SUPPLEMENTAL MATERIAL

External validation of e-ASPECTS software for interpreting brain CT in stroke

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Supplement Table 1. Summary of published evidence for e-ASPECTS

Ref	Centre, Country	Design	Sample size	Aim of study	Sensitivity, specificity, Accuracy**	Software vs human agreement	Described population ***	Reported software failures	Only anterior circulation ischaemic stroke	Input lesion side	Excluded cases with artefacts/ poor quality	COI with company	Tested impact of imaging or patient factors	Other potential biases
1	Kiel, Germany	R	52	Compare humans & other software against ground truth	e-ASPECTS: 14-34,83-99,68-72% Experts: 34-40,93-96,77%	-	Y	N	Y	NS	Y	N	N	Assessed individual ASPECTS regions as if independent
2	Rochester, USA	R	60	Compare humans with/out software & ground truth	Experts -, -, 78%	0.25 weighted agreement	Incomplete: No time from onset	N	Y	NS	Y	N	N	Assessed individual ASPECTS regions as if independent
3	Brno, Czech Rep	R	81	Compare humans & other software against ground truth	e-ASPECTS: 41, 91, 76% Experts: 46, 93, 79%	-	Y	N	Y	NS	Y	Y Consultancy	N	N
4	Leuven, Belgium	R	156	Compare humans & ground truth, predict outcome	-	ICC 0.47	Y	N	Y	Y	Y	N	N	N
5	Curitiba, Brazil	R	116	Compare humans & ground truth	e-ASPECTS 61, 96, 74% Experts: 28-75, 69-98, 60-84%		Y	N	Y	NS	NS	N	N	N
6	Essen, Germany	R	150*	Compare humans & other software		ICC 0.81	Y	Y	N	Y	Y	N	N	N
7	Homburg, Germany	P	15	Compare humans	-	-	Y	Y	N	NS	N	Y Authorship	N	N
8	Essen, Germany	R	119*	Compare humans & ground truth	e-ASPECTS: 83, 57, 67% Experts: 63-81, 76-91, 77-80%	-	Y	N	Y	NS	N	N	Y Brain changes	Assessed individual ASPECTS regions as if independent
9	Heidelberg, Germany	R	34*	Compare humans & ground truth	e-ASPECTS: 40, 94, -% Experts: 16-39, 96-99, -%	-	Y	N	Y	NS	Y	Y Consultancy, funding	N	
10	Erlangen, Germany	R	131	Compare humans & other software	-	ICC 0.87	Incomplete: No time from onset	Y	Y	Y	Y	N	N	Assessed individual ASPECTS regions as if independent

Ref	Centre, Country	Design	Sample size	Aim of study	Sensitivity, specificity, Accuracy**	Software vs human agreement	Described population ***	Reported software failures	Only anterior circulation ischaemic stroke	Input lesion side	Excluded cases with artefacts/ poor quality	COI with company	Tested impact of imaging or patient factors	Other potential biases
11	Ostrava, Czech Rep	P	45	Compare ground truth	-	-	Y	Y	Y	NS	N	N	N	Assessed individual ASPECTS regions as if independent
12	Atlanta, USA	R	150	As biomarker in clinical research	-	-	Incomplete: No time from stroke onset	N	N	NS	NS	N	N	
13	Reading, UK	P	1	Case study of integrated COVID pathway	-	-	Y	N	Y	NS	ND	Y Authorship	N	
14	Heidelberg, Germany	R	132*	Compare humans, and ground truth	e-ASPECTS: 42-44, 91-93, 85-87% Experts: 26-44, 89-97, 84-89%.	-	Incomplete: No recruitment dates	N	Y	N	Y	Y Authorship, funding, consultancy	N	
15	Heidelberg, Germany	R	388*	Compare ground truth (subset) and clinical outcomes	-	-	Incomplete: No selection criteria or recruitment dates	N	Y	NS	NS	Y Authorship, consultancy	N	
16	Heidelberg, Germany	R	390*	As biomarker in clinical research	-	-	Y	N	Y	NS	NS	Y Consultancy	N	
17	Sydney, Australia	R	1480	Predictor of outcome	-	-	Y	Y	Y	(Y)	Y	Y Consultancy	N	
18	Heidelberg, Germany	R	258*	Impact of CT slice thickness on results	-	-	Incomplete: No time to CT	Y	Y	NS	Y	Y Consultancy	Y Slice thickness	
19	Rochester, USA	R	178	Compare humans	-	Kappa 0.25 ICC 0.66	Incomplete; No time to CT	N	Y	NS	Y	N	N	Assessed individual ASPECTS regions as if independent
20	Barcelona, Spain	R	184	Compare humans & ground truth	-	Spearman's rank corr 0.44	Y	N	Y	NS	Y	N	N	
21	Heidelberg, Germany	R	220*	Predictor of outcome	-	ICC 0.72-0.76	Y	Y	Y	NS	Y	Y Funding, consultancy	N	
22	Heidelberg, Germany	R	102*	As biomarker in clinical research	-	-	Y	N	Y	Y	Y	Y Consultancy	Y Imaging factors	

Ref	Centre, Country	Design	Sample size	Aim of study	Sensitivity, specificity, Accuracy**	Software vs human agreement	Described population ***	Reported software failures	Only anterior circulation ischaemic stroke	Input lesion side	Excluded cases with artefacts/ poor quality	COI with company	Tested impact of imaging or patient factors	Other potential biases
23	Heidelberg, Germany	R	43*	Assessing impact of CT reconstruction on results	-	-	Y	N	Y	NS	NS	Y Consultancy	Y CT recon	
24	New York, USA	R	58	Compare humans & ground truth	-	Kappa 0.84	Y	N	Y	NS	NS	Y Advisory board for partner company	N	
Total	**8 countries 15 centres**	**21 R, 3 P**	**4543 (3247 definitely unique) Median 125 Mean 189**	**16 comparisons, 5 as biomarker in research, 2 assessed technical features, 1 case study**	**e-ASPECTS Sens 14-83% Spec 57-99% Acc 67-87%** **EXPERTS Sens 16-81% Spec 69-99% Acc 60-89%**	**Kappa 0.25-0.84 ICC 0.47-0.87**	**17 Y, 7 incomplete**	**7 reported software failures, 17 did not**	**21 only included anterior circulation stroke, 3 included other patient types**	**5 input lesion side**	**14 excluded poor-quality cases, 3 did not, 7 not stated**	**14 have COI, 10 do not**	**4 tested impact of patient factors**	**8 assessed individual ASPECTS regions as if independent**

Notes:

Results from PubMed search of terms: 'e-ASPECTS' and 'Brainomix', correct to 6th August 2021.

NS = not stated, R = retrospective, P = Prospective, ICC = intraclass correlation coefficient, COI = conflict of interest.

* Likely population overlap between different studies at same centres, i.e. not necessarily unique cases.

** Including at least dates for recruitment, inclusion/exclusion criteria, and clinical/demographic details of final cohort, particularly time from symptom onset.

*** Only includes estimates based on total ASPECTS (i.e. not estimates of individual ASPECTS regions). If multiple results available, only most statistically robust method presented.

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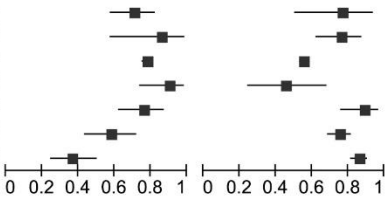
Supplement Figure 1. Forest plots for e-ASPECTS diagnostic accuracy testing.

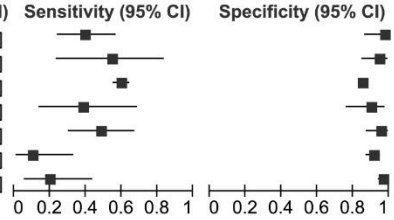
i)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ATTEST	41	4	17	13	0.71 [0.57, 0.82]	0.76 [0.50, 0.93]
EuroHYP	12	12	2	38	0.86 [0.57, 0.98]	0.76 [0.62, 0.87]
IST-3	584	655	166	810	0.78 [0.75, 0.81]	0.55 [0.53, 0.58]
PISTE	27	12	3	10	0.90 [0.73, 0.98]	0.45 [0.24, 0.68]
POSH	38	5	12	39	0.76 [0.62, 0.87]	0.89 [0.75, 0.96]
PRACTISE	29	46	21	139	0.58 [0.43, 0.72]	0.75 [0.68, 0.81]
RIGHT-2	22	34	38	206	0.37 [0.25, 0.50]	0.86 [0.81, 0.90]



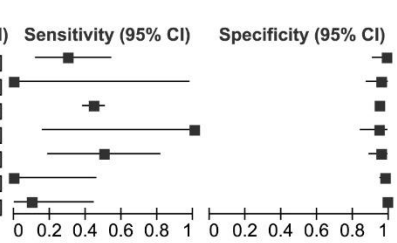
ii)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ATTEST	15	1	23	36	0.39 [0.24, 0.57]	0.97 [0.86, 1.00]
EuroHYP	6	3	5	50	0.55 [0.23, 0.83]	0.94 [0.84, 0.99]
IST-3	276	264	187	1488	0.60 [0.55, 0.64]	0.85 [0.83, 0.87]
PISTE	5	4	8	35	0.38 [0.14, 0.68]	0.90 [0.76, 0.97]
POSH	15	3	16	60	0.48 [0.30, 0.67]	0.95 [0.87, 0.99]
PRACTISE	2	19	17	197	0.11 [0.01, 0.33]	0.91 [0.87, 0.95]
RIGHT-2	4	10	16	270	0.20 [0.06, 0.44]	0.96 [0.94, 0.98]



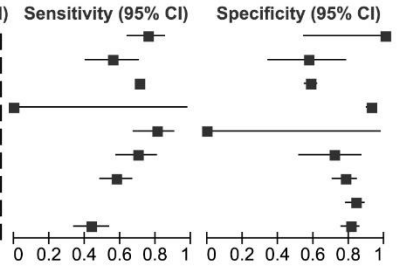
iii)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ATTEST	6	1	14	54	0.30 [0.12, 0.54]	0.98 [0.90, 1.00]
EuroHYP	0	3	1	60	0.00 [0.00, 0.97]	0.95 [0.87, 0.99]
IST-3	111	113	140	1851	0.44 [0.38, 0.51]	0.94 [0.93, 0.95]
PISTE	2	3	0	47	1.00 [0.16, 1.00]	0.94 [0.83, 0.99]
POSH	5	4	5	80	0.50 [0.19, 0.81]	0.95 [0.88, 0.99]
PRACTISE	0	6	6	223	0.00 [0.00, 0.46]	0.97 [0.94, 0.99]
RIGHT-2	1	4	9	286	0.10 [0.00, 0.45]	0.99 [0.97, 1.00]



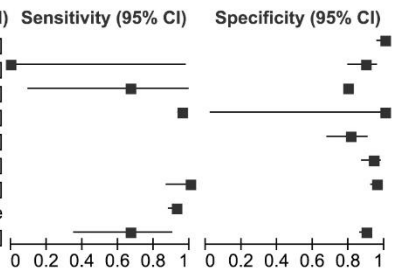
iv)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ATTEST	52	0	17	6	0.75 [0.64, 0.85]	1.00 [0.54, 1.00]
EuroHYP	25	9	20	12	0.56 [0.40, 0.70]	0.57 [0.34, 0.78]
IST-3	1107	282	462	393	0.71 [0.68, 0.73]	0.58 [0.54, 0.62]
LINCHPIN	0	30	1	361	0.00 [0.00, 0.97]	0.92 [0.89, 0.95]
PISTE	41	1	10	0	0.80 [0.67, 0.90]	0.00 [0.00, 0.97]
POSH	46	8	20	20	0.70 [0.57, 0.80]	0.71 [0.51, 0.87]
PRACTISE	68	32	50	112	0.58 [0.48, 0.67]	0.78 [0.70, 0.84]
RESTART	0	32	0	163	Not estimable	0.84 [0.78, 0.88]
RIGHT-2	43	44	56	185	0.43 [0.33, 0.54]	0.81 [0.75, 0.86]



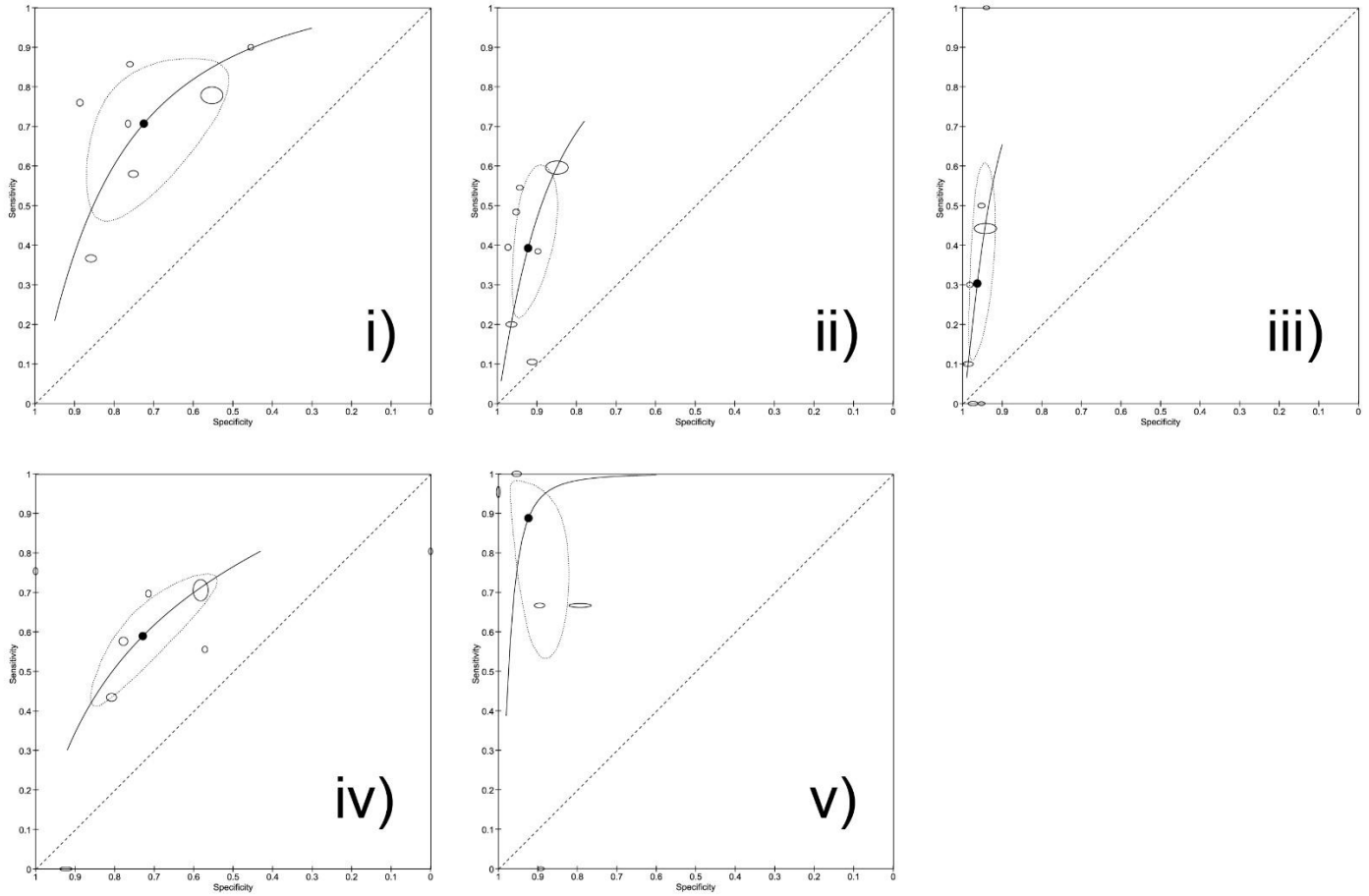
v)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
ATTEST	0	0	0	75	Not estimable	1.00 [0.95, 1.00]
EuroHYP	0	7	1	58	0.00 [0.00, 0.97]	0.89 [0.79, 0.96]
IST-3	2	464	1	1777	0.67 [0.09, 0.99]	0.79 [0.78, 0.81]
LINCHPIN	373	0	18	1	0.95 [0.93, 0.97]	1.00 [0.03, 1.00]
PISTE	0	10	0	42	Not estimable	0.81 [0.67, 0.90]
POSH	0	6	0	88	Not estimable	0.94 [0.87, 0.98]
PRACTISE	25	11	0	226	1.00 [0.86, 1.00]	0.95 [0.92, 0.98]
RESTART	180	0	15	0	0.92 [0.88, 0.96]	Not estimable
RIGHT-2	8	33	4	283	0.67 [0.35, 0.90]	0.90 [0.86, 0.93]



Note: i) e-ASPECTS 10 vs 0-9, ii) e-ASPECTS 8-10 vs 0-7, iii) e-ASPECTS 6-10 vs 0-5, iv) e-ASPECTS detecting ischaemic signs, v) e-ASPECTS detecting haemorrhage.
i)-iii) uses 'Core' testing dataset with 3035 cases. iv)-v) use 'Enriched' dataset and include cases with imaging features outside software scope: non-MCA ischaemia (116/3708, 3.1%) and structural stroke mimics (80/3708, 2.2%). TP = true positive, TN = true negative, FP = false positive, FN = false negative. See Table 2 for more details.

Supplement Figure 2. ROC curves for e-ASPECTS diagnostic accuracy testing.



Note: i) e-ASPECTS 10 vs 0-9, ii) e-ASPECTS 8-10 vs 0-7, iii) e-ASPECTS 6-10 vs 0-5, iv) e-ASPECTS detecting ischaemic signs, v) e-ASPECTS detecting haemorrhage. iv)-v) use 'Enriched' dataset and include cases with imaging features outside software scope: non-MCA ischaemia (116/3708, 3.1%) and structural stroke mimics (80/3708, 2.2%). See Table 2 for more details.
Open circles are individual study results proportional to sample size, closed circles are summary results. Dotted lines enclose 95% confidence regions.

Appendix 1. TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) Checklist: Prediction model validation.

Section/ Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Cover
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	4
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	Describe eligibility criteria for participants.	4-5
	5c	Give details of treatments received, if relevant.	4
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	3
	6b	Report any actions to blind assessment of the outcome to be predicted.	5
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	5
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	5
Sample size	8	Explain how the study size was arrived at.	4
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	6
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	4
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	4-6
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	-
Risk groups	11	Provide details on how risk groups were created, if done.	-
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	-
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Fig 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	-
Model performance	16	Report performance measures (with CIs) for the prediction model.	7-8
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	-
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	10-11
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	9-10
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	9,11
Implications	20	Discuss the potential clinical use of the model and implications for future research.	9-11
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Refs, 12
Funding	22	Give the source of funding and the role of the funders for the present study.	6, 12

Appendix 2. STARD (STAndards for Reporting Diagnostic accuracy studies) Guideline.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	3
	4	Study objectives and hypotheses	3
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	4-5
Participants	**6**	Eligibility criteria	4-5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	4-5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	4
	9	Whether participants formed a consecutive, random or convenience series	4
Test methods	**10a**	Index test, in sufficient detail to allow replication	5
	10b	Reference standard, in sufficient detail to allow replication	4-6
	11	Rationale for choosing the reference standard (if alternatives exist)	4, 10
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	5-6, 9
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	6, 9
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	-
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	5
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	6
	15	How indeterminate index test or reference standard results were handled	4-5
	16	How missing data on the index test and reference standard were handled	6
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	6
	18	Intended sample size and how it was determined	4-5
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Fig 1
	20	Baseline demographic and clinical characteristics of participants	7, Table 1, Supp Table 3
	21a	Distribution of severity of disease in those with the target condition	7, Table 1
	21b	Distribution of alternative diagnoses in those without the target condition	7, Supp Table 3
	22	Time interval and any clinical interventions between index test and reference standard	7
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	-
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	8, Table 2
	25	Any adverse events from performing the index test or the reference standard	-
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	10-11
	27	Implications for practice, including the intended use and clinical role of the index test	2, 9-11
OTHER INFORMATION			
	28	Registration number and name of registry	-
	29	Where the full study protocol can be accessed	6
	30	Sources of funding and other support; role of funders	1, 6, 12

From: Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, et al. STARD Group. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527. Doi: 10.1136/bmj.h5527.

Appendix 3. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Checklist.

TITLE			**Page**
Title	1	Identify the report as a systematic review.	-
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	-
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	-
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	-
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	-
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	-

	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	-
Study characteristics	17	Cite each included study and present its characteristics.	4-5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	App 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 2, Supp Figs 1-2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8, Table 2, Supp Figs 1-2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7-8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-11
	23b	Discuss any limitations of the evidence included in the review.	10-11
	23c	Discuss any limitations of the review processes used.	-
	23d	Discuss implications of the results for practice, policy, and future research.	2, 9-11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1, 6, 12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	12

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 4. PROBAST (Prediction model study Risk Of Bias Assessment Tool).

Step 1: Specify your systematic review question

State your systematic review question to facilitate the assessment of the applicability of the evaluated models to your question. *The following table should be completed once per systematic review.*

Criteria	Specify your systematic review question
Intended use of model:	Validation of artificial intelligence software (e-ASPECTS by Brainomix Ltd.) designed to automate the identification of imaging features indicative of stroke on CT brain scans (and thus assist human readers to correctly diagnose stroke)
***Participants** including selection criteria and setting:*	Patients presenting acutely to hospital with symptoms and signs of stroke, and where baseline CT brain imaging is acquired.
***Predictors** (used in prediction modelling), including types of predictors (e.g. history, clinical examination, biochemical markers, imaging tests), time of measurement, specific measurement issues (e.g., any requirements/ prohibitions for specialized equipment):*	Three CT imaging biomarkers of stroke assessed by e-ASPECTS are 1) ischaemic brain lesions, 2) arterial blood clots (dense arteries), and 3) brain haemorrhage.
Outcome to be predicted:	Final diagnosis of ischaemic or haemorrhagic stroke

Step 2: Classify the type of prediction model evaluation

Use the following table to classify the evaluation as model development, model validation or model update, or combination. Different signalling questions apply for different types of prediction model evaluation. If the evaluation does not fit one of these classifications then PROBAST should not be used.

Classify the evaluation based on its aim			
Type of prediction study	**PROBAST boxes to complete**	**Tick as appropriate**	**Definition for type of prediction model study**
Development only	Development		Prediction model development without external validation. These studies may include internal validation methods, such as bootstrapping and cross-validation techniques.
Development and validation	Development and validation		Prediction model development combined with external validation in other participants in the same article.
Validation only	Validation	✓	External validation of existing (previously developed) model in other participants.

This table should be completed once for each publication being assessed and for each relevant outcome in your review.

1. ATTEST

Publication reference	Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, Ford I, Muir KW. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol*. 2015;14:368-376
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

2. EuroHYP

Publication reference	van der Worp HB, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, Gebhardt B, Gluud C, Kollmar R, Krieger DW, Lees KR, et al. EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. *Int J Stroke*. 2014;9:642-645
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

3. IST-3

Publication reference	IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet*. 2012;379:2352-2363
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

4. LINCHPIN

Publication reference	Samarasekera N, Lerpiniere C, Fonville AF, Farrall AJ, Wardlaw JM, White PM, Torgersen A, Ironside JW, Smith C, Al-Shahi Salman R, et al. Consent for Brain Tissue Donation after Intracerebral Haemorrhage: A Community-Based Study. *PLoS One*. 2015;10:e0135043
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

5. PISTE

Publication reference	Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88:38-44
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

6. POSH

Publication reference	MacDougall NJ, McVerry F, Huang X, Welch A, Fulton R, Muir K. Post-stroke hyperglycaemia is associated with adverse evolution of acute ischaemic injury. *Cerebrovasc Dis*. 2014;37(suppl 1):267
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

7. PRACTISE

Publication reference	El-Tawil S, Wardlaw J, Ford I, Mair G, Robinson T, Kalra L, Muir KW. Penumbra and re-canalization acute computed tomography in ischemic stroke evaluation: PRACTISE study protocol. *Int J Stroke*. 2017;12:671-678

Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

8. RESTART

Publication reference	RESTART Collaboration. Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial. *Lancet*. 2019;393:2613-2623
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

9. RIGHT-2

Publication reference	RIGHT-2 Investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet*. 2019;393:1009-1020
Models of interest	e-ASPECTS
Outcome of interest	Final diagnosis of ischaemic or haemorrhagic stroke, or stroke mimic

Step 3: Assess risk of bias and applicability

PROBAST is structured as four key domains. Each domain is judged for risk of bias (low, high or unclear) and includes signalling questions to help make judgements. Signalling questions are rated as yes (Y), probably yes (PY), probably no (PN), no (N) or no information (NI). All signalling questions are phrased so that "yes" indicates absence of bias. Any signalling question rated as "no" or "probably no" flags the potential for bias; you will need to use your judgement to determine whether the domain should be rated as "high", "low" or "unclear" risk of bias. The guidance document contains further instructions and examples on rating signalling questions and risk of bias for each domain.
The first three domains are also rated for concerns regarding applicability (low/ high/ unclear) to your review question defined above.
Complete all domains separately for each evaluation of a distinct model. Shaded boxes indicate where signalling questions do not apply and should not be answered.

DOMAIN 1: Participants

A. Risk of Bias

Describe the sources of data and criteria for participant selection:

All studies with imaging available to RITeS aimed to identify patients presenting acutely to hospital with symptoms of stroke. Most studies recruited patients with ischaemic stroke (ATTEST, EuroHYP, IST-3, PISTE, POSH, PRACTISE). RESTART and LINCHPIN recruited patients with haemorrhagic stroke. With ambulance-based recruitment (i.e. pre-hospital recruitment before brain imaging), RIGHT-2 ultimately included a mix of ischaemic stroke, haemorrhagic stroke, and stroke mimics. Patient selection for ATTEST, EuroHYP, IST-3, PISTE, POSH, PRACTISE, RESTART, and RIGHT-2 was based on individual trial inclusion/exclusion criteria. LINCHPIN included all consecutive patients in the local geographical region diagnosed with intracerebral haemorrhage over 2 years, with no exclusion criteria.

Case selection for RITeS differed between the available studies. For 6/9 of the RITeS studies (ATTEST, EuroHYP, IST-3, PISTE, POSH, PRACTISE) all cases with an available baseline CT and/or CTA scan were included. For the remaining 3/9 RITeS studies (LINCHPIN, RESTART, RIGHT-2) we used subsamples. For LINCHPIN and RESTART, cases were sequentially selected (ordered by trial ID) until sufficient numbers of haemorrhagic stroke were included. For RIGHT-2 we included all cases with a final diagnosis of mimic in addition to a random subsample of 150 cases with a final diagnosis of ischaemic stroke.
Case selection was not related to imaging features or results for any of the RITeS studies.

		Dev	Val
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?			Y
1.2 Were all inclusions and exclusions of participants appropriate?			Y
Risk of bias introduced by selection of participants	**RISK:** *(low/ high/ unclear)*		**LOW**

Rationale of bias rating:

Despite differing requirements of individual RITeS studies (which may help to improve the range of available patient characteristics), all recruited patients were clinically diagnosed with ischaemic, haemorrhagic or mimic stroke and were therefore relevant for RITeS. Imaging was not used to select cases for RITeS.
Ultimately, only some patients had visible imaging biomarkers of stroke and this proportion was not controlled and thus expected to replicate routine practice.

B. Applicability

Describe included participants, setting and dates:

All patients recruited to RITeS collaborative studies presented acutely to hospital with symptoms of stroke and had baseline CT imaging for assessment.
e-ASPECTS software was developed using the CT scans of patients presenting acutely to hospital with symptoms of stroke. Although the specific cases used for software development are not publically available, Brainomix is a UK-based company, a spin out from Oxford University. It is highly likely that the imaging of local (UK) stroke patients were used in development. All RITeS studies included UK recruitment, but several were international thus increasing the diversity and wider applicability of patients used for assessment.

Concern that the included participants and setting do not match the review question	**CONCERN:** *(low/ high/ unclear)*		**LOW**

Rationale of applicability rating:

High likelihood that development (Brainomix) and validation (RITeS) patients have similar demographics.
All patients are the same clinically.

DOMAIN 2: Predictors

A. Risk of Bias

List and describe predictors included in the final model, e.g. definition and timing of assessment:

Three e-ASPECTS predictors are considered:

1. Ischaemic brain lesions (within middle cerebral artery, MCA territory, with lesion extent conveyed using ASPECT scoring where 10 = no MCA lesion, and 0 = entire MCA affected)
2. Dense arteries (a surrogate measure of arterial occlusion, e-ASPECTS assesses MCA branches and the internal carotid artery, ICA which supplies MCA)
3. Brain haemorrhage (presence vs absence, if present defined as a volume).

All 3 of these same predictors were also scored by our (reference standard) expert human readers. Predictors 1 and 2 were scored identically, 3 was scored by humans as presence/absence but volume was only estimated (and is therefore not included in our analysis). In all cases, predictor assessment was based only on baseline CT imaging. This means CT imaging acquired at initial presentation to hospital assessed while masked to all other data.

		Dev	Val
2.1 Were predictors defined and assessed in a similar way for all participants?			Y
2.2 Were predictor assessments made without knowledge of outcome data?			Y
2.3 Are all predictors available at the time the model is intended to be used?			Y
Risk of bias introduced by predictors or their assessment	**RISK:** *(low/ high/ unclear)*		**LOW**

Rationale of bias rating:

All 3 predictors are available on baseline CT, human and software scoring was identical and was conducted blind to outcome.

B. Applicability

Concern that the definition, assessment or timing of predictors in the model do not match the review question	**CONCERN:** *(low/ high/ unclear)*		**LOW**

Rationale of applicability rating:

Definition, assessment and timing of predictors are an excellent match with the review question.

DOMAIN 3: Outcome

A. Risk of Bias

Describe the outcome, how it was defined and determined, and the time interval between predictor assessment and outcome determination:

Outcome was final diagnosis for patients, either ischaemic stroke or haemorrhagic stroke. Final diagnosis was determined by clinical experts at follow-up using all available information including the results of any clinical tests used such as additional brain imaging (when ischaemic stroke lesions are much clearer). Owing to the retrospective use of RITeS data for this assessment, outcome determination occurred before predictor assessment.

		Dev	Val
3.1 Was the outcome determined appropriately?			Y
3.2 Was a pre-specified or standard outcome definition used?			Y
3.3 Were predictors excluded from the outcome definition?			Y
3.4 Was the outcome defined and determined in a similar way for all participants?			Y
3.5 Was the outcome determined without knowledge of predictor information?			Y
3.6 Was the time interval between predictor assessment and outcome determination appropriate?			Y
Risk of bias introduced by the outcome or its determination	**RISK:** *(low/ high/ unclear)*		**LOW**

Rationale of bias rating:

Outcome assessment was consistent, is reflective of standard practice, and was conducted completely separate from e-ASPECTS predictor acquisition.

B. Applicability

At what time point was the outcome determined:

In routine clinical practice, final diagnosis would usually be defined during the first 1-2 weeks after presentation to hospital. This is also true in RITeS but was additionally confirmed at dedicated 3- or 6-month follow-up.

If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome:

Concern that the outcome, its definition, timing or determination do not match the review question	**CONCERN:** *(low/ high/ unclear)*		**LOW**

Rationale of applicability rating:

Outcome assessment is based on routine clinical practice.
Good match for review question.

DOMAIN 4: Analysis

Risk of Bias

Describe numbers of participants, number of candidate predictors, outcome events and events per candidate predictor:
4100 unique participants, each with a baseline CT scan. Total RITeS sample identified to be representative of routine clinical practice. All 3 predictors possible in all participant scans but present in fewer: 34% (1390) had MCA ischaemia, 19% (768) had dense artery, 16% (643) had haemorrhage. These figure representative of routine practice.
Outcome available for all participants.

Describe how the model was developed (for example in regards to modelling technique (e.g. survival or logistic modelling), predictor selection, and risk group definition):
Not applicable, our assessment validation not development.

Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, different type of participants):
Externally validated in a different, large group of participants. RITeS participants were separately assessed for UK clinical representation but include participants from several international studies, thus also enabling geographical validation.

Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, net benefit, and whether they were adjusted for optimism:
Not applicable, our assessment validation not development.

Describe any participants who were excluded from the analysis:
No participants from the RITeS representative sample were excluded from the analysis.

Describe missing data on predictors and outcomes as well as methods used for missing data:
Approximately 10% (429/4100) of participant CT scans failed software processing, therefore no predictors available for these participants. We reported but did not impute missing data.
Outcome data (final diagnosis) was complete for all participants.

		Dev	Val
4.1	Were there a reasonable number of participants with the outcome?		Y
4.2	Were continuous and categorical predictors handled appropriately?		Y
4.3	Were all enrolled participants included in the analysis?		Y
4.4	Were participants with missing data handled appropriately?		Y
4.5	Was selection of predictors based on univariable analysis avoided?		
4.6	Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?		Y
4.7	Were relevant model performance measures evaluated appropriately?		Y
4.8	Were model overfitting and optimism in model performance accounted for?		
4.9	Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?		
Risk of bias introduced by the analysis	**RISK:** *(low/ high/ unclear)*		**LOW**

Rationale of bias rating:
Large number of participants, with clinically appropriate representation of predictors. Outcome available for all participants. No excluded participants, missing data reported.

Step 4: Overall assessment

Use the following tables to reach overall judgements about risk of bias and concerns regarding applicability of the prediction model evaluation (development and/or validation) across all assessed domains.
Complete for each evaluation of a distinct model.

Reaching an overall judgement about risk of bias of the prediction model evaluation	
Low risk of bias	If all domains were rated low risk of bias. If a prediction model was developed without any external validation, and it was rated as low risk of bias for all domains, consider downgrading to **high risk of bias**. Such a model can only be considered as low risk of bias, if the development was based on a very large data set and included some form of internal validation.
High risk of bias	If at least one domain is judged to be at **high risk of bias**.
Unclear risk of bias	If an unclear risk of bias was noted in at least one domain and it was low risk for all other domains.

Reaching an overall judgement about applicability of the prediction model evaluation	
Low concerns regarding applicability	If low concerns regarding applicability for all domains, the prediction model evaluation is judged to have **low concerns regarding applicability**.
High concerns regarding applicability	If high concerns regarding applicability for at least one domain, the prediction model evaluation is judged to have **high concerns regarding applicability**.
Unclear concerns regarding applicability	If unclear concerns (but no "high concern") regarding applicability for at least one domain, the prediction model evaluation is judged to have **unclear concerns regarding applicability** overall.

Overall judgement about risk of bias and applicability of the prediction model evaluation		
Overall judgement of risk of bias	**RISK:** *(low/ high/ unclear)*	**LOW**
Summary of sources of potential bias:		
Overall judgement of applicability	**CONCERN:** *(low/ high/ unclear)*	**LOW**
Summary of applicability concerns:		