ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Rapid to aid the diagnosis of patients suspected of stroke

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ACE agency for care effectiveness

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Summary of Key Points

- Stroke is the second leading cause of death globally. Locally, stroke is the fourth highest cause of death, contributing to 6.1% of all deaths caused by cerebrovascular diseases in 2021.
- Patients with a suspected stroke undergo a full medical assessment including a 12-lead electrocardiogram, and laboratory and neurological assessments. Brain imaging is done as soon as possible and is then used to aid the diagnosis.
- Rapid is a neuroimaging platform that uses artificial intelligence (AI) to process brain images to aid clinicians in the diagnosis of patients with suspected stroke. Rapid has various software modules (Rapid NCCT, ICH, Hyperdensity, ASPECTS, CTA, LVO, CTP, MRI) with specific functions.
- The key evidence base for this brief consists of a National Institute for Health and Care Excellence (NICE) medical innovation brief and 13 additional studies. Evidence for the performance of Rapid varied for different modules, with more studies available for Rapid ASPECTS, Rapid CTA and Rapid CTP. Only a few clinical utility studies were identified.
- Rapid was found to be generally safe. The diagnostic performance of the various Rapid modules is summarised in the following table.
    - Overall, when used to aid diagnosis of stroke, Rapid showed moderate to good accuracy in most measures, except specificity for some modules (eg. Rapid ASPECTS) and positive predictive value (PPV) for most modules, reflecting a high false positive rate.

Rapid Module	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Rapid ICH	NR	85%	92% to 96%	84% to 95%	45% to 96%	95% to 99%
Rapid ASPECT	0.76	83%	60% to 88%	31% to 91%	31%	88%
Rapid CTA	0.94	NR	92% to 97%	74% to 85%	52%	98% to 99%
Rapid LVO	0.99	86% to 87%	87% to 96%	85% to 98%	45% to 53%	97% to 99%
Rapid MRI	NR	NR	100%	91%	91%	100%

Abbreviations: AUC, receiver operating characteristics area under curve; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

- Among the limited studies that reported on clinical utility compared to standard care without Rapid, reduced time to treatment was reported for Rapid CTA (by 25 minutes) and Rapid CTP (by 36 minutes), and reduced turnaround times for CT reports for Rapid LVO (by nine minutes).
- No economic analysis comparing Rapid with standard care was identified. A cost-effectiveness study showed Rapid ASPECTS was more cost-effective than WhatsApp-based manual ASPECTS calculation, however there is concern about the imaging quality from WhatsApp which may impact on its interpretation. The applicability of this to the local context is likely to be low.
- According to NICE, the annual cost of Rapid license was £20,000 (S$34,164), which includes Rapid ICH, ASPECTS, CTA, LVO, CTP and MRI). The annual license cost also includes training. NICE considered that the Rapid platform would typically cost more than standard care, however it might result in cost savings due to reduced time required by the neuroradiologist to review CT or MRI brain scans.
- Rapid has recently been adopted into two local public healthcare institutions. Local clinician feedback on the need for Rapid is mixed, with some expressing a strong desire

for its adoption. However, there are also doubts about the clinical significance of its benefits. In addition, the Hospital Services Division is generally supportive of AI technologies that aid in clinical decision making but is agnostic of the technology used as long as it is safe and cost saving.

- Potential adoption considerations include the need for software training, alignment of healthcare resources, related regulation of AI medical devices and local study to address concerns of the platform and gaps in the evidence.

I. Background

Stroke is a neurovascular condition that can cause damage to the brain, disability or even death.[1] There are two main types of stroke: ischaemic and haemorrhagic stroke. Ischaemic stroke is the more common form of stroke but haemorrhagic stroke is more severe.[2] Common risk factors for stroke include hypertension, hyperlipidaemia, diabetes, atrial fibrillation, smoking and old age.[2]

The global burden from stroke is huge, with 12.2 million incident cases of stroke and 6.55 million deaths from stroke in 2019.[3] In Singapore, stroke is the fourth leading cause of death, contributing to 6.1% of all deaths caused by cerebrovascular diseases in 2021.[4] In 2018, the prevalence of stroke for Singapore residents aged 60 years and above was 7.6%, and the burden from this condition is expected to increase due to an aging population, alongside a high prevalence of risk factors.[5,6]

Currently, computed tomography (CT) and magnetic resonance imaging (MRI) scans are used to diagnose stroke. These brain images are assessed manually by neuroradiologists to determine the type of stroke and the extent of ischaemic damage.[1] However, this assessment may be subjected to inter-observer variability. Given the time-sensitive nature of stroke intervention, there is a need for a rapid and more accurate method to assist clinicians in diagnosing and treating patients with a suspected stroke.

II. Technology

Rapid (iSchemaView, Inc, United States) is a neuroimaging platform that uses artificial intelligence (AI) to process brain scan images and also provides summary maps to aid clinicians in the diagnosis and treatment of patients with a suspected stroke. Note that RapidAI is another legal company name used in some regions and countries whilst Rapid is the product, with multiple available software modules. The manufacturer claims that the software can process scans such as non-contrast CT (NCCT), CT angiography, CT perfusion, MRI diffusion and MRI perfusion in under two minutes.

The platform provides multiple modules with various specific functions that aid clinicians in diagnosis of stroke and guide treatment (Figure 1):

- Rapid NCCT uses AI to determine the suspicion of intracranial haemorrhage (ICH) and large vessel occlusion (LVO) based on NCCT images. Clinicians are notified of suspected ICH and LVO cases via a mobile application.

- Rapid ICH uses AI to speed up the triage of NCCT and to notify clinicians of suspected ICH cases within three minutes of receiving the case.
- Rapid Hyperdensity uses AI to identify hyperdense regions of the brain after Rapid ICH detects suspected ICH.
- Rapid ASPECTS uses a machine learning algorithm for automatic identification of the Alberta Stroke Program Early CT Score (ASPECTS) regions of the brain to generate an ASPECT score.
- Rapid CTA automatically processes CT scans for clear CT angiography images to detect regions of asymmetry in blood vessel density.
- Rapid LVO assists clinicians in rapidly locating suspected LVOs in the distal internal carotid artery (ICA) or the middle cerebral artery (MCA-M1) regions within three minutes of receiving the case.
- Rapid CTP quantifies and colour-codes CT perfusion maps to locate brain regions with compromised cerebral blood flow volume, density and transit time, to assess salvageable brain tissue.
- Rapid MRI quantifies and colour-codes MRI diffusion and perfusion maps to locate brain regions with compromised apparent diffusion coefficient (ADC) and transit time to assess salvageable brain tissue.

There is also a Rapid mobile application that allows clinicians to be notified of new cases, view results, preview source files and communicate about patient care on a smartphone.

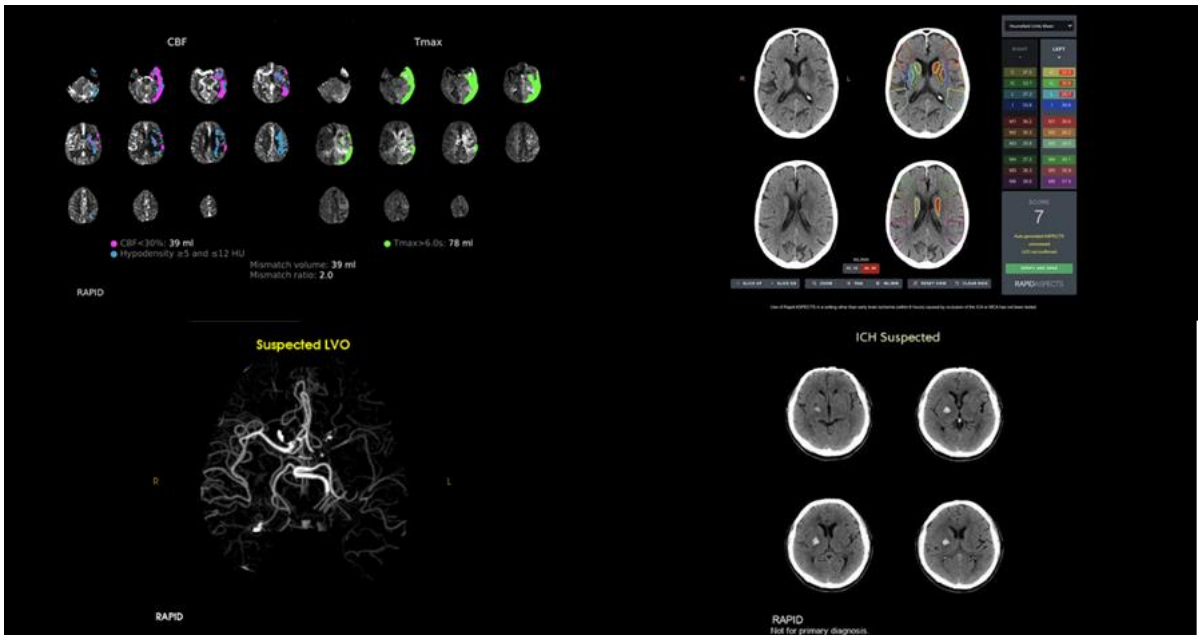

Figure 1: Screenshots of the Rapid modules. Images adapted from https://www.rapidai.com/stroke

The use of AI platforms to analyse brain images for automated stroke diagnosis and treatment selection could lead to faster triage and treatment, increased clinical efficiency and improved patient outcomes. Rapid and other similar triaging AI systems can be used to ensure that no

eligible patient is denied the opportunity to undergo mechanical thrombectomy or endovascular treatment, where increasing the penetration of such treatments can reduce the overall healthcare burden of stroke on society (Personal communication: Senior Consultant from National University Hospital, 7 October 2023). Currently, as Rapid is predominantly used to assist diagnosis of stroke, this brief will focus on this function.

III. Regulatory and Subsidy Status

Rapid modules have received clearance from the US Food and Drug Administration (FDA) as summarised in Table 1. However, we were unable to identify the registration details of Rapid Hyperdensity on the FDA website.

Table 1: Regulatory status of various Rapid modules

Rapid Module	HSA	FDA*
Rapid NCCT	Not Approved	510K clearance (K222884) obtained in March 2023
Rapid ICH	Not Approved	510K clearance (K221456) obtained in September 2022
Rapid Hyperdensity	Not Approved	Claimed to have received 510K clearance but unable to find on FDA
Rapid ASPECTS	Not Approved	510K clearance (K200760) obtained in June 2020
Rapid CTA	Approved	510K clearance (K172477) obtained in April 2018
Rapid LVO	Not Approved	510K clearance (K221248) obtained in March 2022
Rapid CTP	Approved	510K clearance (K182130) obtained in December 2018
Rapid MRI	Approved	510K clearance (K182130) obtained in December 2018

*Information sourced from the FDA 510(k) database (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CTA, computed tomography angiography; CTP, computed tomography perfusion; FDA, U.S. Food and Drug Administration; HSA, Health Sciences Authority; ICH, intracranial haemorrhage; LVO, large vessel occlusion; MRI, magnetic resonance imaging; NCCT, non-contrast computed tomography.

Currently, the primary software modules: Rapid MRI, Rapid CTP and Rapid CTA have been registered with the Health Sciences Authority (HSA) with a registration number of DE0503930. The manufacturer is planning to submit the other software modules for HSA registration.

According to the National Institute for Health and Care Excellence (NICE), Rapid has received its Conformité Européene (CE) mark as a class IIa medical device, though no specific module was mentioned. Only Rapid ASPECTS was reported to have received a CE mark in May 2018 by the manufacturer.[7]

IV. Stage of Development in Singapore

☐ Yet to emerge

☐ Established

☐ Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)

☐ Established *but* modification in indication or technique

☒ Nearly established ☐ Established *but* should consider for reassessment (due to perceived no/low value)

The National University Hospital started using Rapid in February 2023. As of May 2023, more than 400 patients have been assessed by Rapid and over 30 patients have received guided endovascular treatment.[8] The National Neuroscience Institute in the Tan Tock Seng campus has also recently implemented Rapid in August 2023 (Personal communication: Senior Consultant from National Neuroscience Institute, 13 October 2023). However, it is not clear what Rapid modules were installed in the PHIs. The local clinician expert who chairs the Singapore Stroke Improvement team commented that the SingHealth cluster has been actively advocating for the adoption of Rapid (Personal communication: Senior Consultant from National Neuroscience Institute, 27 June 2023).

V. Treatment Pathway

The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (Figure A1 in Appendix A) recommends that patients showing signs and symptoms of possible stroke should first undergo both neurological assessment and a series of clinical assessments such as 12-lead electrocardiogram (ECG) and laboratory tests.[9] In addition, CT or MRI scans of the brain should be obtained as soon as possible, ideally within one to 24 hours of symptom onset depending on the patient risk level according to NICE[10], to confirm stroke diagnosis and identify the stroke type (i.e. ischaemic or haemorrhagic) to help guide treatment strategy.[9] The treatment decision hinges on both the results of the brain imaging and the time since symptom onset.[10]

Locally, the Ministry of Health Clinical Practice Guidelines on stroke and transient ischaemic attacks (2011) follow a similar pathway (Figure A2 in Appendix A), recommending a full medical assessment and CT or MRI imaging as soon as possible.[11,12] An assessment of the extent of early ischaemic change should be done based on the brain images to then guide treatment decisions (Personal communication: Senior Consultant from National Neuroscience Institute, 25 August 2023). Rapid would help to process and accelerate imaging assessment, assisting clinical treatment decision-making (Personal communication: Senior Consultant from National Neuroscience Institute, 25 August 2023).

VI. Summary of Evidence

This assessment was conducted using the Population, Intervention, Comparator and Outcome (PICO) criteria (Table 2). Literature searches were performed in Cochrane, Pubmed, Embase and International Network of Agencies for Health Technology Assessment (INAHTA) databases.

Table 2: PICO Criteria

Population	Patients with suspected stroke
Intervention	Rapid
Comparator	Conventional stroke diagnosis methods
Outcome	Safety, Clinical and Cost Effectiveness

The key evidence base consists of a NICE medical technology innovation briefing on Rapid (MIB262),[10] summarising seven studies: six accuracy studies on various modules [13-18] (a total of 1409 brain scans) and one additional clinical utility study on Rapid CTP.[19] Other than MIB262, 13 additional studies were included for this evaluation, consisting of eight comparative studies and five single-arm studies. A further six studies comparing Rapid to other commercial software with similar functions, and one clinical utility study of the Rapid mobile application (not technically a Rapid software module but part of the Rapid platform) were considered as supplementary evidence (Appendix B, Table B1). The reference standard of the comparative studies in the evidence base was manual assessment by a single neuroradiologist or multiple neuroradiologists in consensus. Of note, some of these studies did not specify the respective Rapid module used but just used the general name "Rapid". However, a specific Rapid module was assumed based on the descriptions of the software. These included four key studies on Rapid CTA,[20] and Rapid CTP.[21-23] NICE was uncertain about the modules assessed in two studies included in MIB262 (2021),[17,18] but assumed they were Rapid MRI and Rapid CTP modules.[10] No evidence was identified that evaluated Rapid NCCT and Rapid Hyperdensity. Table 3 summarises the types of evidence based on each Rapid module (Appendix B, Table B2). More details of the studies can be found in Appendix B.

Table 3: Summary of key and supplementary evidence for each Rapid module

Rapid Module	Evidence
Rapid ICH	One accuracy study from NICE[10] and another additional accuracy study.[24]
Rapid ASPECTS	One accuracy study from NICE[10], six additional accuracy studies[25-30] and one cost-effectiveness study.[31]
Rapid CTA	One accuracy study from NICE[10] and three additional accuracy studies.[20,26,32]
Rapid LVO	One accuracy study from NICE[10] and three additional accuracy studies.[33-35]
Rapid CTP	One accuracy study and one clinical utility study from NICE[10], three additional accuracy studies[21,22,36] and one clinical utility study.[23]
Rapid MRI	One accuracy study from NICE[10], one additional clinical utility study.[37]
Abbreviation: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CTA, computed tomography angiography; CTP, computed tomography perfusion; ICH, intracranial haemorrhage; LVO, large vessel occlusion; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence.	

Safety

No major adverse events were reported with the use of the Rapid modules. However, inaccuracies in any of the Rapid modules may lead to delays or inappropriate treatments. A search on the FDA's manufacturer and user facility device experience (MAUDE) database found no records of any adverse events.

Effectiveness

Rapid ICH

Accuracy

Two studies, Heit et al (2021)[13] and Eldaya et al (2022),[24] examined the diagnostic performance of Rapid ICH, compared to the reference standard of manual assessment by neuroradiologists.[10,24] The reported sensitivity (92% to 96%) and negative predictive value (NPV) (95% to 99%) were similar between the studies (Table 4). However, specificity varied

between 84% to 95%, and positive predictive value (PPV) 45% to 96%. The high rates of false positives reported by Eldaya et al (2022)[24] were determined to be mostly due to issues with the image. Of note, the authors also compared the diagnostic accuracy of a neuroradiologist assisted by Rapid ICH with Rapid ICH alone, which showed neuroradiologist assisted by Rapid ICH to be more accurate, with a reported accuracy, sensitivity, specificity, PPV and NPV of 99%, 92%, 100%, 97% and 99% respectively.[24] This observation highlights that Rapid should be used as an aid to neuroradiologists' assessment, rather than to replace it.

Table 4: Summary of diagnostic accuracy of Rapid ICH

Study (year)	Population (N), Reference Standard	Accuracy	Sensitivity	Specificity	PPV	NPV
Eldaya et al (2022)[24]	Symptomatic patients suspected of stroke (N=307), Consensus neuroradiologists assessment	85.3%	91.9%	84.4%	44.7%	98.7%
*Heit et al (2021)[13]	Patients suspected of ICH (N=308), Consensus neuroradiologists assessment	NR	95.6%	95.3%	95.6%	95.3%
*Study found in MIB262 (2021)[10] Abbreviations: ICH, intracranial haemorrhage; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.						

Rapid ASPECTS

Accuracy

Two studies assessed the diagnostic accuracy of Rapid ASPECTS,[25,26] using manual assessment by neuroradiologists as the reference. A moderate area under the curve (AUC) of 0.76 was reported in the study by Chen et al (2023).[25] Sensitivity ranged from 60% to 88% and specificity ranged widely from 31% to 91%.[25,26] A high false positive rate for detecting acute ischaemic parenchymal changes, as reflected by the low specificity and PPV, was reported for Rapid ASPECTS in Chan et al (Table 5). This was suggested to be related to the softwares tendency to wrongly identify isolated regions of ischaemia in otherwise normal CT images.[26]

Table 5: Summary of diagnostic accuracy of Rapid ASPECTS

Study (year)	Population (N), Reference Standard	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Chan et al (2023)[26]	Patients suspected of stroke (N=104), Consensus neuroradiologists assessment	NR	NR	87.5%	30.9%	30.9%	87.5%
Chen et al (2023)[25]	Patients with AIS (N= 276), Consensus neuroradiologists assessment	0.76	83%	60%	91%	NR	NR
Abbreviations: AIS, acute ischaemic stroke; AUC, receiver operating characteristics area under curve; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.							

Concordance between Rapid ASPECTS and manual ASPECTS calculation by a single neuroradiologist against the reference standard (manual assessment by multiple neuroradiologists in consensus) was assessed in a few studies with various measures reported (Table 6).[14,25,27,28] The concordance varied, with the interclass correlation coefficient in Li et al (2023) ranging from 0.83 to 0.87 for Rapid ASPECTS compared to 0.87 to 0.98 for manual ASPECTS.[27] In this same study, when the analysis was stratified by neuroradiologist

experience, concordance of manual ASPECTS by senior radiologists with the reference standard was higher than that of the junior radiologist, who showed similar concordance as Rapid ASPECTS (senior radiologist: 0.97 to 0.98 vs junior radiologist: 0.87 vs Rapid ASPECTS: 0.83 to 0.87).[27] Other studies found the intraclass correlation coefficient ranged from 0.55 to 0.77 for Rapid ASPECTS versus 0.29 to 0.78 for manual ASPECTS.[10,25] Overall, Rapid ASPECTS generally had similar or higher concordance to reference standards when compared to manual ASPECTS.

Table 6: Summary of concordance data of Rapid ASPECTS

Study (Year)	Population (N), Reference Standard	Concordance parameter	Rapid ASPECTS	Manual ASPECTS
Chen et al (2023)[25]	Patients with AIS (N=276), Consensus neuroradiologists assessment	IntraCC	0.77	0.57 to 0.78
Li et al (2023)[27]	Patients with AIS, (N=61), Consensus neuroradiologists assessment	InterCC	0.83 to 0.87	0.87 to 0.98
*Albers et al (2019)[14]	Patients with stroke (N=65), Consensus neuroradiologists assessment	IntraCC	0.55	0.29
Maegerlein et al (2019)[28]	Patients with suspected or known stroke (N=100), Consensus neuroradiologists assessment	κ	0.60 to 0.90	0.30 to 0.60

*Study included in MIB262[10]

Abbreviations: AIS, acute ischaemic stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; InterCC, interclass correlation coefficient; IntraCC, intraclass correlation coefficient; κ, Cohen's Kappa.

Furthermore, one key and two supplementary studies compared the diagnostic accuracy of the Rapid ASPECTS software with other automated ASPECT scoring software.[25,29,30] Rapid ASPECTS performed similarly to other ASPECT scoring softwares, with some indication that Rapid ASPECTS tended to overestimate the size of the infarctions (Appendix C, Table C1).

Cost Effectiveness

No studies were identified that assessed the cost-effectiveness of Rapid ASPECTS against manual ASPECTS interpretation. A cost-effectiveness analysis study by Mansour et al (2020) used a decision tree model to compare a WhatsApp-based manual interpretation of ASPECTS with the Rapid ASPECTS software, based on rate-adjusted total cost of treatment.[31] WhatsApp-based interpretation involved using a phone to first photograph the CT image on the workstation and then send the image (over WhatsApp) to the neuroradiologist to manually calculate ASPECTS. Overall, the study suggests Rapid ASPECTS is cheaper and more effective than a WhatsApp interpretation of ASPECTS resulting in an ICER of LE (Livre égyptienne, Egyptian Pounds) 9,738.35 (S$ 427)[1] per QALY gained (Appendix C, Table C2). However, there are concerns for image quality from WhatsApp which would in turn affect its interpretation and the applicability of this analysis remains unclear.

[1] Based on the Google exchange rate as of 29 August 2023: LE 1=S$0.044. Figures were rounded to the nearest dollar.

Rapid CTA

Accuracy

The study by Amukotuwa et al (2019a)[15] included in MIB262 (2021)[10] and three additional studies assessed the diagnostic performance of using Rapid CTA to detect LVOs.[20,26,32] Only one study reported a relatively high AUC at 0.94. Overall, the studies revealed a moderate to high sensitivity (80% to 97%), specificity (74% to 85%) and NPV (97% to 99%). However, the low PPV of 52% indicates a high false positive rate (Table 7).

Table 7: Summary of diagnostic accuracy of Rapid CTA

Study (year)	Population (N), Reference Standard	AUC	Sensitivity	Specificity	PPV	NPV
Chan et al (2023)[26]	Patients suspected of stroke (N=104), Consensus neuroradiologists assessment	NR	92.3%	85.3%	52.2%	98.5%
Adhya et al (2021)[32]	Symptomatic patients suspected of stroke (N=310), Consensus neuroradiologists assessment	NR	NR	NR	52%	NR
*Amukotuwa et al (2019a)[15]	Patients suspected of stroke (N=477), Consensus neuroradiologists assessment	NR	94%	76%	NR	98%
Amukotuwa et al (2019b)[20]	Patients from DEFUSE 2 and DEFUSE 3 stroke trials, a cohort of endovascular clot retrieval candidates, Patients imaged for non-stroke related indications and code stroke patients (N=926), Consensus neuroradiologists assessment	0.94	96.87%	74.32%	NR	NR

*Study found in MIB262[10]

Abbreviations: AUC, receiver operating characteristics area under curve; CTA, computed tomography angiography; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

Clinical Utility

Amukotuwa et al (2019a)[15] in MIB262 (2021)[10] observed that the average processing time by Rapid CTA of the brain images was 158 seconds, suggesting that the software module can be used in emergency settings as a screening tool to alert and expedite cases for formal diagnosis.[10] Adhya et al (2021) reported that the use of Rapid CTA reduced time between CTA imaging to treatment (93 minutes versus 68 minutes, $p<0.05$) compared to standard care.[32] Although not statistically significant, Adhya et al (2021) also observed that Rapid CTA resulted in a lower average 90 day modified Rankin Scale score (4.43 versus 3.90, $p=0.07$) and a higher percentage of patients (34% versus 23%, $p=0.15$) with functional independence.[32]

Rapid LVO

Accuracy

Dehkharghani et al (2021)[16] included in MIB262 (2021)[10] and three other studies assessed the diagnostic performance of Rapid LVO.[33-35] NICE reported a high AUC of 0.99.[10] Across these studies, sensitivity and specificity were reported to be good, varying between 87% and 96% and 85% to 98%, respectively (Table 8). Similarly, a low PPV was observed ranging from 45% to 53%, indicating a high false positive rate.[33-35] According to Delora et al (2023), a large

number of false positives for Rapid LVO could desensitise alarms, leading to missed alarms or delayed responses.[34]

Table 8: Summary of diagnostic accuracy of Rapid LVO

Study (year)	Population (N), Reference Standard	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV
Delora et al (2023)[34]	Patients suspected of LVO (N=360), Consensus neuroradiologists assessment	NR	NR	87%	85%	46%	97%
Soun et al (2023)[35]	Patients suspected of stroke (N=760), Consensus neuroradiologists assessment	NR	87%	96%	85%	53%	99%
Schlossman et al (2022)[33]	Patients suspected of stroke (N=263), Consensus neuroradiologists assessment	NR	86%	90%	86%	45%	98%
*Dehkharghani et al (2021)[16]	Patients with and without LVO (N=217), Consensus neuroradiologists assessment	0.99	NR	96%	98%	NR	NR

*Study found in MIB262[10]

Abbreviations: AUC, receiver operating characteristics area under curve; LVO, large vessel occlusion; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

Two of the supplementary studies compared Rapid LVO to other commercially available LVO detection software and reported that Rapid LVO tended to have similar higher sensitivity and NPV values, but lower specificity and PPV (Appendix C, Table C3).[33,34]

Clinical Utility

Soun et al assessed the impact of Rapid LVO on acute stroke workflow and clinical outcomes. They found that although the use of Rapid LVO reduced the turnaround times for the radiology CTA report from 31 minutes to 22 minutes ($p<0.0005$), there was no significant impact on the door-to-treatment times.[35]

<u>Rapid CTP</u>

Accuracy

No study was identified that directly reported on the diagnostic accuracy of Rapid CTP. Austein et al (2016)[18] included in MIB262 (2021)[10] compared Rapid (unclear if technology described in the study is same as the currently used Rapid CTP) with two other commercially available software packages. They found Rapid to be the most accurate in predicting infarct core volume after thrombectomy, with an accuracy of 83%. Muehlen et al (2020) compared Rapid with two other automated CT perfusion software applications and found Rapid's hypoperfusion analysis had the highest correlation with the final infarct volume.[38] This result suggests that Rapid would be the most precise in predicting the final infarct volume after futile mechanical thrombectomy.

Two studies noted that Rapid CTP might underestimate the core infarct in certain populations when using the volume of relative cerebral blood flow of less than 30%, calculated by Rapid, as a surrogate for irreversible core infarct. A multivariate linear regression analysis by Copelan et al (2020) demonstrated that for symptomatic patients suspected of stroke, recent (less

than eight hours) intravenous iodinated contrast administration was associated with decreased core infarct estimation (by about two-thirds) by Rapid.[21] Similarly, John et al (2020) observed that among 134 patients with acute ischaemic stroke who had CT images and also CTP post-processed by Rapid software, 8 (6%) had gross discrepancies in core infarct between the CT and CTP images. These discrepancies were mainly an underestimation of the infarct by CTP, and likely due to recanalization of LVO.[22]

A study by Lasocha et al (2020) found that the automated Rapid CTP measurements of brain region volumes of time to maximum (TMAX) greater than 6 seconds were less than half those calculated by manual TMAX (125 vs. 331), indicating a lack of concordance.[36] TMAX is defined as the time taken for contrast bolus to travel from the proximal large vessel arterial circulation to the brain parenchyma. A region with TMAX of more than six seconds indicates a location with hypofusion and can be used to identify regions of the brain at risk of infarction for ischaemic stroke.

Clinical Utility

Two studies reporting on the clinical utility of Rapid CTP were identified. Aghaebrahim et al (2018)[19] included in MIB262 (2021)[10] found that the median time to treatment was reduced when using Rapid CTP compared to no CTP imaging (12 minutes vs 48.5 minutes, p<0.001). However, a study by Bulwa et al (2019) found that 13% of CTP maps from thrombectomy candidates who received automated CTP imaging had unreliable CTP maps as a result of motion artifact or contrast bolus flow issues.[23] It was noted that heart failure was more common in patients with unreliable CTP maps, though other clinical outcomes which were determined by the patient discharge destination were not significantly different between patients with and without unreliable studies.[23]

<u>Rapid MRI</u>

Accuracy

Straka et al (2010)[17] included in MIB262 (2021) [10] reported that in patients with stroke, Rapid MRI positively identified diffusion-perfusion mismatch, and showed high concordance with clinician assessment (Cohen's Kapa = 0.90), with a 100% sensitivity, 91% specificity, 91% PPV and 100% NPV. The analysis of the brain images took between five to seven minutes with Rapid MRI.[17] Diffusion-perfusion mismatch criteria can be used to identify patients with acute stroke that could benefit from reperfusion therapies.

Clinical Utility

A retrospective analysis by Pistocchi et al (2021)[37] found that based on Rapid MRI, 19.4% fewer patients who had a favourable outcome would not have been treated, compared to another semi-automated MRI software (Olea Sphere), indicating that the sole use of Rapid MRI to guide patient selection for endovascular thrombectomy might deprive some of successful treatment.

<u>Rapid Mobile Application</u>

Although not specifically a Rapid module, as part of the Rapid platform, the use of the Rapid mobile application reduced the time for door-to-groin-puncture time (33 minutes, p=0.02),

door-to-first-pass time (35 minutes, p=0.02) and door-to-recanalization time (37 minutes, p=0.02) compared to without the Rapid mobile application.[39] It also resulted in a reduction in National Institutes of Health Stroke Scale (NIHSS) 24 hours after procedure and at discharge for patients with LVOs.[39]

Impact on healthcare system

In the NICE report, clinical experts commented that the introduction of the Rapid platform could potentially improve patient triage and enable timely thrombectomy treatment for eligible patients. The use of Rapid to prioritise critical cases might reduce complications due to delayed treatment. The clinical experts also commented that using Rapid could also benefit patients by reducing cost of care due to shorter hospital stays and shorter stroke rehabilitation therapy.[10] However, no identified studies reported on these outcomes.

Ongoing trials

A search on ScanMedicine (NIHR Observatory) yielded no ongoing clinical trials for any Rapid modules.

Summary

Among the various Rapid modules, there are more studies available on Rapid ASPECTS, Rapid CTA and Rapid CTP. Only limited evidence was identified for other Rapid modules. NICE highlighted the limitations of the evidence base, noting that most of the evidence was retrospective studies, which may increase the risk of selection bias.

Overall, evidence on diagnostic accuracy showed moderate to high sensitivity and NPV for most modules, ranging from 60% to 100% and 88% to 100%, respectively. Where reported, the accuracy ranged between 83% to 86%. However, specificity and PPV varied from 31% to 98% and 31% to 96%, respectively.[13, 15, 16, 20, 24-26, 32-35] Specifically, high false positive rates were observed for Rapid ICH, Rapid ASPECTS, Rapid CTA and Rapid LVO. Limited studies reported on the clinical utility of some Rapid modules, showing reduction in time to treatment for Rapid CTA and CTP,[15, 19, 32] and reduction in processing time of CT reports for Rapid LVO.[35] Improved patient outcomes were observed in a study on Rapid CTA, however it was not statistically significant.[32] There is a general lack of studies on the cost-effectiveness of the various Rapid modules relative to standard care. NICE considered that the Rapid platform would typically cost more than standard care, however it might result in cost savings due to reduced time required by the neuroradiologist to review CT or MRI brain scans.[10]

VII. Estimated Costs

According to NICE, the license cost for Rapid is £20,000 (S$34,164)[2] per year.[10] This includes the cost for Rapid ICH, ASPECTS, CTA, LVO and MRI modules and associated costs such as Rapid mobile application, training and maintenance. It is possible to purchase specific Rapid modules individually. However, the company states that the cost of each module varies based on local circumstances, such as the number of modules.[10] A local clinician has voiced concerns

[2] Based on the Monetary Authority of Singapore exchange rate as of 28 August 2023: £1=S$ 1.7082. Figures were rounded to the nearest dollar.

that the manufacturer is trying to sell each module as a separate device and that some modules are being sold separately for individual scanners as this could make the Rapid software platform very expensive (Personal communication: Senior Consultant from National University Hospital, 7 October 2023).

Rapid NCCT and Rapid Hyperdensity were not part of MIB262 (2021)[10] and no pricing information for these two modules were found.

VIII. Implementation Considerations

There are multiple factors that could pose a barrier to the adoption of this technology in local healthcare practice.

To ensure effective decision making, healthcare professionals who will be exposed to the Rapid platform will need training to familiarise them with the workflow of the software. According to NICE, the training and certification programme is included in the annual license cost of Rapid and is delivered remotely as Rapid U.[10]

As the software allows for automated processing of brain images and allows healthcare systems to process more brain images faster, there is a potential for increased consumption of healthcare resources – as clinicians might have to go through more suspected cases of stroke.

As an AI-based software, the Rapid platform needs to follow the regulation of AI medical devices, based on the Ministry of Health (MOH)'s Artificial Intelligence in Healthcare Guidelines (AIHGIe).[40] There is a need for clear indication of the technology's role and place in clinical pathways, risk assessment and mitigation measures, potential cybersecurity vulnerabilities and performance tracking. In addition, long-term performance monitoring is required after its introduction into local healthcare practice.

Also, before widespread adoption of Rapid locally, there may be a need for further evidence, in the context of a local study in the local healthcare institutions that have already implemented Rapid. This is to address the potential concerns of the Rapid platform, like the high false positive rates observed in some of the modules as well as evaluation of the clinical utility and cost effectiveness of Rapid in the local context.

IX. Concurrent Developments

There are five other software products that use AI to process brain images to aid clinicians in guiding treatment (Table 9).

Table 9: Concurrent developments

Technology	Regulatory Status
e-Stroke (Brainomix Inc., United Kingdom)	FDA 510k cleared, CE marked
Viz™ Neuro (Viz.AI, United States)	FDA 510k cleared, Viz LVO module CE marked
Methinks Stroke Suite (Methinks AI, Spain)	CE marked
StrokeViewer (Nicolab, The Netherlands)	FDA 510k cleared for StrokeViewer LVO, CE marked
AUTOStroke Solution (Canon, Japan)	None
Abbreviations: CE, Conformité Européene; FDA, United States Food and Drug Administration.	

e-Stroke's platform (Brainomix Inc, United Kingdom) has three modules: e-ASPECTS, e-CTP and e-CTA, which have all received 510k clearances individually from FDA. Similarly, Viz™ Neuro's individual modules, LVO, CTP, ICH, Subdural and Aneurysm, have all received individual 510k clearances from FDA. Nicolab's StrokeViewer platform has five modules: Hemorrhage detection, ASPECTS, LVO, Collaterals and Automated perfusion, only the LVO module has received FDA 510k clearance from FDA.

X. Additional Information

Local clinician feedback is mixed. Some clinicians commented that the Rapid suite was well verified in scientific studies and well tested in various centres globally. They highlighted a strong local need for automated brain image processing software like Rapid, particularly the CT modules (Rapid NCCT, Rapid CTA and Rapid CTP), Rapid ASPECTS and the MRI module (Rapid MRI). In their opinion, the use of Rapid could significantly reduce the time required for image processing and dissemination, while also making assessment (eg. ASPECTS) more objective (Personal communication: Senior Consultant from National University Hospital; Senior Consultant from National Neuroscience Institute; June to September 2023). The other main advantages of Rapid highlighted are: 1) to rule out stroke mimics; and 2) to assist in predicting high risk for complications based on specific patterns, when detected (Personal communication: Senior Consultant from National Neuroscience Institute, 2 October 2023). Although no local evidence is currently available, anecdotal experience with Rapid was positive. Rapid was able to rapidly process imaging data and quick dissemination of standardised information for relevant stakeholders to make a clinical decision (Personal communication: Senior Consultant from National University Hospital, 7 October 2023).

However, other feedback indicated that thrombolysis and endovascular treatments are administered by trained stroke neurologists and interventional radiologists, and most are familiar with brain anatomy and able to accurately read CT scans without the need for additional software. Even though Rapid software might save time in reading scans (arguably by seconds), it might not make a significant difference clinically, as most patients would already need to undergo a diagnostic angiogram before endovascular clot retrieval (Personal communication: Senior Consultant from National University Hospital, 22 May 2023). On the other hand, there was report that the current local clinical pathway of reviewing brain scans, however efficient, inherently has a delay of 15 minutes. This 15-minute delay may be a difference between independent survival and lifelong disability for patients with stroke (Personal communication: Senior Consultant from National University Hospital, 7 October 2023).

The Hospital Services Division (HSD) in MOH is generally supportive of AI systems that assists in clinical decision making, but is agnostic to the system used, as long as it demonstrates safety and cost savings. Ideally, a single system should be used across the three healthcare clusters in Singapore (Personal communication: Director from HSD, 4 July 2023). HSD cited potential concerns from clinicians should there be a negative recommendation on the use of Rapid (Personal communication: Director from HSD, 1 November 2023).

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Appendix

Appendix A: Stroke background information

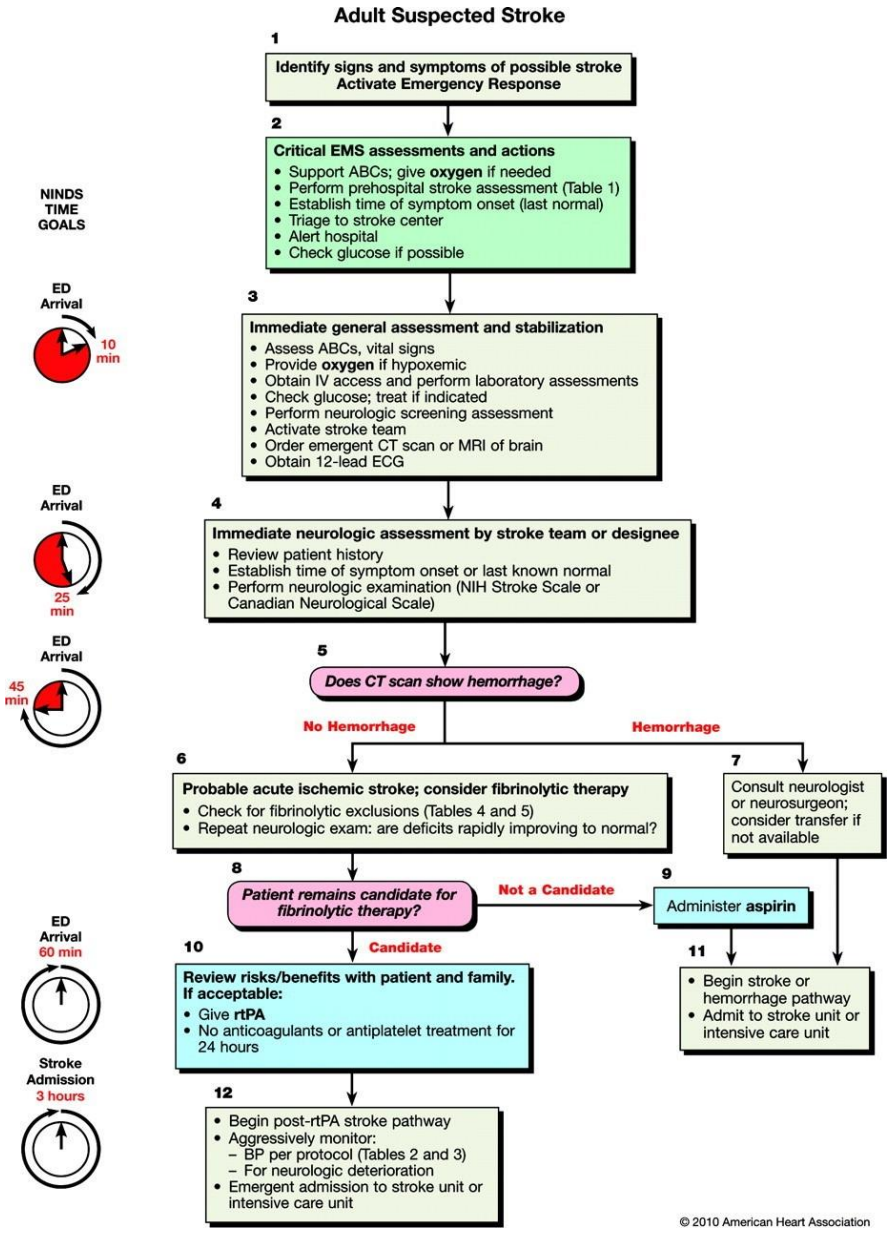

Figure A1: Stroke management pathway. Adapted from Part 11: Adult Stroke, 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (2011).[9]
Abbreviations: ABC, age, biomarker, clinical history; CT, computed tomography; ECG, electrocardiogram; EMS, emergency medical services; IV, intravenous; MRI, magnetic resonance imaging; NIH, National Institutes of Health, rtPA, recombinant tissue plasminogen activator.

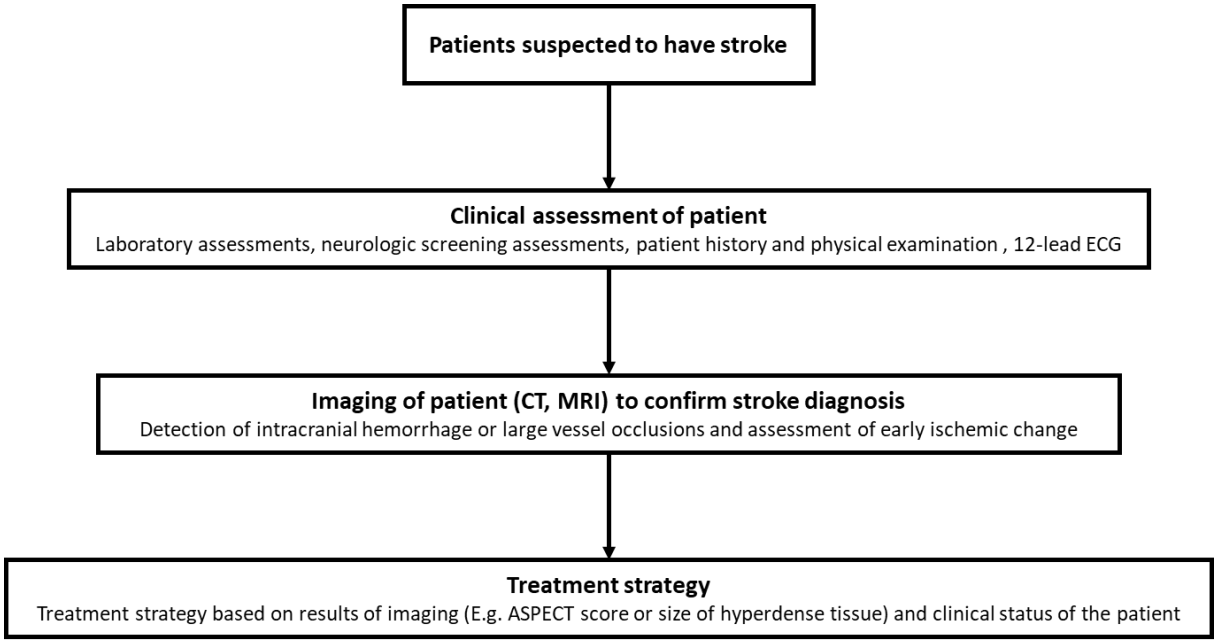

Figure A2: Local diagnostic pathway for patients suspected to have stroke. Adapted from both 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Part 11: Adult Stroke and Singapore Ministry of Health Clinical Practice Guidelines on stroke and transient ischaemic attacks (2011)[9] with inputs from a local clinician (Personal communication: Senior Consultant from National Neuroscience Institute, 25 August 2023).
Abbreviations: ASPECT, Alberta Stroke Program Early (non-contrast) Computed Tomography; CT, computed tomography; ECG, electrocardiogram; MRI, magnetic resonance imaging.

Appendix B: Details of evidence base

Table B1: Number of studies in evidence base

Type of study	Number of studies
Key Evidence Base	
Review (Medtech Innovation Brief)	1
Comparative study	5
Single-arm study	8
Supplementary Evidence Base	
Comparative study	7

Note:

1. Inclusion criteria
    a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
    a. Studies only available in abstract form.

Table B2: Number of studies grouped by Rapid modules

Rapid Module[a]	Number of Studies	
	Key Evidence[b]	Supplementary
Rapid ICH	2	None
Rapid ASPECTS	6	2
Rapid CTA	4	None
Rapid LVO	2	2
Rapid CTP	6	1
Rapid MRI	1	1

[a]Rapid NCCT and Rapid Hyperdensity are not listed as there was no evidence found for these Rapid modules.

[b]MIB262 published by NICE had evidence for each of the modules listed and was considered as one count of key evidence in each listed Rapid module except Rapid CTP, which had two studies included in MIB262.

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CTA, computed tomography angiography; CTP, computed tomography perfusion; ICH, intracranial haemorrhage; LVO, large vessel occlusion; MRI, magnetic resonance imaging.

Table B3: Evidence base study details

Study (Year)	Study design	Number of studies/patients	Population	Intervention	Comparator	Reference Standard
Key Evidence						
NICE MIB262 (2021)[10]	HTA	7 studies	Patients suspected of stroke	Rapid ICH, Rapid ASPECTS, Rapid CTA, Rapid LVO, Rapid CTP, Rapid MRI	Manual evaluation by Neuroradiologists, No CTP imaging, other commercially available software packages	Manual assessment by neuroradiologists in consensus
Eldaya et al (2022)[24]	Retrospective Comparative	307 patients	Symptomatic patients	Rapid ICH	Rapid ICH + Neuroradiologist	Manual assessment by

			suspected of stroke			neuroradiologists in consensus
Chen et al (2023)[25]	Retrospective Comparative	276 patients	Patients with acute ischaemic stroke	Rapid ASPECTS	NeuBrainCare, Manual assessment by neuroradiologist	Manual assessment by neuroradiologists in consensus
Chan et al (2023)[26]	Single-arm	104 patients	Patients suspected of stroke	Rapid ASPECTS, Rapid CTA	None	Manual assessment by neuroradiologists in consensus
Li et al (2023)[27]	Retrospective Comparative	61 patients	Patients with acute ischaemic stroke	Rapid ASPECTS	NSK, Manual assessment by neuroradiologist	Manual assessment by neuroradiologists in consensus
Maegerlein et al (2019)[28]	Retrospective Comparative	100 patients	Patients suspected of and known stroke	Rapid ASPECTS	Manual assessment by neuroradiologist	Manual assessment by neuroradiologists in consensus
Mansour et al (2020)[31]	Comparative	122 patients	Patients with stroke	Rapid ASPECTS	Manual assessment by neuroradiologist, Manual assessment by neuroradiologist using WhatsApp	Manual assessment by neuroradiologists in consensus
Adhya et al (2021)[32]	Single-arm	310 patients	Symptomatic patients suspected of stroke	Rapid CTA	None	Manual assessment by neuroradiologists in consensus
Amukotuwa et al (2019)[20]	Retrospective Single-arm	926 patients	Patients from DEFUSE 2 and DEFUSE 3 stroke trials, a cohort of endovascular clot retrieval candidates, Patients imaged for non-stroke related indications and code	Rapid CTA	None	Manual assessment by neuroradiologists in consensus

			stroke patients.			
Soun et al (2023)[35]	Single-arm	760 patients	Patients suspected of stroke	Rapid LVO	None	Manual assessment by neuroradiologists in consensus
Lasocha et al (2020)[36]	Single-arm	100 patients	Patients suspected of stroke	Rapid CTP	None	Manual assessment by neuroradiologist
Copelan et al (2020)[21]	Single-arm	271 patients	Symptomatic Patients suspected of stroke	Rapid CTP	None	None
John et al (2020)[22]	Retrospective Single-arm	635 patients	Patients with acute ischaemic stroke	Rapid CTP	None	None
Bulwa et al (2019)[23]	Retrospective Single-arm	99 patients	Patients who were thrombectomy candidates	Rapid CTP	None	None
Supplementary Evidence						
Hoelter et al (2020)[29]	Retrospective Comparative	131 patients	Patient with acute ischaemic stroke	Rapid ASPECTS	Frontier ASPECT Score Prototype V2, Brainomix e-ASPECTS	Manual assessment by neuroradiologists in consensus
Mallon et al (2022)[30]	Retrospective Comparative	90 patients	Patients suspected of stroke	Rapid ASPECTS	Brainomix e-ASPECTS	Manual assessment by neuroradiologist
Schlossman et al (2022)[33]	Retrospective Comparative	263 patients	Patients suspected of stroke	Rapid LVO	CINA LVO	Manual assessment by neuroradiologists in consensus
Delora et al (2023)[34]	Retrospective Comparative	360 patients	Patients suspected of LVO	Rapid LVO	Viz LVO	Manual assessment by radiologist
Muehlen et al (2022)[38]	Retrospective Comparative	39 patients	Patients with acute ischaemic stroke	Rapid CTP	Brainomix e-CTP, Syngo.via	Manual assessment by neuroradiologists in consensus
Pistocchi et al (2021)[37]	Comparative	144 patients	Patients with acute	Rapid MRI	Olea Sphere	Manual assessment by neuroradiologi

			ischaemic stroke			sts in consensus
Al-Kawaz et al (2022)[39]	Single-arm	64 patients	Patients with LVO	Rapid Mobile Application	None	Without Rapid Mobile Application
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CTA, computed tomography angiography; CTP, computed tomography perfusion; HTA, health technology assessment; ICH, intra cranial haemorrhage; LVO, large vessel occlusion; MRI, magnetic resonance imaging; N.A., not applicable.						

Table B4: Studies included in NICE MIB262[10]

Study (Year)	Study design	Number of patients	Population	Intervention	Comparator	Reference Standard
Heit et al (2021)[13]	Retrospective Comparative	308	Patients suspected of ICH	Rapid ICH	Manual assessment by neuroradiologist	Manual assessment by neuroradiologists in consensus
Aghaebrahim et al (2018)[19]	Retrospective Single-arm	132	Patients suspected of stroke	Rapid CTP	None	No CTP imaging
Albers et al (2019)[14]	Retrospective Comparative	65	Patients with stroke	Rapid ASPECTS	Manual assessment by neuroradiologists in consensus	Manual assessment by neuroradiologists in consensus using DWI images
Amukotuwa et al (2019)[15]	Retrospective Single-arm	477	Patients suspected of stroke	Rapid CTA	None	Manual assessment by neuroradiologists in consensus
Dehkharghani et al (2021)[16]	Retrospective Single-arm	217	Patients with and without LVO	Rapid LVO	None	Manual assessment by neuroradiologists (One in US and one outside of US)
Straka et al (2010)[17]	Retrospective Single-arm	63	Patients with stroke	Rapid MRI	None	Manual assessment by neuroradiologist
Austein et al (2016)[18]	Retrospective Comparative	147	Patients with stroke	Rapid CTP	Philips, Siemens	MRI image assessed by OsiriX
Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CTA, computed tomography angiography; CTP, computed tomography perfusion; DWI, diffusion weighted imaging; ICH, intracranial haemorrhage; LVO, large vessel occlusion; MRI, magnetic resonance imaging; US, United States.						

Appendix C: Notable evidence of Rapid

Table C1: Accuracy of Rapid ASPECTS in comparison with other ASPECTS scoring software

Study (year)	AUC	
	Rapid ASPECTS	Other ASPECTS software
[a]Chen et al. (2023)[25]	0.76	NeuBrainCare: 0.71
Hoelter et al. (2020)[29]	0.734	Brainomix: 0.759 Frontier V2: 0.752

Note:

[a]Results were based on all regions with 5mm slice thickness. Results were reported only in two decimal places.

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; AUC, receiver operating characteristics area under curve.

Table C2: Cost-effectiveness analysis of WhatsApp-based Manual ASPECT against Rapid ASPECTS

ASPECTS interpretation method	Mean per-patient cost (in LE*)	QALY
WhatsApp-based Manual ASPECTS	16,126.48	0.37
Rapid ASPECTS	12,646.48	0.73

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; LE, Livre égyptienne (Egyptian pounds); QALY, quality-adjusted life-year.

Table C3: Accuracy of Rapid LVO in comparison with other LVO detection software

Study (year)	Population (N), Reference Standard	Intervention	Accuracy	Sensitivity	Specificity	PPV	NPV
Schlossman et al (2022)[33]	Patients suspected of stroke (N=263), Consensus neuroradiologists assessment	Rapid LVO	86%	90%	86%	45%	98%
		CINA LVO	96%	76%	98%	85%	97%
Delora et al (2023)[34]	Patients suspected of LVO (N=360), Consensus neuroradiologists assessment	Rapid LVO	NR	87%	85%	46%	97%
		Viz LVO	NR	87%	96%	75%	98%

Abbreviations: AUC, receiver operating characteristics area under curve; LVO, large vessel occlusion; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.