at most 10% lower than in the control group. More specifically, the lower bound of a two-sided 95% CI of the difference had to be above the threshold of −10%. If noninferiority is successfully demonstrated, sequential testing for superiority is justified[25]. Statistical superiority is demonstrated if the lower bound of the CI exceeds 0. For recall, AI-supported reading was considered noninferior if the recall rate in the AI group was at most 10% higher than in the control group.

Model-based predictions of the BCDR (in total and by invasiveness, stage, grade and tumor size) and the rates of recall (including the PPV), consensus conference and biopsy (including the PPV) in the AI and control groups were derived from the regressions. Subgroup analyses (by screening round, breast density and age group) were conducted by fitting regressions, as described above, to the data restricted to the respective subgroup and by deriving model-based predictions as before.

Sensitivity analyses addressing additional and residual confounding, sampling error and model decisions were performed ('Results'). All analyses were conducted with R (version 4.1.3) using the packages PSweight (version 1.2.0)[24], dagitty (version 0.3.1)[26] and marginaleffects (version 0.18)[27], as well as Python (version 3.10)[28] using the package dowhy (version 0.11.1)[29]. All analyses are shared as part of the code (Code availability statement). Further information is also available upon request to the authors.

Causal graph (directed acyclic graph)

A causal effect of the intervention (use of AI, main predictor) on the endpoints (breast cancer detection, recall, consensus conference, biopsy) was investigated. All direct paths between all variables considered were evaluated for plausibility based on theory, domain knowledge and previous empirical evidence: breast density decreases with age[30]; participation in more screening rounds increases with age; breast cancer risk increases with age[31]; breast density is associated with breast cancer risk[32,33]; breast cancer prevalence is higher among women attending the first screening round[34]; reader variability exists in the classification of breast density categories[35]; AI predictions are associated with the presence or absence of breast cancer[18]; a reading behavior exists whereby AI predictions influence the use of AI-enabled software; radiologists' personal preferences and attitudes affect their decision to adopt AI[36]; radiologists have varied levels of expertise and competence in interpreting mammography examinations[37]; the involvement of a supervising radiologist introduces a third reader, affecting both cancer detection and recall; and there are unknown factors that may be associated with increased breast cancer risk.

The resulting causal graph is shown in Extended Data Fig. 2. 'Reader set' is a confounder according to the backdoor criterion[38]. As it is impossible to adjust for the latent (unobservable) confounder 'breast cancer (present or absent)', we adjusted for a proxy (that is, the correlated variable 'AI prediction'), which was also the direct cause of the observed reading behavior: once radiologists observed the AI prediction in the worklist, they reconsidered which viewer software to use for submitting the report[39]. Therefore, the main analysis model controlled for these two confounders: reader set and AI prediction.

The three variables 'screening round', 'age at screening' and 'breast density' are ancestors of the intervention and outcome, whereas 'supervision' is the ancestor of the outcome. Some authors recommend adjusting for all ancestors of the intervention and/or outcome[39]. Therefore, we have also verified that adding the four variables just mentioned forms a valid adjustment set, using the R package dagitty (version 0.3.1)[26]. Results from a sensitivity analysis in which all four variables were additionally adjusted for are provided (Extended Data Table 3). Adjustment was done by adding the covariates to the propensity score model.

Overall, the causal graph implies the 12 (conditional) independences that should hold in the observed data. We tested this using the kernel-based test of statistical independence by Gretton et al.[40]. Indeed, all independence statements hold, showing that the defined causal graph is consistent with the observed data.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The study protocol is available at https://research.uni-luebeck.de/en/projects/prospective-multicenter-observational-study-of-an-integrated-ai-s. The anonymized analysis dataset, including individual participant data and a data dictionary defining each field, is available via Dryad at https://doi.org/10.5061/dryad.zs7h44jgn (ref. 41). Detailed information on sensitivity analyses and the simulation study is available from nora.eisemann@uksh.de. Requests will be answered within 1 month.

Code availability

The code and supporting information necessary to reproduce the results are available via Zenodo at https://doi.org/10.5281/zenodo.10822135 (ref. 42). The code for training the evaluated AI system is part of a proprietary system and cannot be shared for commercial reasons. However, the AI system is available for external research evaluation collaborations for researchers who provide a methodologically sound proposal. Proposals should be directed to stefan.bunk@vara.ai and will be answered within 1 month.

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Author contributions

N.E. and A.K. conceptualized the study and wrote the study protocol with input from S.B. and C.L. N.E. and H.B. did the statistical analysis with review from S.B. and C.L. N.E., H.B. and S.B. verified the underlying data reported in the paper. N.E., S.B. and T.M. wrote the first draft of the report. All authors reviewed and edited the paper and provided important intellectual content. All authors discussed the results and contributed to the final paper. All authors had full access to all study data and have agreed to the published version.

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Competing interests

The study was funded by Vara. Vara was involved in the study design, collection and interpretation of data, and writing of the report. All authors had access to all the data and were responsible for the decision to submit the paper. S.B., T.M. and C.L. are current employees of Vara with stock options as part of the standard compensation package. G.H., R.R., T.G., T.T. and T.W.V. actively participated in the study as radiologists and as customers of Vara. T.T. received speaker fees from Vara. A.K. received general consulting and speaker fees from Vara. K.S.-L. received consulting fees from Hologic. S.H.-K. has research cooperations with iCAD and ScreenPoint (no payments). The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-024-03408-6.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-024-03408-6.

Correspondence and requests for materials should be addressed to Stefan Bunk or Alexander Katalinic.

Peer review information *Nature Medicine* thanks Suzette Delaloge and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editors: Ming Yang and Lorenzo Righetto, in collaboration with the *Nature Medicine* team.

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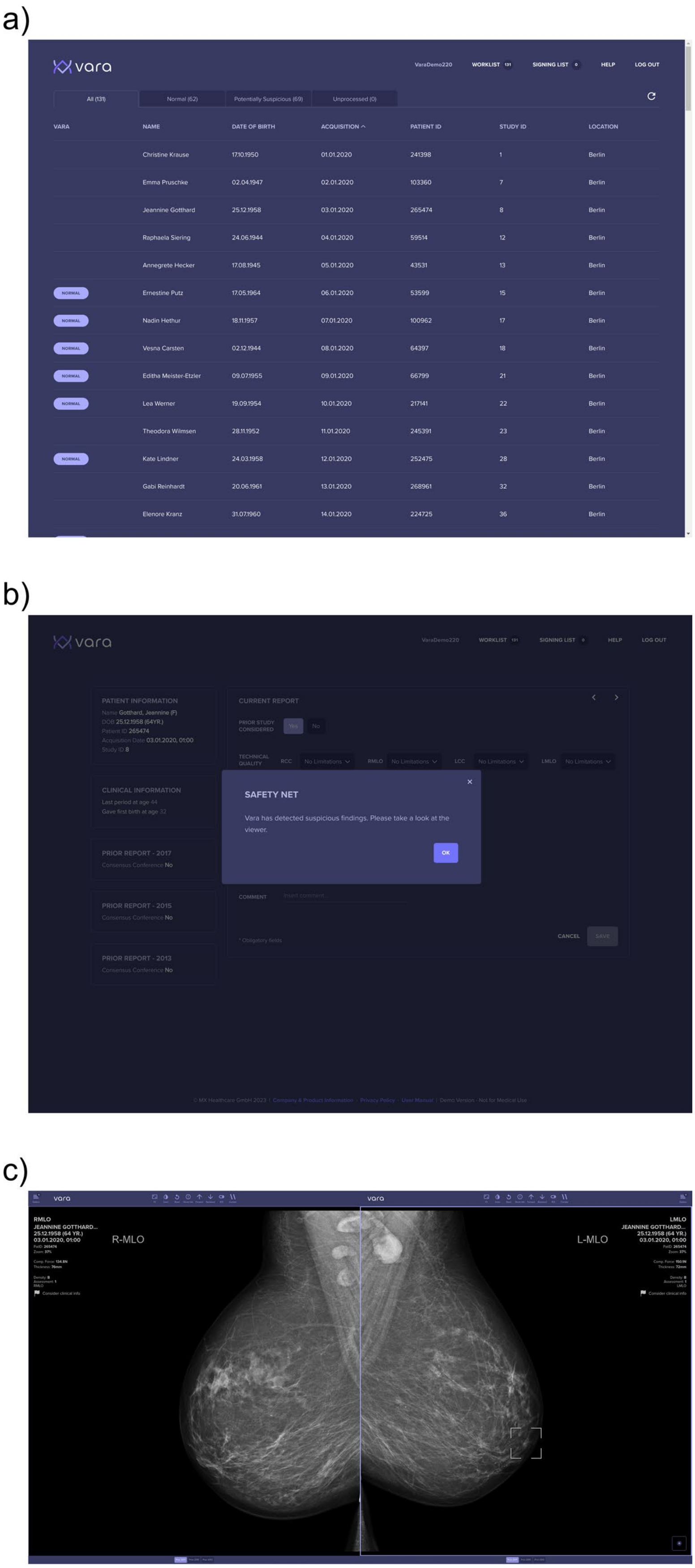


a)

vara VaraDemo220 WORKLIST 131 SIGNING LIST 0 HELP LOG OUT

All (131) | Normal (62) | Potentially Suspicious (69) | Unprocessed (0)

VARA	NAME	DATE OF BIRTH	ACQUISITION ^	PATIENT ID	STUDY ID	LOCATION
	Christine Krause	17.10.1950	01.01.2020	241398	1	Berlin
	Emma Pruschke	02.04.1947	02.01.2020	103360	7	Berlin
	Jeannine Gotthard	25.12.1958	03.01.2020	265474	8	Berlin
	Raphaela Siering	24.06.1944	04.01.2020	59514	12	Berlin
	Annegrete Hecker	17.08.1945	05.01.2020	43531	13	Berlin
NORMAL	Ernestine Putz	17.05.1964	06.01.2020	53599	15	Berlin
NORMAL	Nadin Hethur	18.11.1957	07.01.2020	100962	17	Berlin
NORMAL	Vesna Carsten	02.12.1944	08.01.2020	64397	18	Berlin
NORMAL	Editha Meister-Etzler	09.07.1955	09.01.2020	66799	21	Berlin
NORMAL	Lea Werner	19.09.1954	10.01.2020	217141	22	Berlin
	Theodora Wilmsen	28.11.1952	11.01.2020	245391	23	Berlin
NORMAL	Kate Lindner	24.03.1958	12.01.2020	252475	28	Berlin
	Gabi Reinhardt	20.06.1961	13.01.2020	268961	32	Berlin
	Elenore Kranz	31.07.1960	14.01.2020	224725	36	Berlin

b)

vara VaraDemo220 WORKLIST 131 SIGNING LIST 0 HELP LOG OUT

PATIENT INFORMATION
Name Gotthard, Jeannine (F)
DOB 25.12.1958 (64YR.)
Patient ID 265474
Acquisition Date 03.01.2020, 01:00
Study ID 8

CLINICAL INFORMATION
Last period at age 44
Gave first birth at age 32

PRIOR REPORT - 2017
Consensus Conference No

PRIOR REPORT - 2015
Consensus Conference No

PRIOR REPORT - 2013
Consensus Conference No

CURRENT REPORT

PRIOR STUDY CONSIDERED Yes No

TECHNICAL QUALITY RCC No Limitations RMLO No Limitations LCC No Limitations LMLO No Limitations

SAFETY NET

Vara has detected suspicious findings. Please take a look at the viewer.

OK

COMMENT Insert comment...

* Obligatory fields

CANCEL SAVE

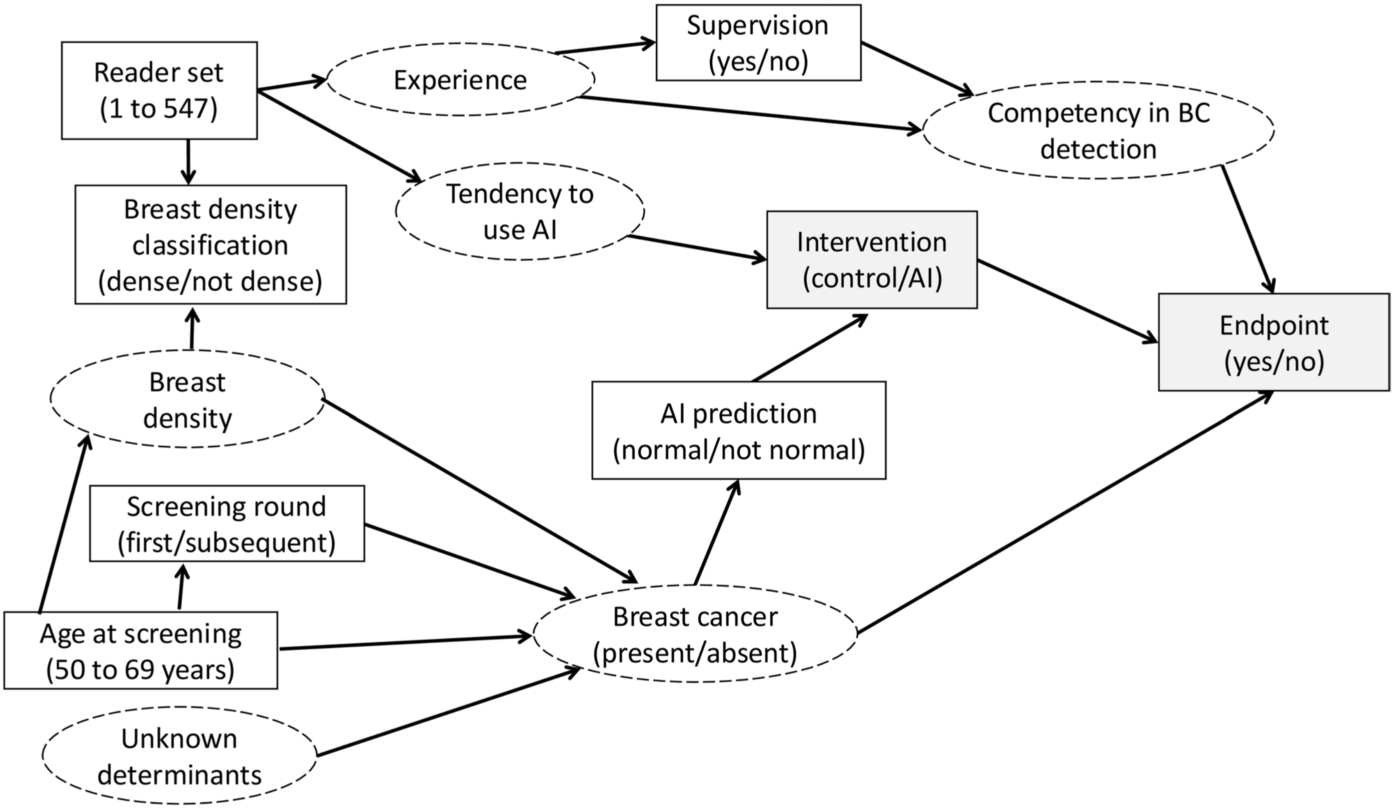
© MX Healthcare GmbH 2023 | Company & Product Information · Privacy Policy · User Manual | Demo Version - Not for Medical Use

c)

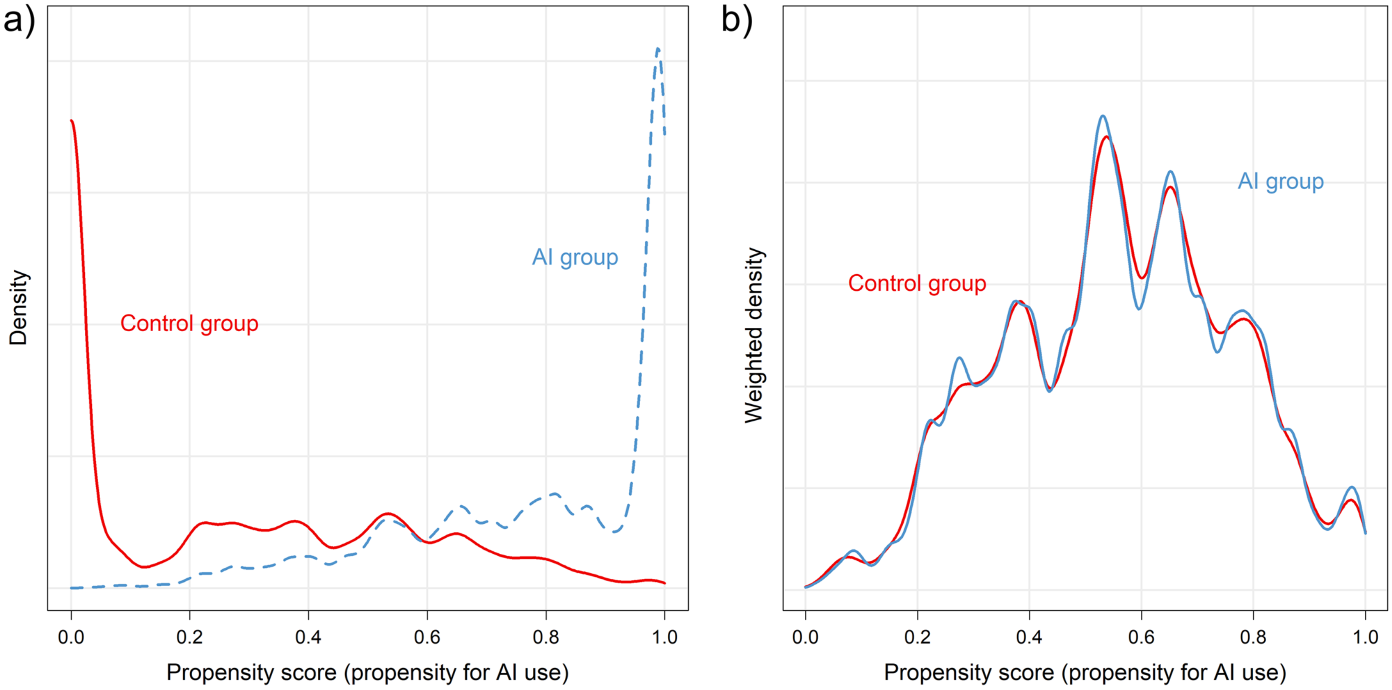
RMLO
JEANNINE GOTTHARD...
25.12.1958 (64 YR.)
03.01.2020, 01:00
PatID: 265474
Zoom: 37%
Comp. Force: 134.8N
Thickness: 76mm
Density: B
Assessment: 1
RMLO
Consider clinical info

LMLO
JEANNINE GOTTHARD...
25.12.1958 (64 YR.)
03.01.2020, 01:00
PatID: 265474
Zoom: 37%
Comp. Force: 150.1N
Thickness: 72mm
Density: B
Assessment: 1
LMLO
Consider clinical info

Extended Data Fig. 1 | AI-supported Viewer Screenshots. a) The screenshot shows a worklist with subset of examinations tagged as normal. Radiologists can also choose to read only normal examinations or only not normal examinations ('potentially suspicious'). Names and dates of birth are not real and were sampled randomly from a list of common first and last names. **b)** and **c)** When radiologists assess a case as normal (BI-RADS 1 or 2) but the safety net triggered, an alert is shown (**b**) and a suspicious region is highlighted in the viewer (**c**), asking the radiologists to reconsider.

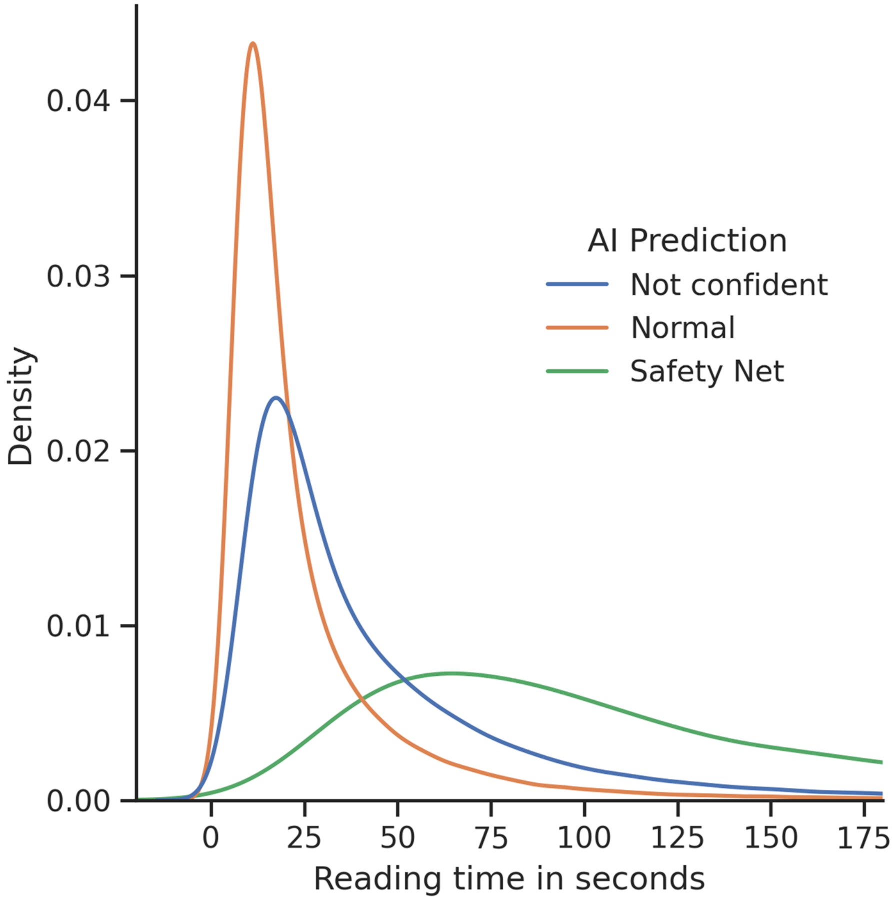


Extended Data Fig. 2 | Causal Graph (Directed Acyclic Graph, DAG). Causal graph of assumed relationships between intervention, characteristics of the radiologists and the women screened, and the endpoint (breast cancer detection; recall; consensus conference; biopsy). Before being included in the DAG, possible direct paths between all variables considered were evaluated for plausibility based on theory, domain knowledge and previous empirical evidence. BC: Breast cancer; AI: Artificial Intelligence. Box: observed variable; round and dashed: latent variable.

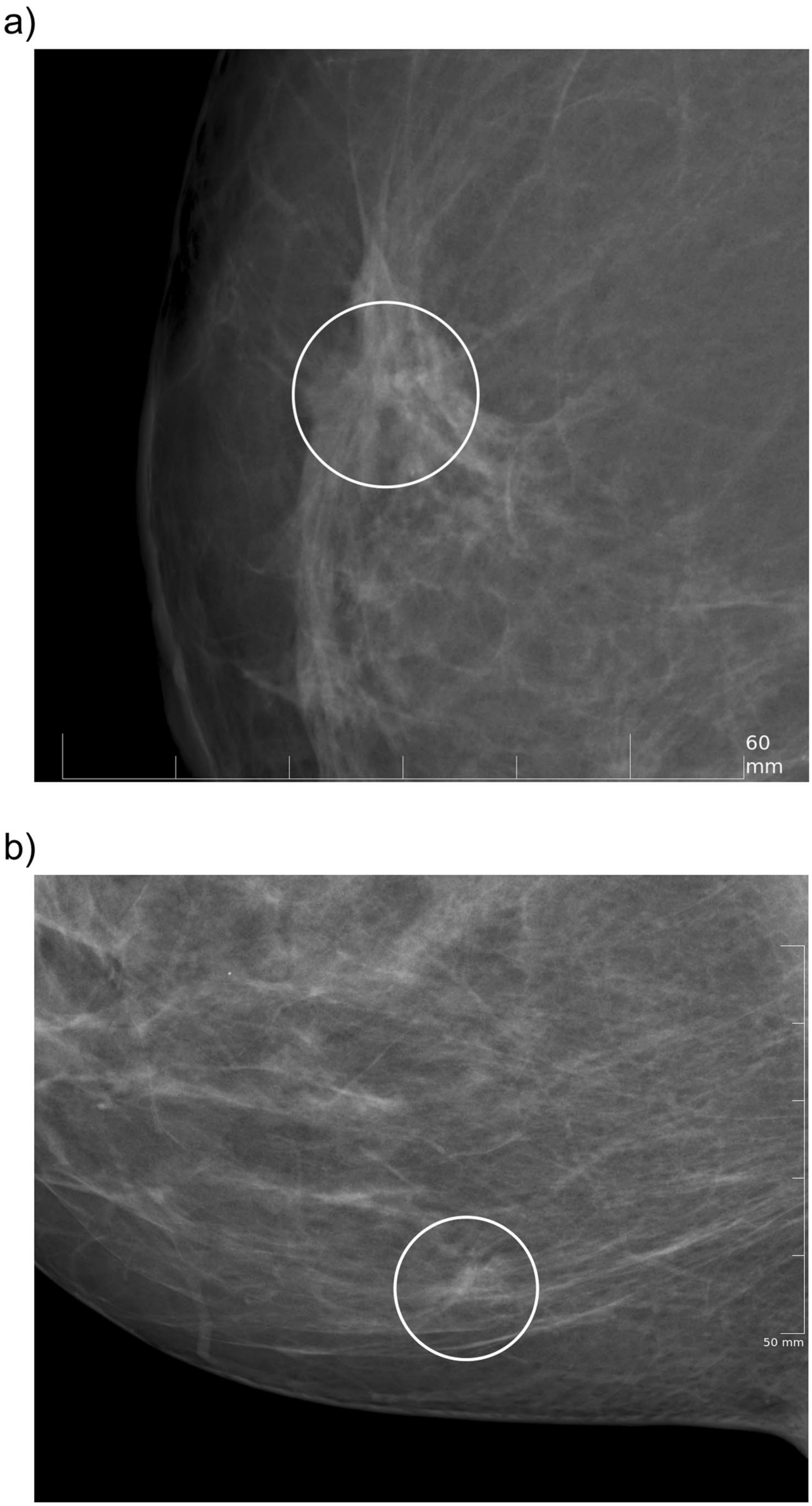


Extended Data Fig. 3 | Propensity Scores and Weights. a) Distribution of propensity scores (for being in AI group), stratified by being in control group or in AI group. **b**) Extent to which screening exams with a given propensity score (for being in AI group) contribute to the overall sample weight.

https://doi.org/10.1038/s41591-024-03408-6

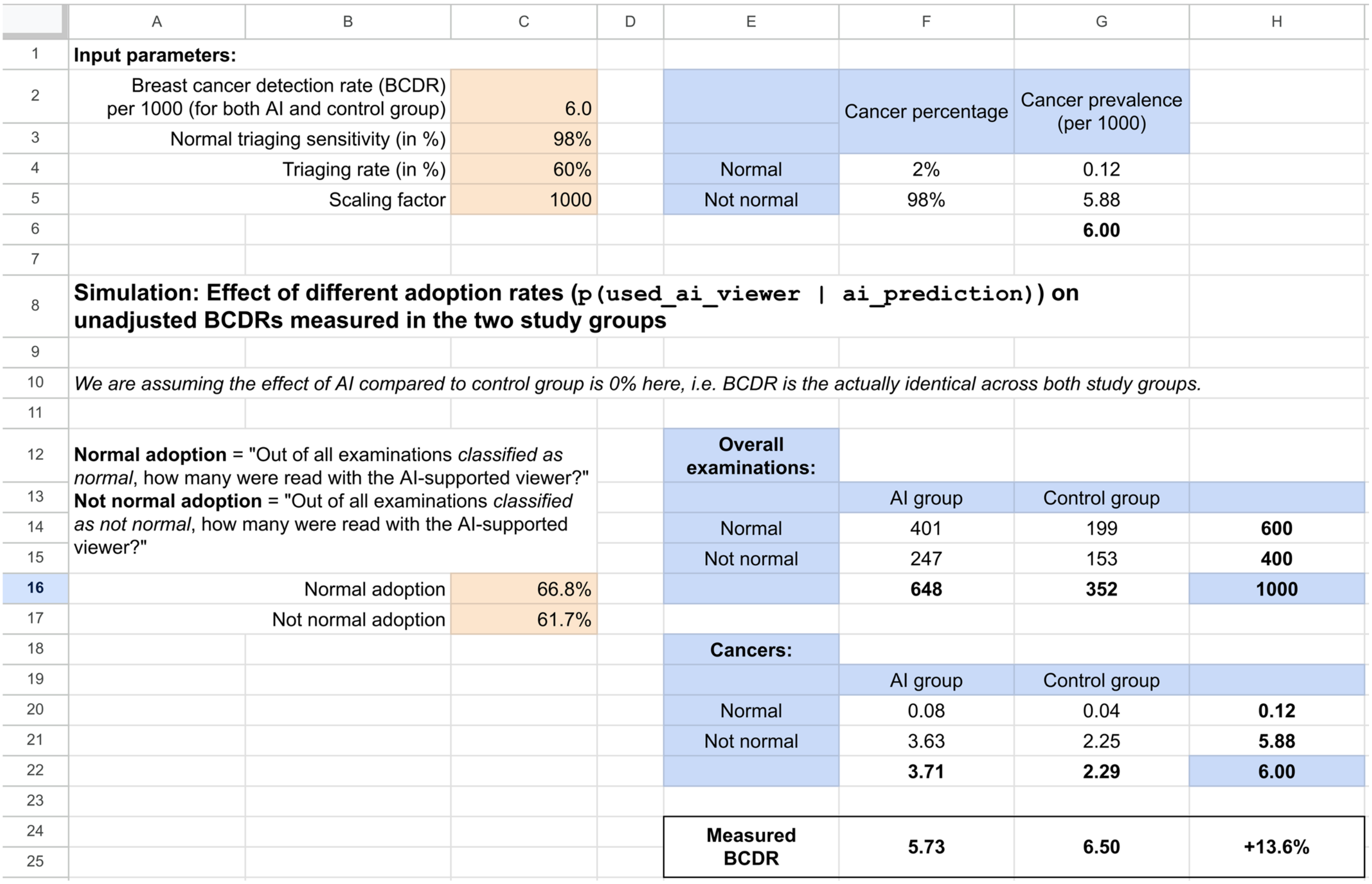


Extended Data Fig. 4 | Reading Time. Reading times in the AI group for normal, safety net, and unconfident predictions. On average, examinations that were tagged as normal were read more quickly, with a median reading time of 16 seconds, compared to unclassified examinations, which had a median reading time of 30 seconds, and safety net examinations, which had a median reading time of 99 seconds.



Extended Data Fig. 5 | See next page for caption.

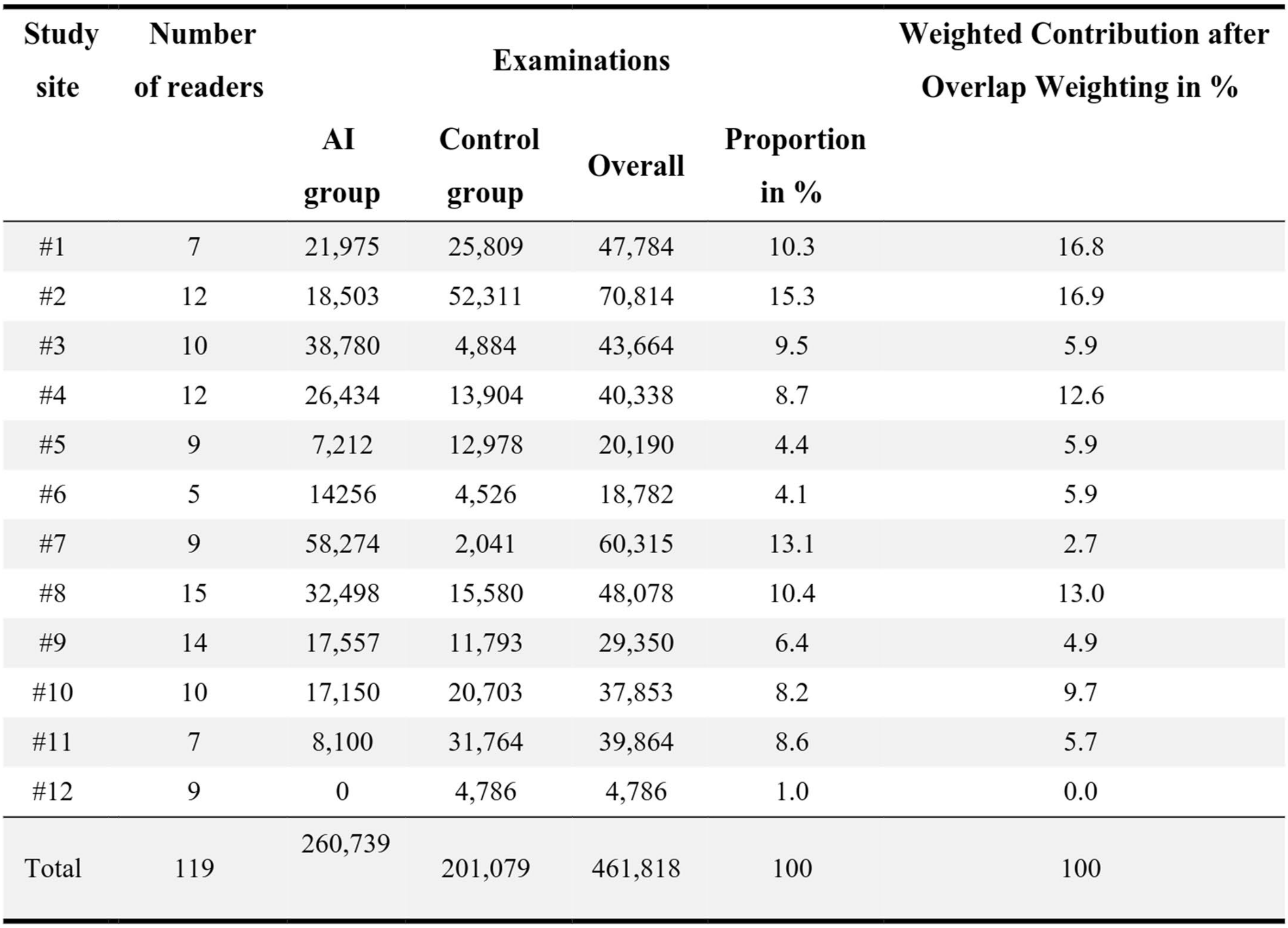
Extended Data Fig. 5 | Example Examinations. a) This cancer was only diagnosed because of the safety net activation. Neither reader initially saw the invasive carcinoma (BI-RADS 1/2), but both changed their assessment to BI-RADS 4 A after the safety net was displayed. The MLO view of the right breast shows an architectural distortion. Ultrasound during recall identified highly suspicious malignant findings. Histology: Invasive breast cancer, no special type, pT1b (9 mm) pre-therapy, pT1c (19 mm) post-op, N0, M0, G2. **b**) This examination was classified as 'normal' by the AI. Both readers used the AI-supported viewer and overruled the AI (BI-RADS 4B and BI-RADS 4 A respectively). The MLO view of the right breast shows a mass. Histology: Invasive breast cancer, no special type, pT1b (9 mm) pre-therapy, ypT1c (12 mm) post-op, N0, M0, G2.



	A	B	C	D	E	F	G	H
1	**Input parameters:**							
2		Breast cancer detection rate (BCDR) per 1000 (for both AI and control group)	6.0			Cancer percentage	Cancer prevalence (per 1000)	
3		Normal triaging sensitivity (in %)	98%					
4		Triaging rate (in %)	60%		Normal	2%	0.12	
5		Scaling factor	1000		Not normal	98%	5.88	
6							**6.00**	
7								
8	**Simulation: Effect of different adoption rates (`p(used_ai_viewer | ai_prediction)`) on unadjusted BCDRs measured in the two study groups**							
9								
10	*We are assuming the effect of AI compared to control group is 0% here, i.e. BCDR is the actually identical across both study groups.*							
11								
12	**Normal adoption** = "Out of all examinations *classified as normal*, how many were read with the AI-supported viewer?" **Not normal adoption** = "Out of all examinations *classified as not normal*, how many were read with the AI-supported viewer?"				**Overall examinations:**			
13						AI group	Control group	
14					Normal	401	199	**600**
15					Not normal	247	153	**400**
16		Normal adoption	66.8%			**648**	**352**	**1000**
17		Not normal adoption	61.7%					
18					**Cancers:**			
19						AI group	Control group	
20					Normal	0.08	0.04	**0.12**
21					Not normal	3.63	2.25	**5.88**
22						**3.71**	**2.29**	**6.00**
23								
24					**Measured BCDR**	**5.73**	**6.50**	**+13.6%**
25								

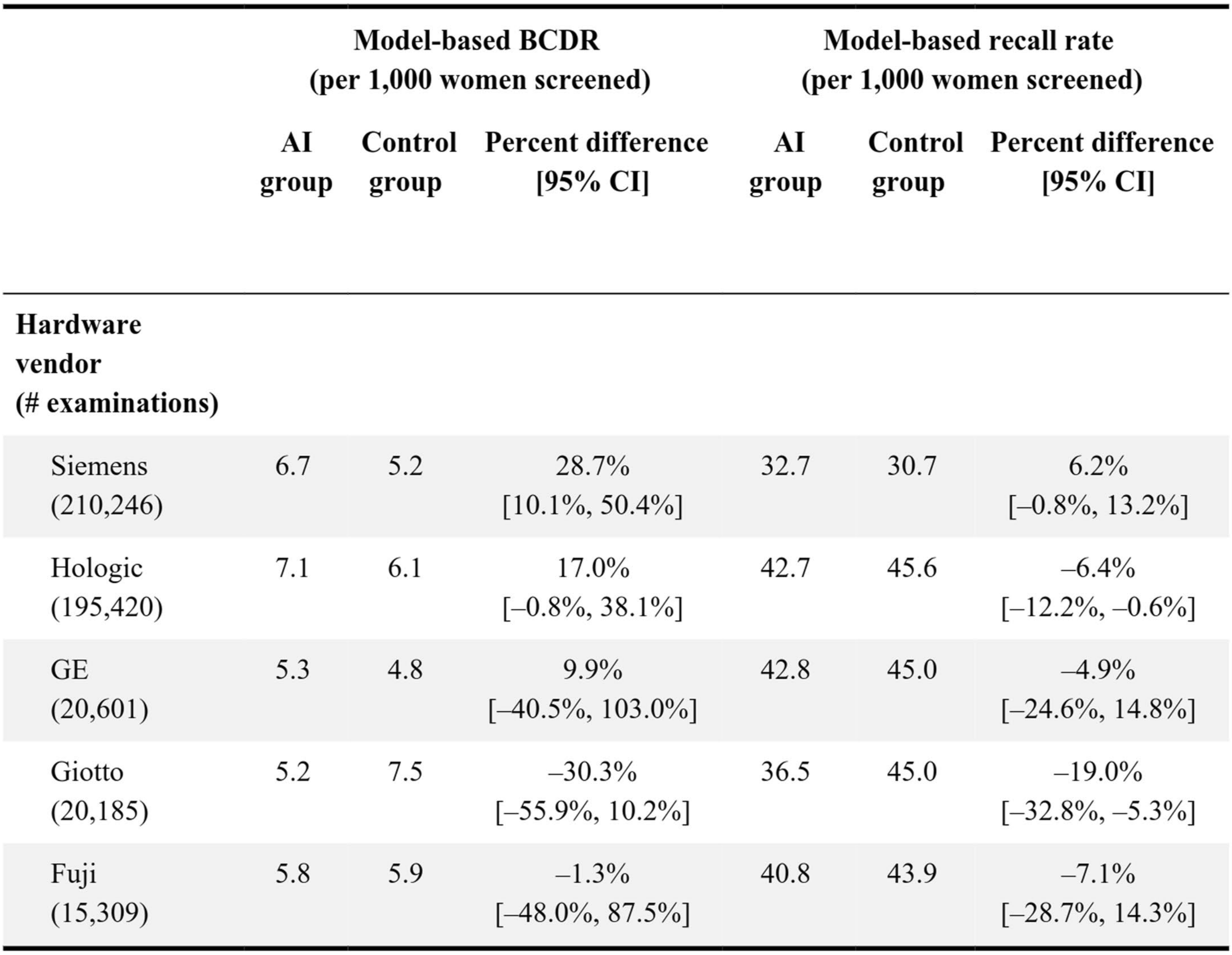
Extended Data Fig. 6 | Bias due to self-selection of radiologists to AI or control group. Excel file illustrating the effect of the reading behaviour on measured unadjusted breast cancer detection rate across study groups, even if breast cancer detection rate were identical in both study groups. The figure shows that even a minor adoption rate difference from 61.7% to 66.8% would lead to an unadjusted measured breast cancer detection rate difference of 13.6% (bias). Therefore, it was necessary to control for this reading behavior in the main analysis. The Excel file is available for further analysis (10.5281/zenodo.10822135).

Extended Data Table 1 | Screening sites participating in PRAIM



Study site	Number of readers	Examinations				Weighted Contribution after Overlap Weighting in %
		AI group	Control group	Overall	Proportion in %	
#1	7	21,975	25,809	47,784	10.3	16.8
#2	12	18,503	52,311	70,814	15.3	16.9
#3	10	38,780	4,884	43,664	9.5	5.9
#4	12	26,434	13,904	40,338	8.7	12.6
#5	9	7,212	12,978	20,190	4.4	5.9
#6	5	14256	4,526	18,782	4.1	5.9
#7	9	58,274	2,041	60,315	13.1	2.7
#8	15	32,498	15,580	48,078	10.4	13.0
#9	14	17,557	11,793	29,350	6.4	4.9
#10	10	17,150	20,703	37,853	8.2	9.7
#11	7	8,100	31,764	39,864	8.6	5.7
#12	9	0	4,786	4,786	1.0	0.0
Total	119	260,739	201,079	461,818	100	100

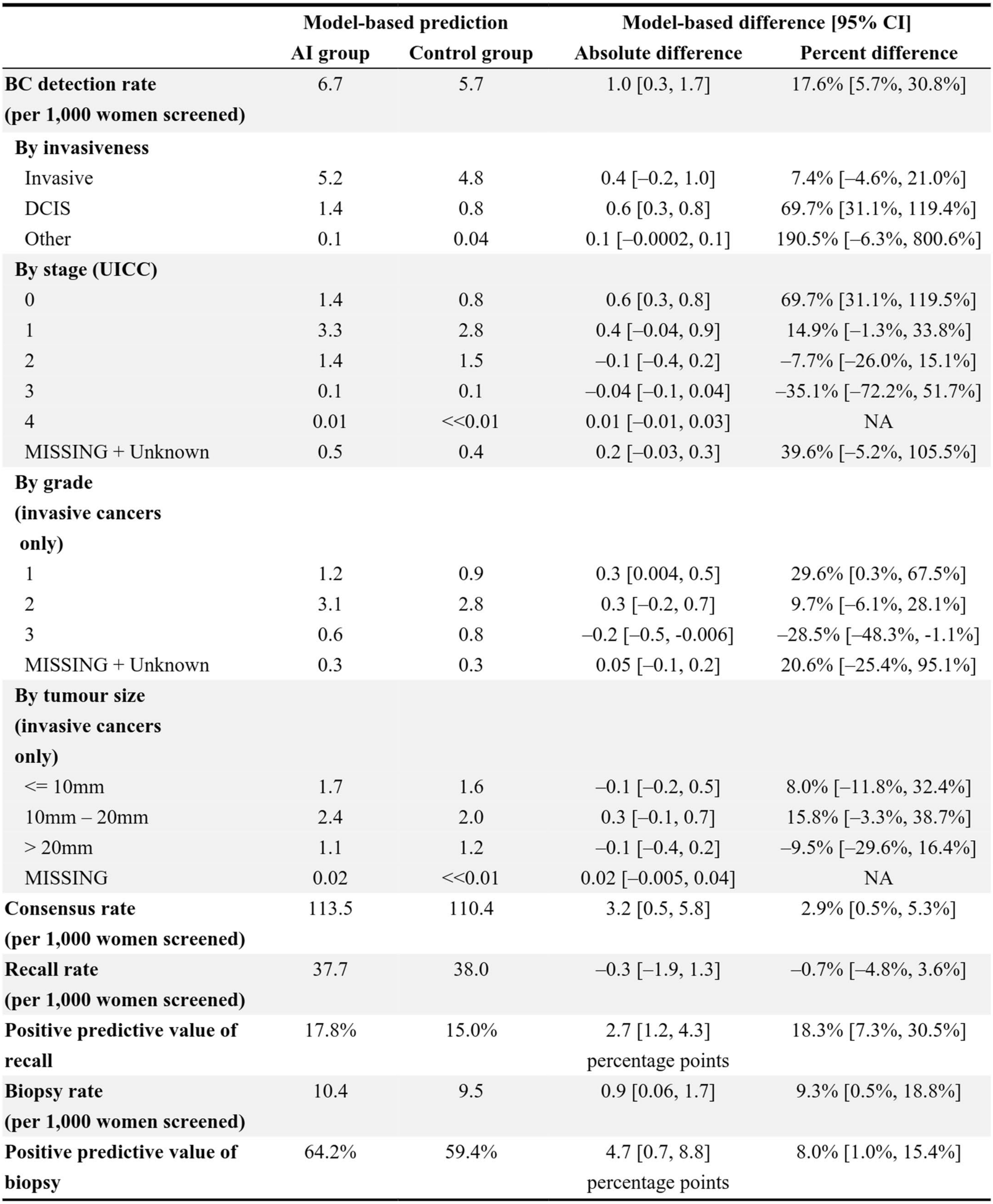
Extended Data Table 2 | Mammography Hardware Vendors



	Model-based BCDR (per 1,000 women screened)			Model-based recall rate (per 1,000 women screened)		
	AI group	Control group	Percent difference [95% CI]	AI group	Control group	Percent difference [95% CI]
Hardware vendor (# examinations)						
Siemens (210,246)	6.7	5.2	28.7% [10.1%, 50.4%]	32.7	30.7	6.2% [–0.8%, 13.2%]
Hologic (195,420)	7.1	6.1	17.0% [–0.8%, 38.1%]	42.7	45.6	–6.4% [–12.2%, –0.6%]
GE (20,601)	5.3	4.8	9.9% [–40.5%, 103.0%]	42.8	45.0	–4.9% [–24.6%, 14.8%]
Giotto (20,185)	5.2	7.5	–30.3% [–55.9%, 10.2%]	36.5	45.0	–19.0% [–32.8%, –5.3%]
Fuji (15,309)	5.8	5.9	–1.3% [–48.0%, 87.5%]	40.8	43.9	–7.1% [–28.7%, 14.3%]

Model-predicted breast cancer detection and recall rates, and corresponding differences in AI and control group by hardware vendors. For 57 screening examinations, the hardware vendor could not be determined, and therefore those exams are left out of this analysis.

Extended Data Table 3 | Regression with further covariate adjustment (extended propensity score model)



	Model-based prediction		Model-based difference [95% CI]	
	AI group	Control group	Absolute difference	Percent difference
BC detection rate (per 1,000 women screened)	6.7	5.7	1.0 [0.3, 1.7]	17.6% [5.7%, 30.8%]
By invasiveness				
Invasive	5.2	4.8	0.4 [–0.2, 1.0]	7.4% [–4.6%, 21.0%]
DCIS	1.4	0.8	0.6 [0.3, 0.8]	69.7% [31.1%, 119.4%]
Other	0.1	0.04	0.1 [–0.0002, 0.1]	190.5% [–6.3%, 800.6%]
By stage (UICC)				
0	1.4	0.8	0.6 [0.3, 0.8]	69.7% [31.1%, 119.5%]
1	3.3	2.8	0.4 [–0.04, 0.9]	14.9% [–1.3%, 33.8%]
2	1.4	1.5	–0.1 [–0.4, 0.2]	–7.7% [–26.0%, 15.1%]
3	0.1	0.1	–0.04 [–0.1, 0.04]	–35.1% [–72.2%, 51.7%]
4	0.01	<<0.01	0.01 [–0.01, 0.03]	NA
MISSING + Unknown	0.5	0.4	0.2 [–0.03, 0.3]	39.6% [–5.2%, 105.5%]
By grade (invasive cancers only)				
1	1.2	0.9	0.3 [0.004, 0.5]	29.6% [0.3%, 67.5%]
2	3.1	2.8	0.3 [–0.2, 0.7]	9.7% [–6.1%, 28.1%]
3	0.6	0.8	–0.2 [–0.5, -0.006]	–28.5% [–48.3%, -1.1%]
MISSING + Unknown	0.3	0.3	0.05 [–0.1, 0.2]	20.6% [–25.4%, 95.1%]
By tumour size (invasive cancers only)				
<= 10mm	1.7	1.6	–0.1 [–0.2, 0.5]	8.0% [–11.8%, 32.4%]
10mm – 20mm	2.4	2.0	0.3 [–0.1, 0.7]	15.8% [–3.3%, 38.7%]
> 20mm	1.1	1.2	–0.1 [–0.4, 0.2]	–9.5% [–29.6%, 16.4%]
MISSING	0.02	<<0.01	0.02 [–0.005, 0.04]	NA
Consensus rate (per 1,000 women screened)	113.5	110.4	3.2 [0.5, 5.8]	2.9% [0.5%, 5.3%]
Recall rate (per 1,000 women screened)	37.7	38.0	–0.3 [–1.9, 1.3]	–0.7% [–4.8%, 3.6%]
Positive predictive value of recall	17.8%	15.0%	2.7 [1.2, 4.3] percentage points	18.3% [7.3%, 30.5%]
Biopsy rate (per 1,000 women screened)	10.4	9.5	0.9 [0.06, 1.7]	9.3% [0.5%, 18.8%]
Positive predictive value of biopsy	64.2%	59.4%	4.7 [0.7, 8.8] percentage points	8.0% [1.0%, 15.4%]

Model-predicted breast cancer detection rates, recall rates, biopsy rates, consensus rates and corresponding differences in AI and control group (propensity score controlling for reader set and AI prediction and additionally for age, screening round, breast density, and supervision).

Extended Data Table 4 | Average Treatment Effect (ATE) via Inverse Propensity Score Weighting (IPTW) and Trimming

		Number screening exams (%)	Breast cancer detection rate (per 1,000 women screened)			Recall rate (per 1,000 women screened)		
			AI group	Control group	Model-based percent difference [95% CI]	AI group	Control group	Model-based percent difference [95% CI]
Overlap weighting (ATO)		461,818 (100%)	6.7	5.7	+17.6% [+5.7%, +30.8%]	37.4	38.3	–2.5% [–6.5%, +1.7%]
IPTW (ATE)	**PS Trimming**							
	[0.00, 1.00] *no trimming*	461,818 (100%)	6.7	5.8	14.4% [–16.7%, 57.1%]	42.4	41.6	1.8% [–6.7%, 11.1%]
	[0.05, 0.95]	274,187 (59.4%)	6.5	5.7	14.9% [2.5%, 28.7%]	36.6	38.6	–5.2% [–9.5%, –0.7%]
	[0.10, 0.90]	253,207 (54.8%)	6.7	5.7	17.0% [4.5%, 31.0%]	36.8	38.1	–3.5% [–7.8%, 0.9%]
	[0.15, 0.85]	232,057 (50.2%)	6.8	5.7	19.2% [6.4%, 33.5%]	36.7	37.6	–2.4% [–6.7%, 2.2%]
	[0.20, 0.80]	208,075 (45.1%)	6.7	5.8	16.8% [3.9%, 31.3%]	35.9	36.9	–2.3% [–6.9%, 2.4%]
	[0.25, 0.75]	174,415 (37.8%)	6.9	5.7	21.0% [6.9%, 36.9%]	36.7	35.9	2.1% [–2.9%, 7.4%]
	[0.30, 0.70]	139,857 (30.3%)	6.4	5.5	16.8% [1.6%, 34.3%]	35.6	35.8	–0.7% [–6.1%, 5.0%]

Number of included screening examinations and results (breast cancer detection and recall rates) for different propensity score weighting schemes (overlap weighting and IPTW with various trimming cut-offs).

nature portfolio

Corresponding author(s): Alexander Katalinic

Last updated by author(s): Oct 28, 2024

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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□	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
□	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
□	☒	A description of all covariates tested
□	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
□	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	□	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	□	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
□	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	□	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection: Data was collected via SQL from the anonymized evaluation database.

Data analysis: All analyses were conducted with R 4.1.3 using the packages PSweight 1.2.0, marginaleffects 0.18 and dagitty 0.3.1., as well as Python 3.10 using the package dowhy 0.11.1.
The statistical analysis plan is described in the methods section of the manuscript. The original analysis plan had to be updated for reasons detailed there as well. The code is available via Zenodo (https://doi.org/10.5281/zenodo.10822135), see also the corresponding statement in the manuscript.

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- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data on the procedure, outcomes, participants and detected cancers were retrieved from the standardised documentation of the official German mammography screening programme (MaSc and MammaSoft databases), linked to the data of the AI system, and then transferred in anonymised form to an evaluation database. See the study protocol, available here: https://pure.uni-luebeck.de/ws/portalfiles/portal/62001433/PRAIM_study_protocol_v2.0_final.pdf

The anonymised analysis data set including individual participant data and a data dictionary defining each field is available at Dryad https://datadryad.org/stash/dataset/doi:10.5061/dryad.zs7h44jgn. Detailed information on sensitivity analyses as well as the simulation study are available from nora.eisemann@uksh.de and will be answered within 3 months.
The specific AI models used in this publication are available for external research collaborations for researchers who provide a methodologically sound proposal. Proposals should be directed to stefan.bunk@vara.ai and will be answered within 1 month.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	The study deals with breast cancer detection in the context of the German mammography screening. Only those registered as women in the registry office are invited to this programme.
Reporting on race, ethnicity, or other socially relevant groupings	No data on race, ethnicity or other socially relevant groupings are collected in the German mammography screening programme.
Population characteristics	The study population consists of women aged 50 to 69 years, who participate in the German Mammography Screening Programme. Detailed population statistics across both study arms are given in Table 1.
Recruitment	All women attending screening at one of the 12 screening sites in the study time frame were included in the study, no exclusion criteria.
Ethics oversight	The study was approved by the Ethics Committee of the University of Lübeck (22-043). In brief, the study is a non-interventional, observational study with no additional risks for the patients. Only data routinely collected from the mammography screening program linked to the AI system was used. The data were transferred to an anonymized database for analysis. Therefore, the ERB waived the need for informed consent for the study. Further details can be found in the study protocol (https://pure.uni-luebeck.de/ws/portalfiles/portal/62001433/PRAIM_study_protocol_v2.0_final.pdf)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	A sample size of 200,000 women per study arm was targeted for assessing non-inferiority of AI in breast cancer detection rate (BCDR) with the originally planned analysis. The sample size was based on a power analysis via a simulation study with 10,000 simulation runs and a target of 80% power. After the described necessary change of analysis plan was recognized (see methods section), a simulation study (1,000 simulation runs) was conducted to (1) identify a statistical method that can successfully correct for the described reading behaviour bias when estimating the effect of AI and (2) estimate the expected power for each considered statistical method, given the originally planned study accrual. Only one of the considered methods – a simple regression model with cancer detection (yes/no) as outcome variable, intervention (AI vs. control group) as predictor, a quasibinomial error distribution, and overlap weighting using propensity scores – provided unbiased results and a sufficiently high power (94.6%) in the new simulation study. In the end, data from 461,818 women (260,739 in AI group, 201,079 in control group) were included.
Data exclusions	1303 women were excluded because of technical issues, cancellation of the screening process by the women or unfinished screening process.

Replication	Results can be reproduced given the publicly available data in Dryad and code in Zenodo. NE, HB, and SB checked the correctness of the results. We report several sensitivity analyses in the manuscript and results are shown in the extended data.
Randomization	No randomization was performed (real-world data study).
Blinding	Assignment of study arm was unknown to women and radiographers as it was not yet assigned at the time of image acquisition. No blinding of radiologists was performed/possible.

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We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	German Clinical Trials Register (DRKS00027322) (https://drks.de/search/en/trial/DRKS00027322)
Study protocol	Available here: https://pure.uni-luebeck.de/ws/portalfiles/portal/62001433/PRAIM_study_protocol_v2.0_final.pdf
Data collection	Between July 1, 2021, and February 23, 2023, data from all screened women was collected from 12 screening sites across Germany (Mittelrhein, Niedersachsen-Süd-West, Niedersachsen-Nord, Hannover, Herford/Minden-Lübbecke, Steinfurt, Köln rechtsrheinisch / Leverkusen, Wuppertal / Remscheid / Solingen / Mettmann, Niedersachsen-Mitte, Südwestliches Schleswig-Holstein, Wiesbaden, Niedersachsen-Nordwest).
Outcomes	The primary outcomes were breast cancer detection and recall rate. Breast cancer has to be confirmed either through pre-operative biopsy or surgical biopsy. Recall was defined as a woman being reinvited for further diagnostic examinations. Secondary outcomes were the AI metrics (normal/not normal; safety net) and their role in diagnosis, as well as the screen-reading workload (reading times stratified by AI prediction).

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a