Use of artificial intelligence for image analysis in breast cancer screening programmes: systematic review of test accuracy

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ABSTRACT

OBJECTIVE
To examine the accuracy of artificial intelligence (AI) for the detection of breast cancer in mammography screening practice.

DESIGN
Systematic review of test accuracy studies.

DATA SOURCES
Medline, Embase, Web of Science, and Cochrane Database of Systematic Reviews from 1 January 2010 to 17 May 2021.

ELIGIBILITY CRITERIA
Studies reporting test accuracy of AI algorithms, alone or in combination with radiologists, to detect cancer in women’s digital mammograms in screening practice, or in test sets. Reference standard was biopsy with histology or follow-up (for screen negative women). Outcomes included test accuracy and cancer type detected.

STUDY SELECTION AND SYNTHESIS
Two reviewers independently assessed articles for inclusion and assessed the methodological quality of included studies using the QUality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. A single reviewer extracted data, which were checked by a second reviewer. Narrative data synthesis was performed.

RESULTS
Twelve studies totalling 131 822 screened women were included. No prospective studies measuring test accuracy of AI in screening practice were found. Studies were of poor methodological quality. Three retrospective studies compared AI systems with the clinical decisions of the original radiologist, including 79 910 women, of whom 1878 had screen detected cancer or interval cancer within 12 months of screening. Thirty four (94%) of 36 AI systems evaluated in these studies were less accurate than a single radiologist, and all were less accurate than consensus of two or more radiologists. Five smaller studies (1086 women, 520 cancers) at high risk of bias and low generalisability to the clinical context reported that all five evaluated AI systems (as standalone to replace radiologist or as a reader aid) were more accurate than a single radiologist reading a test set in the laboratory. In three studies, AI used for triage screened out 53%, 45%, and 50% of women at low risk but also 10%, 4%, and 0% of cancers detected by radiologists.

CONCLUSIONS
Current evidence for AI does not yet allow judgement of its accuracy in breast cancer screening programmes, and it is unclear where on the clinical pathway AI might be of most benefit. AI systems are not sufficiently specific to replace radiologist double reading in screening programmes. Promising results in smaller studies are not replicated in larger studies. Prospective studies are required to measure the effect of AI in clinical practice. Such studies will require clear stopping rules to ensure that AI does not reduce programme specificity.

STUDY REGISTRATION
Protocol registered as PROSPERO CRD42020213590.

WHAT IS ALREADY KNOWN ON THIS TOPIC
A recent scoping review of 23 studies on artificial intelligence (AI) for the early detection of breast cancer highlighted evidence gaps and methodological concerns about published studies
Published opinion pieces claim that the replacement of radiologists by AI is imminent
Current mammography screening is repetitive work for radiologists and misses 15-35% of cancers—a prime example of the sort of role we would expect AI to be fulfilling

WHAT THIS STUDY ADDS
This systematic review of test accuracy identified 12 studies, of which only one was included in the previous review
Current evidence on the use of AI systems in breast cancer screening is of insufficient quality and quantity for implementation into clinical practice
In retrospective test accuracy studies, 94% of AI systems were less accurate than the original radiologist, and all were less accurate than original consensus of two radiologists; prospective evaluation is required.
more likely to be associated with fewer deaths.\textsuperscript{5} Cancer is detected in between 0.6% and 0.8% of women during screening.\textsuperscript{6,7} Breast screening programmes also miss between 15% and 35% of cancers owing either to error or because the cancer is not visible or perceptible to the radiologist. Some of these missed cancers present symptomatically as interval cancers.\textsuperscript{8}

Considerable interest has been shown in the use of artificial intelligence (AI) either to complement the work of humans or to replace them. In 2019, 3.8% of all peer reviewed scientific publications worldwide on Scopus related to AI.\textsuperscript{9} Claims have been made that image recognition using AI for breast screening is better than experienced radiologists and will deal with some of the limitations of current programmes.\textsuperscript{10-13} For instance, fewer cancers might be missed because an AI algorithm is unaffected by fatigue or subjective diagnosis,\textsuperscript{14,15} and AI might reduce workload or replace radiologists completely.\textsuperscript{11,12}

AI might, however, also exacerbate harm from screening. For example, AI might alter the spectrum of disease detected at breast screening if it differentially detects more microcalcifications, which are associated with lower grade ductal carcinoma in situ. In such a case, AI might increase rates of overdiagnosis and overtreatment and alter the balance of benefits and harms.

Autopsy studies suggest that around 4\% of women die with, not because of, breast cancer,\textsuperscript{16} so there is a “reservoir” of clinically unimportant disease, including incidental in situ carcinoma, which might be detected by AI. The spectrum of disease is correlated with mammographic features (for example, ductal carcinoma in situ is often associated with microcalcifications). Therefore, the cases on which AI systems were trained, and the structures within the AI system, might considerably affect the spectrum of disease detected. These structures and algorithms within an AI system are not always transparent or explicable, making interpretation a potential problem. Unlike human interpretation, how or why an algorithm has made a decision can be difficult to understand (known as the “black box” problem).\textsuperscript{17} Unlike human decision makers, algorithms do not understand the context, mode of collection, or meaning of viewed images, which can lead to the problem of “shortcut” learning,\textsuperscript{18} whereby deep neural networks reach a conclusion to a problem through a shortcut, rather than the intended solution. Thus, for example, DeGrave et al\textsuperscript{19} have shown how some deep learning systems detect covid-19 by means of confounding factors, rather than pathology, leading to poor generalisability. Although this problem does not preclude the use of deep learning, it highlights the importance of avoiding potential confounders in training data, an understanding of algorithm decision making, and the critical role of rigorous evaluation.

This review was commissioned by the UK National Screening Committee to determine whether there is sufficient evidence to use AI for mammographic image analysis in breast screening practice. Our aim was to assess the accuracy of AI to detect breast cancer when integrated into breast screening programmes, with a focus on the cancer type detected.

Methods

Data sources

Our systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of diagnostic test accuracy (PRISMA-DTA) statement.\textsuperscript{20} The review protocol is registered on PROSPERO (international prospective register of systematic reviews).

We conducted literature searches for studies published in English between 1 January 2010 and 9 September 2020 and updated our searches on 17 May 2021. The search comprised four themes: breast cancer, artificial intelligence, mammography, and test accuracy or randomised controlled trials. A number of additional synonyms were identified for each theme. Databases searched were Medline (Ovid), Embase (Ovid); Web of Science, and the Cochrane Database of Systematic Reviews (CENTRAL). Details of the search strategies are shown in supplementary appendix 1. We screened the reference lists of systematic reviews and included additional relevant studies and contacted experts in the field.

Study selection

Two reviewers independently reviewed the titles and abstracts of all retrieved records against the inclusion criteria, and subsequently, all full text publications. Disagreements were resolved by consensus or discussion with a third reviewer.

We applied strict inclusion/exclusion criteria to focus on the evaluation of the integration of AI into a breast cancer screening programme rather than the development of AI systems. Studies were eligible for inclusion if they reported test accuracy of AI algorithms applied to women’s digital mammograms to detect breast cancer, as part of a pathway change or a complete read (reading+decision resulting in classification). Eligible study designs were prospective test accuracy studies, randomised controlled trials, retrospective test accuracy studies using geographical validation only, comparative cohort studies, and enriched test set multiple reader multiple case laboratory studies. The enriched test set multiple reader multiple case laboratory studies included retrospective data collection of images and prospective classification by standalone AI or AI assisted radiologists. The reference standard was cancer confirmed by histological analysis of biopsy samples from women referred for further tests at screening and preferably also from symptomatic presentation during follow-up.

All studies will necessarily have differential verification because not all women can or should be biopsied. In prospective test accuracy studies this will not introduce significant bias because those positive on either an index or comparator test will receive follow-up tests. In retrospective studies and enriched test set studies (with prospective readers), the decision
as to whether women receive biopsy or follow-up is based on the decision of the original reader, which introduces bias because cancer, when present, is more likely to be found if the person receives follow-up tests after recall from screening. We assessed this using the QUality Assessment of Diagnostic Accuracy Studies-2 tool (QUADAS-2). When AI is used as a pre-screen to triage which mammograms need to be examined by a radiologist and which do not, we also accepted a definition of a normal mammogram as one free of screen detected cancer based on human consensus reading, as this allows estimation of accuracy in the triage.

We excluded studies that reported the validation of AI systems using internal validation test sets (eg, x-fold cross validation, leave one out method), split validation test sets, and temporal validation test sets as they are prone to overfitting and insufficient to assess the generalisability of the AI system. Furthermore, studies were excluded if less than 90% of included mammograms were complete full field digital mammography screening mammograms. Additionally, studies were excluded if the AI system was used to predict future risk of cancer, if only detection of cancer subtypes was reported, if traditional computer aided detection systems without machine learning were used, or if test accuracy measures were not expressed at any clinically relevant threshold (eg, area under the curve only) or did not characterise the trade-off between false positives and false negative results (eg, sensitivity for cancer positive samples only). Finally, we excluded simulation results of the hypothetical integration of AI with radiologists’ decisions as they do not reliably estimate radiologist behaviour when AI is applied.

Data extraction and quality assessment
One reviewer extracted data on a predesigned data collection form. Data extraction sheets were checked by a second reviewer and any disagreements were resolved by discussion. Study quality was assessed independently by two reviewers using QUADAS-221 tailored to the review question (supplementary appendix 2).

Data analysis
The unit of analysis was the woman. Data were analysed according to where in the pathway AI was used (for example, standalone AI to replace one or all readers, or reader aid to support decision making by a human reader) and by outcome. The primary outcome was test accuracy. If test accuracy was not reported, we calculated measures of test accuracy where possible. Important secondary outcomes were cancer type and interval cancers. Cancer type (eg, by grade, stage, size, prognosis, nodal involvement) is important in order to estimate the effect of cancer detection on the benefits and harms of screening. Interval cancers are also important because they have worse average prognosis than screen detected cancers,22 and by definition, are not associated with overdiagnosis at screening. We synthesised studies narratively owing to their small number and extensive heterogeneity. We plotted reported sensitivity and specificity for the AI systems and any comparators in a receiver operating characteristic plot using the package “ggplot2”23 in R version 3.6.1 (Vienna, Austria).24

Patient and public involvement
The review was commissioned on behalf of the UK National Screening Committee (UKNSC), and the scope was determined by the UKNSC adult reference group, which includes lay members. The results were discussed with patient contributors.

Results
Study selection
Database searches yielded 4016 unique results, of which 464 potentially eligible full texts were assessed. Four additional articles were identified: one through screening the reference lists of relevant systematic reviews, one through contact with experts, and two by hand searches. Overall, 13 articles reporting 12 studies were included in this review (see supplementary fig 1 for full PRISMA flow diagram). Exclusions on full text are listed in supplementary appendix 3.

Characteristics of included studies
The characteristics of the 12 included studies are presented in table 1, table 2, and table 3 and in supplementary appendix 4, comprising a total of 131 822 screened women. The AI systems in all included studies used deep learning convolutional neural networks. Four studies evaluated datasets from Sweden,26 35 36 three of which had largely overlapping populations,26 35 36 one from the United States and Germany,22 one from Germany,25 one from the Netherlands,33 one from Spain31 and four from the US.28-30 37 Four studies enrolled women consecutively or randomly,25 27 31 36 while the remaining studies selected cases and controls to enrich the dataset with patients with cancer. Three studies included all patients with cancer and a random sample of those without cancer.26 35 36 One study included all patients with cancer and controls matched by age and breast density.28 In two studies, patients and controls were sampled to meet predefined distributions and were reviewed by one radiologist to exclude images not meeting quality standards and images with obvious signs of cancer.30 32 One study used a range of rules for selection, including by perceived difficulty and mammographic features.33 Finally, one study included only false negative mammograms.37 No prospective test accuracy studies in clinical practice were included, only retrospective test accuracy studies,25-27 29 31 35 36 and enriched test set multiple reader multiple case laboratory studies.28 30 32 33 37 Of these enriched test set laboratory studies, three reported test accuracy for a single AI read as a reader aid.30 32 37 Another nine studies reported test accuracy for a single AI read as a standalone system in a retrospective test accuracy study 25-27 29 31 35 36 or an enriched test set multiple reader multiple case laboratory study.28 33
In studies of standalone systems, the AI algorithms provided a cancer risk score that can be turned into a binary operating point to classify women as high risk (recall) or low risk (no recall). The in-house or commercial standalone AI systems (table 1, table 2, table 3) were evaluated in five studies as a replacement for one or all radiologists. Three studies compared the performance of the AI system with the original decision recorded in the database, based on either a single US radiologist or two radiologists with consensus within the Swedish screening programme. Two studies compared the performance of the AI system with the average performance of nine Dutch single radiologists and five US single radiologists, respectively, who read the images under laboratory conditions. Four commercial AI systems were evaluated as a pre-screen to remove normal cases or were used as a post-screen of negative mammograms after double reading to predict interval and next round screen detected cancers.

In studies of assistive AI, the commercial AI systems provided the radiologist with a level of suspicion for the area clicked. All three studies compared the test accuracy of the AI assisted read with an unassisted read by the same radiologists under laboratory conditions. The experience of the radiologists in the reader assisted studies ranged from 3 to 25 years (median 9.5 years) in 14 radiologists, from 0 to 25 years (median 8.5 years) in 14 American Board of Radiology and Mammography Quality Standards Act (MQSA) certified radiologists, and from less than 5 to 42 years in 7 MQSA certified radiologists. The role of the AI system in the screening pathway in the 12 studies is summarised in figure 1.

Assessment of risk of bias and applicability
The evidence for the accuracy of AI to detect breast cancer was of low quality and applicability across all studies (fig 2) according to QUADAS-2 (supplementary

### Table 1 | Summary of study characteristics for studies using AI as standalone system

| Study          | Study design                  | Population                                      | Mammography vendor                  | Index test                                                                 | Comparator                                                                 | Reference standard                                                                 |
|----------------|-------------------------------|-------------------------------------------------|--------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Lotter 2021    | Enriched test set MRMC laboratory study (accuracy of a read) | 285 women from 1 US health system with 4 centres (46.0% screen detected cancer); age and ethnic origin NR | Hologic 100% | In-house AI system (DeepHealth); threshold NR (set to match readers sensitivity and specificity, respectively) | 5 MQSA certified radiologists (US), single reading; threshold of BI-RADS scores 3, 4, and 5 considered recall | Cancer: pathology confirmed cancer within 3 months of screening; confirmed negative: a negative examination followed by an additional BI-RADS score 1 or 2 interpretation at the next screening examination 9-19 months later |
| Schaffer 2020  | Retrospective test accuracy study (accuracy of a read) | 68 008 consecutive women from 1 Swedish centre (1.1% cancer within 12 months of screening) mean age 53.3 (SD 9.4) | NR | 4 in-house AI systems: 1 top performing model submitted to the DREAM challenge, 1 ensemble method of the eight best performing models (CEM), CEM combined with reader decision (single reader or consensus reading); threshold: corresponding to the sensitivity of single and consensus reading, respectively | Original radiologist decision (Sweden); (1) single reader (R1; R2), (2) consensus reading, no threshold | Cancer: tissue diagnosis within 12 months of screening; non-cancer: no cancer diagnosis ≤12 months after screening |

AI=artificial intelligence; BI-RADS=breast imaging reporting and data system; CEM=challenge ensemble method; DREAM=Dialogue on Reverse Engineering Assessment and Methods; IQR=interquartile range; MQSA=Mammography Quality Standards Act; MRMC=multiple reader multiple case; NR=not reported; R1=first reader; R2=second reader; SD=standard deviation.
Table 3 | Summary of study characteristics for studies using AI as reader aid

| Study                  | Study design  | Population                       | Mammography vendor | Index test                                                                 | Comparator                      | Reference standard                                                                 |
|-----------------------|---------------|----------------------------------|---------------------|----------------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------|
| Paclit 2020           | Enriched test set MRMC laboratory study, counterbalance design (accuracy of a read) | 240 women from 1 US centre (50.0% cancer), mean age 59 (range 37-85) | Siemens 70% Hologic 30% | Transpara version 1.6.0 (Screenpoint Medical BV, Nijmegen, Netherlands); preselection of probably normal mammograms; Transpara risk score of 1-10, different cutoff points evaluated; optimal cutoff point ≤7 low risk | No comparator as human consensus reading decisions used as reference standard for screen negative results | Cancer: biopsy proven screen detected cancers; non-cancer: no information about follow-up for the normal examinations was available. Available, for this review, a normal mammogram was defined as free of screen detected cancer based on human consensus reading |
| Rodriguez-Ruiz 2019   | Enriched test set MRMC laboratory study, fully crossed (accuracy of a read) | 240 women (120 from 1 US centre and 120 from 1 German centre; 4.1% cancer), median age 62 (range 39-89) | Siemens 50% Hologic 50% | Transpara, version 1.6.0 (ScreenPoint Medical BV, Nijmegen, Netherlands); preselection of probably normal mammograms; Transpara risk score of 1-10; different cutoff points evaluated; chosen cutoff point ≤7 low risk | No comparator as human consensus reading decisions used as reference standard for screen negative results | Cancer: histopathologic results of biopsy, screen detected via FFDM or DBT and interval cancers within 24 months of screening; non-cancer: normal reading with 2 years' follow-up |
| Watanabe 2019         | Enriched test set MRMC laboratory study, first without AI support, then AI aided (accuracy of a read) | 122 women from 1 US centre (73.8% cancer, all false negative mammograms), mean age 65.4 (range 40-90) | Siemens 70% Hologic 30% | Transpara version 1.6.0 (Screenpoint Medical BV, Nijmegen, Netherlands); preselection of probably normal mammograms; Transpara risk score of 1-10, different cutoff points evaluated; optimal cutoff point ≤7 low risk | No comparator as human consensus reading decisions used as reference standard for screen negative results | Cancer: biopsy proven screen detected cancers; non-cancer: no information about follow-up for the normal examinations was available. Available, for this review, a normal mammogram was defined as free of screen detected cancer based on human consensus reading |

AI=artificial intelligence, DBT=digital breast tomosynthesis, FFDM=full field digital mammography, IQR=interquartile range, NR=not reported, SD=standard deviation.
Sensitivity to detect cancer detected by screening radiologist
No follow-up of screening radiologist test negatives
Do not know how different prevalence might affect radiologists

Recall
No recall
Arbitration

3 retrospective test accuracy studies compared with original reader decision R1, R2, consensus
2 enriched MRMC laboratory studies compared with average single reader
Range Δ % sens compared with single reader: -10.4 (n=8805) to +14.2 (n=285)
Δ % sens compared with consensus: -3.1 (n=3007)
Range Δ % spec compared with single reader: -8.7 (n=68 008) to +24.0 (n=285)
Δ % spec compared with consensus: -17.3 (n=68 008)

Do not know how AI might affect behaviour of other radiologists and arbitration

4 retrospective studies
Transpara v1.4.0/v1.6.0 score
≤2: sens =100%/100%; spec = 19%/15%
≤5: sens = 90%/96%; spec = 53%/45%
≤7: sens = 84%/88.5% to 92%; spec = 73%/66% to 72.0%
Lunit v5.5.0.16 score
Lowest 50%: sens = 100%; spec = 50%
Lowest 90%: sens = 96%; spec = 90%

Review findings:
No studies evaluating AI as a pathway change
No evidence of impact of AI on screening practice
No prospective evidence (either RCT, test accuracy study or cohort study)
Available evidence of high risk of bias (enriched study design, laboratory effect, differential verification, insufficient follow-up)

Breast screening mammograms

Pre-screen to remove patients at low risk for single or no radiologist review

AI replaces all readers
AI replaces one reader

Recall
No recall

Arbitration

3 enriched MRMC laboratory studies comparing radiologist with and without AI
Range Δ % sens: +3 (n=240) to +11 (n=122);
Range Δ % spec: -0.9 (n=122) to +2.0 (n=240)

Studies affected by laboratory effect, so radiologist comparator not generalisable to clinical practice
Do not know how AI as reader aid might affect subsequent arbitration

Recall
No recall

Post-screen to identify patients missed by double reading and consensus

Double reading + consensus negative

No recall

Recall

1 retrospective study
Lunit v5.5.0.16 score
Highest 2%: sens = 19%; spec = 98%

Sensitivity to detect interval and/or next screen detected cancers (that is, cancers missed by radiologists)
Do not know how knowledge of this “back-up” might affect behaviour of radiologists

Fig 1 | Overview of published evidence in relation to proposed role in screening pathway. Purple shade=current pathway; orange shade=AI added to pathway; green shade=level of evidence for proposed AI role. AI=artificial intelligence; +/−=high/low risk of breast cancer, person icon=radiologist reading of mammograms as single, first, or second reader; MRMC=multiple reader multiple case; R1, R2=reader 1, reader 2; RCT, randomised controlled trial; sens=sensitivity; spec=specificity
appendix 2). Only four studies (albeit the four largest comprising 85% of all 131,822 women in the review) enrolled women consecutively or randomly, with a cancer prevalence of between 0.64% and 1.1%.25 27 31 36 The remaining studies used enrichment leading to breast cancer prevalence (ranging from 7.4%26 to 73.8%37), which is atypical of screening populations. Five studies28 30 32 33 37 used reading under “laboratory” conditions at risk of introducing bias because radiologists read mammograms differently in a retrospective laboratory experiment than in clinical practice.79 Only one of the studies used a prespecified test threshold which was internal to the AI system to classify mammographic images.31

The reference standard was at high (n=8) or unclear (n=3) risk of bias in 11/12 studies. Follow-up of screen negative women was less than two years in seven studies,25-28 30 32 36 which might have resulted in underestimation of the number of missed cancers and overestimation of test accuracy. Furthermore, in retrospective studies of routine data the choice of patient management (biopsy or follow-up) to confirm disease status was based on the decision of the original radiologist(s) but not on the decision of the AI system. Women classified as positive by AI who did not receive biopsy based on the original radiologists’ decision only, received follow-up to confirm disease status. Therefore, cancers with a lead time from screen to symptomatic detection longer than the follow-up time in these studies will be misclassified as false positives for the AI test, and cancers which would have been overdia gnosed and overtreated after detection by AI would not be identified as such because the type of cancer that can indicate overdiagnosis, is unknown. The direction and magnitude of bias is complex and dependent on the positive and negative concordance between AI and radiologists but is more likely to be in the direction of overestimation of sensitivity and underestimation of specificity.

The applicability to European or UK breast cancer screening programmes was low (fig 2). None of the studies described the accuracy of AI integrated into a clinical breast screening pathway or evaluated the accuracy of AI prospectively in clinical practice in any country. Only two studies compared AI performance with the decision from human consensus reading.35 36 The studies included only interval cancers within 12 months of screening, which is not typical for screening.

![Fig 2 | Overview of concerns about risk of bias and applicability of included studies. *Low concerns about applicability for consensus reading; high concerns about applicability for single reading as comparator test. †Low concerns about risk of bias and low applicability for the previous screening round (biopsy proven cancer or at least two years’ follow-up); high concerns about risk of bias and high applicability for the current screening round (biopsy-proven cancer but no follow-up of test negatives)
| Study                                      | Index cancer (manufacturer) | Comparator (reader) | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Δ % Sensitivity, P value or (95% CI) | Δ % Specificity, P value or (95% CI) |
|-------------------------------------------|----------------------------|--------------------|--------------------------|--------------------------|--------------------------------------|--------------------------------------|
| **Standalone AI (5 studies):**            |                            |                    |                          |                          |                                      |                                      |
| Lotter 2021                               | AI (translating single reader) | Comparator (reader) | 96.2 (91.7 to 99.2)     | 95.2 (91.7 to 99.2)     | +14.2, p<0.001                       |                                      |
| Mckenna 2020                              | AI (translating single reader) | Comparator (reader) | 96.0 (91.7 to 99.2)     | 95.2 (91.7 to 99.2)     | +14.2, p<0.001                       |                                      |
| Salim 2020                                | AI (translating single reader) | Comparator (reader) | 82.0 (77.1 to 86.9)     | 81.1 (77.1 to 86.9)     | +14.2, p<0.001                       |                                      |
| Rodríguez-Ruiz 2019                      | AI (Transpara version 1.4.0) | Comparator (reader) | 80 (70 to 90)           | 79 (70 to 90)           | +14.2, p<0.001                       |                                      |
| Salim 2020                                | AI (in-house)               | Comparator (reader) | 82.0 (77.1 to 86.9)     | 81.1 (77.1 to 86.9)     | +14.2, p<0.001                       |                                      |
| **AI for triage pre-screen (4 studies):** |                            |                    |                          |                          |                                      |                                      |
| Balla 2020                                | AI as pre-screen (translating version 1.0) | Comparator (reader) | 99.0 (98.5 to 99.5)     | 98.5 (98.5 to 99.5)     | +0.5, P<0.05                         |                                      |
| Dembrowski 2020                           | AI as pre-screen (translating version 1.0) | Comparator (reader) | 99.0 (98.5 to 99.5)     | 98.5 (98.5 to 99.5)     | +0.5, P<0.05                         |                                      |
| **AI for triage post-screen (1 study):**  |                            |                    |                          |                          |                                      |                                      |
| Dembrowski 2020                           | AI as post-screen (translating version 1.0) | Comparator (reader) | 99.0 (98.5 to 99.5)     | 98.5 (98.5 to 99.5)     | +0.5, P<0.05                         |                                      |
| **AI as reader aid (3 studies):**         |                            |                    |                          |                          |                                      |                                      |
| Pacić 2020                                | AI support (MammoScreen version 1.0) | Comparator (reader) | 86 (81 to 90)           | 85 (81 to 90)           | +1, P=0.05                           |                                      |
| **Table 4 | Summary of test accuracy outcomes**     |                            |                    |                          |                          |                                      |                                      |
Analysis

AI as a standalone system to replace radiologist(s)

No prospective test accuracy studies, randomised controlled trials, or cohort studies examined AI as a standalone system to replace radiologists. Test accuracy of the standalone AI systems and the human comparators from retrospective cohort studies is summarised in table 4. All point estimates of the accuracy of AI systems were inferior to those obtained by consensus of two radiologists in screening with a single radiologist (fig 3). Three studies compared AI accuracy with that of the original radiologist in clinical practice, the specificity of the top performing AI systems evaluated in the competitive phase on the independent Swedish dataset found the specificity of the top performing AI system (by Therapixel in a competition between 31 AI systems evaluated in the competitive phase on the independent Swedish dataset) was inferior in comparison with the original first radiologist (89% v 96.7%) and inferior also in comparison with the original consensus decision (88% v 96.7%) when the AI threshold was set to match the first reader’s sensitivity, respectively. The specificity of an ensemble method of the eight top performing AI systems remained inferior to that of the original first radiologist (92.5% v 96.7%) in comparison with the original first radiologist in clinical practice, the original single radiologist had superior sensitivity (67.4%) in comparison with the original consensus decision (61.4%, P=0.011), even in the same dataset that was used to choose the top performing eight.

AI as a standalone system for triage

Four studies used the Transpara versions 1.4.0 and 1.6.0 and Lunit version 5.5.0.16 AI systems, with reported outcomes for four of these studies included in table 4 (see also supplementary table S5 and supplementary figure S1). The Transpara version 1.4.0 and 1.6.0 AI systems and Lunit version 5.5.0 AI system outperformed the original single radiologist (2.1%, 77.4%, and 72.3% v 77.4%, respectively) in a laboratory setting, but the generalisability to clinical practice is unclear.28 33

Table 4 | Continued

| Study | Comparator | Comparator | Comparator | Comparator |
|-------|------------|------------|------------|------------|
| Phantom study | cmAssist | cmAssist | cmAssist | cmAssist |
| TP (%) | FP (%) | FN (%) | TN (%) | Sensitivity | Specificity |
| 98.7 | 98.7 | 98.7 | 98.7 | 98.7 | 98.7 |
| 98.7 | 98.7 | 98.7 | 98.7 | 98.7 | 98.7 |
| 98.7 | 98.7 | 98.7 | 98.7 | 98.7 | 98.7 |
| 98.7 | 98.7 | 98.7 | 98.7 | 98.7 | 98.7 |

AI=artificial intelligence; CEM=challenge ensemble method of eight top performing AIs from DREAM challenge; CI=confidence interval; DREAM=Dialogue on Reverse Engineering Assessment and Methods; FN=false negatives; FP=false positives; NA=not applicable; NR=not reported; TN=true negatives; TP=true positives.

**Inverse probability weighting: negative cases were upsampled 11 times using replacement weights, resulting in 7487 healthy women and a total simulated screening population of 75,534.**

¶Specificity estimates not based on exact numbers; the numbers were calculated by reviewers from reported proportions applied to 75,534 women (347 screen detected cancers and 74,987 healthy women).

**In enriched test set multiple reader multiple case laboratory studies where multiple readers assess the same images, there are considerable problems in summing 2x2 test data across readers.**
respectively, as a pre-screen to identify women at low risk whose mammograms required less or no radiological review.\textsuperscript{25-27} In this use, AI systems require high sensitivity so that few patients with cancer are excluded from radiological review, and only moderate specificity, which determines the radiology case load saved. In a retrospective consecutive German cohort (n=17,895, 0.64% cancer) the Transpara version 1.6.0 AI system achieved a sensitivity of 92% and a specificity of 66% at the Transpara score 7 to remove patients at low risk from double reading, and 96% sensitivity (45% specificity) at a Transpara score of 5.\textsuperscript{25} A Transpara version 1.4.0 score of 5 had 90% sensitivity and 53% specificity in a Swedish cohort (n=9,581, 0.71% cancer).\textsuperscript{27} Both studies reported 100% sensitivity at a score of 2 (and specificities of 15% and 19%, respectively). The threshold for classification (5\textsuperscript{25} and 5\textsuperscript{27}) was determined by exploring the full range of Transpara scores from 1 to 10 in the same dataset (fig 4A). In these studies, screen negative women were not followed up, so the sensitivity refers to detection of cancers which were detected by the original radiologists.

One study predefined the Transpara score of 7 to identify women at low risk in a Spanish cohort (n=15,986, 0.7% cancer, including 15 interval cancers within 24 months of follow-up) and achieved 88% sensitivity and 72% specificity.\textsuperscript{31} A Swedish case-control study (n=7,364, 7.4% cancer) used a range of thresholds to consider use of the Lunit version 5.5.0.16 AI system as a pre-screen to remove normal patients (fig 4A) and then as a post-screen of patients who were negative after double reading to identify additional cancers (interval cancers and next round screen detected cancers; fig 4B).\textsuperscript{26} Using 11 times upsampling of healthy women to simulate a screening population, they reported that use of AI alone with no subsequent radiologist assessment in the 50% and 90% of women with the lowest AI scores had 100% and 96% sensitivity and 50% and 90% specificity, respectively. AI assessment of negative mammograms after double reading detected 103 (19%) of 547 interval and next round screen detected cancers if the 2% women with the highest AI scores were post-screened (with a hypothetical perfect follow-up test).\textsuperscript{26}

None of these studies reported any empirical data on the effect on radiologist behaviour of integrating AI into the screening pathway.

**AI as a reader aid**

No randomised controlled trials, test accuracy studies, or cohort studies evaluated AI as a reader aid in clinical practice. The only three studies of AI as a reader aid reported accuracy of radiologists’ reading of an enriched test set in a laboratory environment, with limited generalisability to clinical practice. Sensitivity and specificity were reported as an average of 14,\textsuperscript{30} 14,\textsuperscript{37} or 7\textsuperscript{37} radiologists with and without the AI reader aid. Point estimates of the average sensitivity were higher for radiologists with AI support than for unaided reading (absolute difference +3.0%, P=0.046,\textsuperscript{32} +3.3%, P=0.021,\textsuperscript{30} and +11%, P=0.030\textsuperscript{37}) in all three studies of 240,\textsuperscript{30} 240,\textsuperscript{32} and 122\textsuperscript{37} women. The effect of AI support on average reader specificity in a laboratory setting was small (absolute difference +2.0%, P=0.06,\textsuperscript{32} +1.0%, P=0.63,\textsuperscript{30} and −0.9%,\textsuperscript{37} no P value reported; table 4).

**Cancer type**

Limited data were reported on types of cancer detected, with some evidence of systematic differences between different AI systems. Of the three retrospective cohort studies investigating AI as a standalone system to replace radiologist(s), only one reported measuring whether there was a difference between AI and radiologists in the type of cancer detected. One anonymised AI system detected more invasive cancers (82.8%) than a radiologist (radiologist 1: 76.7%; radiologist 2: 79.7%, n=640) and less ductal carcinoma in situ (83.5%) than a radiologist (radiologist 1: 89.4%; radiologist 2: 89.4%, n=85), though the grades of ductal carcinoma in situ and invasive cancer were not reported.\textsuperscript{35} This same AI system detected more stage 2 or higher invasive cancers (n=204, 78.4% than radiologist 1: 68.1% and radiologist 2: 68.1%).\textsuperscript{35} The other two anonymised AI systems detected fewer stage

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**Fig 3 | Study estimates of sensitivity and false positive rate (1−specificity) in receiver operating characteristic space by index test (artificial intelligence) and comparator (radiologist) for eight included studies. Comparators are defined as consensus of two readers and arbitration (radiologist consensus), or single reader decision/average of multiple readers (radiologist single/average). Vertical dashed lines represent specificity for screening programmes for Denmark (2% false positive rate),\textsuperscript{23} UK (3% false positive rate),\textsuperscript{63,65} and US (11% false positive rate).\textsuperscript{64} Retrospective test accuracy studies: Salim et al,\textsuperscript{35} Schaffter et al,\textsuperscript{36} and McKinney et al.\textsuperscript{29} Enriched test set multiple reader multiple case laboratory studies: Paclé et al,\textsuperscript{36} Watanabe et al,\textsuperscript{35} Rodriguez-Ruiz et al\textsuperscript{33} (Rodriguez-Ruiz 2019a in figure), Lotter 2021,\textsuperscript{28} and Rodriguez-Ruiz et al\textsuperscript{32} (Rodriguez-Ruiz 2019b in figure).**

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**Table 4 | Test accuracy and specificities in three randomised controlled trials**

| Test | Sensitivity | Specificity | Size | Radiologist single/average | Radiologist consensus | AI (index test) |
|------|-------------|-------------|------|---------------------------|----------------------|-----------------|
| Danish | 0.90 | 0.69 | 20,000 | 0.69 | 0.69 | 0.69 |
| English | 0.90 | 0.69 | 40,000 | 0.69 | 0.69 | 0.69 |
| US | 0.90 | 0.69 | 60,000 | 0.69 | 0.69 | 0.69 |
In an enriched test set multiple reader multiple case laboratory study, a standalone in-house AI model (DeepHealth Inc.) detected more invasive cancer (+12.7%, 95% confidence interval 8.5 to 16.5) and more ductal carcinoma in situ (+16.3%, 95% confidence interval 10.9 to 22.2) than the average single reader.28 This trend for higher performance of the AI model was also seen for lesion type, cancer size, and breast density.

In an enriched test set multiple reader multiple case laboratory study, addition of the CureMetrix AI system to assist readers increased detection of microcalcifications (n=17, +20%) preferentially in comparison with other mammographic abnormalities such as masses (n=73, +9%).32 Microcalcifications are known to be more associated with ductal carcinoma in situ than with invasive cancer, but the spectrum of disease was not directly reported.

Forty seven (87%) of 54 screen detected invasive cancers were classified as high risk using Transpara version 1.4.0 with a threshold of 5, in comparison with 14 (100%) of 14 microcalcifications.37 Using Transpara version 1.6.0 with a threshold of 7 as pre-screen, four additional cancers were classified as high risk by AI that had been missed by original double reading without consensus (two ductal carcinoma in situ, one low grade invasive ductal cancer, and one high grade invasive ductal cancer).31 No information on cancer type was reported for the two screen detected cancers that were classed by AI as low risk.

**Discussion**

**Main findings**

In this systematic review of AI mammographic systems for image analysis in routine breast screening, we identified 12 studies which evaluated commercially available or in-house convolutional neural network AI systems, of which nine included a comparison with radiologists. One of the studies reported that they followed STARD reporting guidelines.36 The six smallest studies (total 4183 women) found that AI was more accurate than single radiologists.28-30 32 33 36 The radiologists in five of six of these studies were examining the mammographic images of 932 women in a laboratory setting, which is not generalisable to clinical practice. In the remaining study, the comparison was with a single reading in the US with an accuracy below that expected in usual clinical practice.29 Whether this lower accuracy was due to case mix or radiologist expertise is unclear. In two of the largest retrospective cohort studies of AI to replace radiologists in Europe (n=76813 women),35 36 all AI systems were less accurate than consensus of two radiologists, and 34 of 36 AI systems were less accurate than a single reader. One unpublished study is in line with these findings.40 This large retrospective study (n=275900 women) reported higher sensitivity of AI in comparison with the original first reader decision but lower specificity, and the AI system was less
accurate than consensus reading.²⁰ Four retrospective studies²²–²⁷ ³¹ indicated that at lower thresholds, AI can achieve high sensitivity so might be suitable for triaging which women should receive radiological review. Further research is required to determine the most appropriate threshold as the only study which prespecified the threshold for triage achieved 88.5% sensitivity.³¹ Evidence suggests that the accuracy and spectrum of disease detected between different AI systems is variable.

Considerable heterogeneity in study methodology was found, some of which resulted in high concerns over risk of bias and applicability. Compared with consecutive sampling, case-control studies added bias by selecting cases and controls to achieve an enriched sample. The resulting spectrum effect could not be assessed because studies did not adequately report the distribution of original radiological findings, such as the distribution of the original BI-RADS scores. The effect was likely to be greater, however, when selection was based on image or cancer characteristics rather than if enrichment was achieved by including all available women with cancer and a random sample of those who were negative.

The overlap of populations in three Swedish studies means that they represent only one rather than three separate cohorts.²⁶ ³⁵ ³⁶ Performance of the AI system might have been overestimated if the same AI system read the same dataset more than once and, therefore, could have had the opportunity to learn. We could not confirm this as the three AI systems used by Salim et al were anonymised.³⁵

The included studies have some variation in reference standard for the definition of normal cases, from simply consensus decision of radiologists at screening, to one to three years of follow-up. This inconsistency means accuracy estimates are comparable within, but not between, studies. Overall, the current evidence is a long way from the quality and quantity required for implementation in clinical practice.

Strengths and limitations
We followed standard methodology for conducting systematic reviews, used stringent inclusion criteria, and tailored the quality assessment tool for included studies. The stringent inclusion criteria meant that we included only geographical validation of test sets in the review—that is, at different centres in the same or different countries, which resulted in exclusion of a large number of studies that used some form of internal validation (where the same dataset is used for training and validation—for example, using cross validation or bootstrapping). Internal validation overestimates accuracy and has limited generalisability, and might also result in overfitting and loss of generalisability as the model fits the trained data extremely well but to the detriment of its ability to perform with new data. The split sample approach similarly does not accurately reflect a model’s generalisability.³³

Temporal validation is regarded as an approach that lies midway between internal and external validation and has been reported by others to be sufficient in meeting the expectations of an external validation set to evaluate the effectiveness of AI.³² For screening, however, temporal validation could introduce bias because, for instance, the same women might attend repeat screens, and be screened by the same personnel using the same machines. Only geographical validation offers the benefits of external validation and generalisability.³²

We also excluded computer aided detection for breast screening using systems that were categorised as traditional. The definition was based on expert opinion and the literature.¹⁴ The distinction is not clear cut and this approach might have excluded relevant studies that poorly reported the AI methods or used a combination of methods.

We extracted binary classifications from AI systems, and do not know how other information on a recall to assessment form from a radiologist, such as mammographic characteristics or BI-RADS score/level of suspicion, might affect the provision of follow-up tests. In addition, AI algorithms are short lived and constantly improve. Reported assessments of AI systems might be out of date by the time of study publication, and their assessments might not be applicable to AI systems available at the time.

The exclusion of non-English studies might have excluded relevant evidence. The available methodological evidence suggests that this is unlikely to have biased the results or affected the conclusions of our review.⁴⁴ ⁴⁵ Finally, the QUADAS-2 adaptation was a first iteration and needs further refinement taking into consideration the QUADAS-2 AI version and AI reporting guides such as STARD-AI and CONSORT-AI, which are expected to be published in due course.

Strengths and limitations in comparison with previous studies
The findings from our systematic review disagree with the publicity some studies have received and opinions published in various journals, which claim that AI systems outperform humans and might soon be used instead of experienced radiologists.¹⁰–¹³ Our different conclusion is based on our rigorous and systematic evaluation of study quality. We did not extract the “simulation” parts of studies, which were often used as the headline numbers in the original papers, and often estimated higher accuracy for AI than the empirical data of the studies. In these simulations various assumptions were made about how radiologist arbitrators would behave in combination with AI, without any clinical data on behaviour in practice with AI. Although a great number of studies report the development and internal validation of AI systems for breast screening, our study shows that this high volume of published studies does not reflect commercially available AI systems suitable for integration into screening programmes. Our emphasis on comparisons with the accuracy of radiologists in clinical practice explains why our conclusions are more cautious than many of the included papers.
A recent scoping review with a similar research question, but broader scope, reported a potential role for AI in breast screening but identified evidence gaps that showed a lack of readiness of AI for breast screening programmes. The 23 included studies were mainly small, retrospective, and used publicly available and institutional image datasets, which often overlapped. The evidence included only one study with AI and radiologists. We found overlap of only one study between the scoping review and our review despite the same search start date, probably because we focused on higher study quality. Our review identified nine additional recent eligible studies, which might suggest that the quality of evidence is improving, but as yet no prospective evaluations of AI have been reported in clinical practice settings.

Possible explanations and implications for clinicians and policy makers

Our systematic review should be considered in the wider context of the increasing proposed use of AI in healthcare and screening. Most of the literature focuses, understandably, on those screening programmes in which image recognition and interpretation are central components, and this is indicated by a number of reviews recently published describing studies of AI and deep learning for diabetic retinopathy screening. Beyond conventional screening programmes, the use of deep learning in medicine is increasing, and has been considered in the diagnosis of melanoma, ophthalmic diseases (age-related macular degeneration and glaucoma), and in interpretation of histological, radiological, and electrocardiogram images.

Evidence is insufficient on the accuracy or clinical effect of introducing AI to examine mammograms anywhere on the screening pathway. It is not yet clear where on the clinical pathway AI might be of most benefit, but its use to redesign the pathway with AI complementing rather than competing with radiologists is a potentially promising way forward. Examples of this include using AI to pre-screen easy normal mammograms for no further review, and post-screen for missed cases. Similarly, in diabetic eye screening there is growing evidence that AI can filter which images need to be viewed by a human grader, and which can be reported as normal immediately which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence that AI can filter which images need to be viewed by a human grader, screening there is growing evidence 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commissioners, and other decision makers to press for high quality evidence on test accuracy when considering the future integration of AI into breast cancer screening programmes.

The views expressed are those of the authors and not necessarily those of the UK National Screening Committee, National Institute for Health Research, or Department of Health and Social Care.

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**Web appendix: Supplementary appendices**