A systematic review of next-generation point-of-care stroke diagnostic technologies

Shane Shahrestani, PhD, MS,^{1,2} Danielle Wishart, BA,¹ Sung Min J. Han, MS,¹
Ben A. Strickland, MD,¹ Joshua Bakhsheshian, MD,¹ William J. Mack, MD,¹ Arthur W. Toga, PhD,³
Nerses Sanossian, MD,⁴ Yu-Chong Tai, PhD,² and Gabriel Zada, MD, MS¹

Departments of ¹Neurological Surgery and ⁴Neurology, Keck School of Medicine, University of Southern California, Los Angeles; ²Department of Medical Engineering, California Institute of Technology, Pasadena; and ³Laboratory of Neuroimaging (LONI), USC Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, California

OBJECTIVE Stroke is a leading cause of morbidity and mortality. Current diagnostic modalities include CT and MRI. Over the last decade, novel technologies to facilitate stroke diagnosis, with the hope of shortening time to treatment and reducing rates of morbidity and mortality, have been developed. The authors conducted a systematic review to identify studies reporting on next-generation point-of-care stroke diagnostic technologies described within the last decade.

METHODS A systematic review was performed according to PRISMA guidelines to identify studies reporting noninvasive stroke diagnostics. The QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool was utilized to assess risk of bias. PubMed, Web of Science, and Scopus databases were utilized. Primary outcomes assessed included accuracy and timing compared with standard imaging, potential risks or complications, potential limitations, cost of the technology, size/portability, and range/size of detection.

RESULTS Of the 2646 reviewed articles, 19 studies met the inclusion criteria and included the following modalities of noninvasive stroke detection: microwave technology (6 studies, 31.6%), electroencephalography (EEG; 4 studies, 21.1%), ultrasonography (3 studies, 15.8%), near-infrared spectroscopy (NIRS; 2 studies, 10.5%), portable MRI devices (2 studies, 10.5%), volumetric impedance phase-shift spectroscopy (VIPS; 1 study, 5.3%), and eddy current damping (1 study, 5.3%). Notable medical devices that accurately predicted stroke in this review were EEG-based diagnosis, with a maximum sensitivity of 91.7% for predicting a stroke, microwave-based diagnosis, with an area under the receiver operating characteristic curve (AUC) of 0.88 for differentiating ischemic stroke and intracerebral hemorrhage (ICH), ultrasound with an AUC of 0.92, VIPS with an AUC of 0.93, and portable MRI with a diagnostic accuracy similar to that of traditional MRI. NIRS offers significant potential for more superficially located hemorrhage but is limited in detecting deep-seated ICH (2.5-cm scanning depth).

CONCLUSIONS As technology and computational resources have advanced, several novel point-of-care medical devices show promise in facilitating rapid stroke diagnosis, with the potential for improving time to treatment and informing prehospital stroke triage.

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KEYWORDS eddy current damping; near-infrared spectroscopy; volumetric impedance phase-shift spectroscopy; microwave; ischemic stroke; hemorrhagic stroke

STROKE represents the fifth most common cause of mortality within the United States, with approximately one person dying of stroke every 3.6 minutes.¹ There continues to be an emphasis on accurate and rapid detection, as time to treatment is paramount in optimizing outcomes. The timing of intervention within acute ischemic stroke care is critical, with national guidelines

calling for a door-to-treatment time of less than 1 hour.^{2,3} Several factors may contribute toward delays in stroke diagnosis and treatment. Two established contributors are prolonged stroke imaging (> 20 minutes) and complicated triage/transport by emergency medical services delaying imaging.⁴ Both of these factors stem in part from limitations of currently available diagnostic technologies,

ABBREVIATIONS AUC = area under the receiver operating characteristic curve; ECD = eddy current damping; EEG = electroencephalography; ICH = intracerebral hemorrhage; NIRS = near-infrared spectroscopy; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2; VIPS = volumetric impedance phase-shift spectroscopy.

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FIG. 1. PRISMA flowchart outlining the search and review process used to identify and select articles for inclusion in this systematic review.

including the lack of portability of CT and MRI, which heavily depends on factors such as hospital crowding and geographic location.^{5,6}

To address these shortcomings, several novel technologies and approaches have been developed to facilitate the diagnosis of stroke, with the hope of shortening the time to treatment and reducing the rates of morbidity and mortality. These approaches vary widely and include microwave-based analysis, volumetric impedance phase-shift spectroscopy (VIPS), near-infrared spectroscopy (NIRS), electroencephalography (EEG), transcranial Doppler ultrasound, and eddy current damping (ECD), among others.^{7–14} Several of these technologies have already progressed to clinical trials, and some have gained clearance from the FDA.^{8,15} Despite major differences in operational principles, all of these newly emerging technologies share a similar end goal: to develop portable diagnostic technology in an effort to more efficiently triage stroke care.^{7–14}

As stroke diagnostic technology continues to progress and novel technological avenues are discovered, it is imperative to assess the efficacy of these next-generation medical devices to ensure that the most efficient and accurate diagnostic and treatment plans are utilized. In this study, we conducted a contemporary systematic review of the current state of point-of-care stroke detection.

Methods

Search Strategy

In February 2021, a search of the PubMed, Web of Science, and Scopus databases in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1) was conducted. To identify studies reporting novel stroke diagnostic techniques, we used the following Boolean search terms: ((stroke OR hemorrhagic stroke OR thrombotic stroke OR ischemic stroke OR embolic stroke) AND ((di-

TABLE 1. Summary of QUADAS-2 tool assessment for all reviewed studies

Authors & Year	Risk of Bias: Patient Selection	Risk of Bias: Evaluation of Index Test	Risk of Bias: Evaluation of Reference Standard	Risk of Bias: Flow & Timing
FDA, 2010 ¹⁵	Unclear	Low	High	Unclear
Abtahi et al., 2012 ⁷	Unclear	Low	High	Unclear
Schlachetzki et al., 2012 ²⁶	Low	Low	Low	High
Persson et al., 2014 ¹¹	Unclear	Low	High	Unclear
Michelson et al., 2015 ²³	Low	High	High	Low
Mobashsher et al., 2016 ¹⁴	Low	High	High	Low
Brogan et al., 2017 ⁹	Low	Low	Low	High
Bashri et al., 2017 ²¹	Low	Low	Low	Low
Kellner et al., 2018 ⁸	High	Low	Low	High
Thorpe et al., 2019 ²⁷	High	High	High	Unclear
Coli et al., 2019 ²²	Low	High	Low	Low
Shreve et al., 2019 ¹³	Low	Low	Low	Low
Alqadami et al., 2020 ²⁰	Low	Low	Low	High
Cooley et al., 2021 ²⁹	Low	Low	Low	Unclear
Gottlibe et al., 2020 ¹⁰	Low	Low	Low	Low
Guasch et al., 2020 ²⁵	Low	Low	Low	Low
Shahrestani et al., 2020 ¹²	Low	High	Low	Unclear
Sheth et al., 2021 ²⁸	Low	Low	Low	High
Wilkinson et al., 2020 ²⁴	Low	Low	Low	High

agnos* OR detection) AND (tool OR tech* OR device OR instrument OR machine)) AND (portable OR mobile OR compact OR point-of-care OR prehospital OR rapid)). The same search terms were used for each database, and syntax was adjusted accordingly. The reference lists of all included studies were also reviewed. Two authors (D.W. and S.M.J.H.) independently reviewed each article, and any discrepancies were discussed by an arbitrator (S.S.) until consensus was reached. D.W. and S.M.J.H. performed data extraction once the list of included studies was finalized.

Selection Criteria and Data Collection

Overall, the initial search identified 2646 studies. Removal of duplicates yielded 1895 studies, after which the following search criteria were applied: 1) studies describing stroke diagnostic technologies or devices other than traditional CT or MRI, 2) studies published within the last 10 years, and 3) studies written in the English language. The full text was reviewed if any discrepancies arose while parsing through the studies. This process yielded a total of 92 studies. Studies were excluded if they 1) involved conventional methods such as CT or MRI, 2) were book chapters, 3) were animal and/or nonhuman models, or 4) demonstrated biomarker detection of stroke (rather than medical device development). Nineteen studies met the inclusion and exclusion criteria and were included in the systematic review analysis. Outcomes were prespecified and included the cost of the technology, accuracy and timing compared with standard imaging, potential risks or complications, potential limitations, size/portability, and range/size of detection.

Risk of Bias Analysis

The Quality Assessment of Diagnostic Accuracy Studies–2 (QUADAS-2) tool was used to assess risk of bias (Table 1). This assessment tool is recommended by the Agency for Healthcare Research and Quality, the Cochrane Collaboration, and the United Kingdom National Institute for Health and Clinical Excellence. The QUADAS-2 itself encapsulates the following four metrics that may increase study bias: 1) patient selection, 2) evaluation of index tests, 3) evaluation of reference standards, and 4) flow and timing.^{16–19} Based on several yes/no questions, each of these metrics is then ranked as high risk of bias, low risk of bias, or unclear. The risk of bias was assessed independently by S.S., D.W., and S.M.J.H. for this systematic review, and any discrepancies were discussed until a consensus was reached.

Results

Included Diagnostic Stroke Platforms

Of the 19 studies identified through our systematic review, 6 implemented microwave technology (31.6%), 4 used EEG (21.1%), 3 used ultrasonography (15.8%), 2 used NIRS (10.5%), 2 used portable MRI devices (10.5%), 1 used VIPS (5.3%), and 1 used ECD (5.3%) (Fig. 2). A summary of each study, including the diagnostic tool used, accuracy, and advantages or limitations of the tool are included in Table 2.

Stroke Diagnosis Using Microwaves

Several methods of nonionizing stroke detection are under investigation. The most popular medical device being

FIG. 2. Schematic demonstrating the use of each novel stroke technology. Made with a valid license in ©BioRender - biorender.com.

investigated for stroke diagnosis involves microwave-based stroke sensing.^{7,11,14,20–22} This method was first described by Abtahi et al. in 2012.⁷ All of the studies investigating microwave technology underscored the low-cost, portability, and rapid diagnostic time of this method.⁷ In addition, this technology is good at distinguishing between ischemic and hemorrhagic stroke subtypes (Table 3).¹¹ However, several limitations need to be addressed as they pertain to these sensors. First, the interface between the sensor and the head is an important consideration to maximize radiofrequency transmission through the skull. Abtahi et al. utilized a water bolus between the antenna and head to ensure signal transduction and described signal attenuation and leakage into free space instead of transmission into the head when using this technique.⁷ Similarly, the current spatial and depth resolution of microwave imaging is subpar and requires improvement. Several studies have noted that, at their current capacity, microwave-based technologies are unable to solely dictate thrombolytic therapy because small targets may not actually be detected.^{11,14} One method of addressing the problem of resolution is by multiplexing microwave sensors and placing several on the head; Bashri et al. noted that the accuracy of microwave systems are dependent on the number of antennas.²¹ However, in exchange for increased accuracy in spatial resolution comes the trade-off of increased device size and complexity. In addition, Alqa-

dami et al. reported that a maximum of 32 antennas can be placed to maximize the accuracy of microwave-based stroke detection devices.²⁰ Microwave-based sensors hold significant future promise in rapid stroke detection if these limitations can be overcome.

Stroke Diagnosis Using EEG

Four studies successfully described EEG for stroke detection. The first study was published by Michelson et al. in 2015 and demonstrated acute stroke diagnosis (ischemic and hemorrhagic) with high sensitivity (91.7%) and moderate specificity (50.4%).²³ Further experimentation by Gottlib et al., Shreve et al., and Wilkinson et al. confirmed the efficacy of EEG for ischemic stroke diagnosis using the changes in the revised brain symmetry index, alpha/delta frequency band ratios, and mixed delta/alpha ratio plus pairwise-derived brain symmetry index values, respectively.^{10,13,24} These studies suggested that EEG may accurately predict acute stroke within 3 minutes. In addition, EEG may be able to differentiate between hemorrhagic and ischemic stroke subtypes, since it has been shown to have an overall sensitivity of 91.7% for predicting any stroke, sensitivity of 90.3% for ischemic stroke, and sensitivity of 94.1% for hemorrhagic stroke. However, the main limitation of EEG detection is the massive setup

TABLE 2. Summary of studies, including diagnostic mechanism, benefit of method, limitations, and accuracy

Authors & Year	Mechanism	Time to Diagnosis	Size & Portability	Benefits Compared w/ Standard Imaging	Potential Limitations	Model Used for Testing	Accuracy in Detection
FDA, 2010 ¹⁵	NIRS	NA	Small handheld device	1) Very portable due to size, 2) can be used to easily triage pts	1) Cannot detect very small hematomas or hematomas not close to skin surface, 2) not a replacement for conventional scans	Phantom head	Sensitivity for intracranial hematoma where mean optical density >0.2: 74.6%, specificity for no hematoma: 81.6%
Abtahi et al., 2012 ⁷	Microwave	NA	28 × 28 × 11 mm ³	1) Compact, 2) real-time diagnosis, 3) portable	1) Requirement of water bolus btwn antenna & pt head, 2) radiation can leak out into free space & lose signal instead of transmission into head	Phantom head	NA
Schlachetzki et al., 2012 ²⁸	Ultrasound	5.6 mins	Portable ultrasound	1) Portable, 2) can be used w/ ultrasound microbubbles that can replace thrombolytic agents in the field	Study seems to only be able to provide MCA occlusion diagnosis, cannot detect typical hypertensive basal ganglia ICH	Human	9/10 MCA occlusions correctly identified; sensitivity 90% (95% CI 55.5–99.75%), specificity 98% (95% CI 92.89–99.97%), PPV 90% (95% CI 55.5–99.75%), NPV 98% (95% CI 92.89–99.97%)
Persson et al., 2014 ¹¹	Microwave	NA	NA	1) Safe w/o side effects, 2) portable, 3) potentially more feasible for low-income countries or rural areas that cannot afford CT-equipped mobile stroke units	At current capacity, it is unable to determine thrombolytic treatment	Human	Study 1: ICH vs IS pts AUC 0.88; the hemorrhagic detector aimed at identifying all 9 pts w/ ICH, 7/11 IS pts were separated from the ICH group & 4 were not. Study 2: ICH vs IS pts AUC 0.85, & ICH vs healthy individuals AUC 0.87; the hemorrhagic detector aimed at identifying all 10 pts w/ ICH, 14/15 IS pts were clearly separated from the ICH group & 1 was not.
Michelson et al., 2015 ²³	EEG	10 mins	Portable handheld device	1) Electrophysiological abnormalities may emerge earlier than structural changes & better detect changes in neuronal function, 2) EEG recording on handheld device & using independently derived classifier algorithm as used in this study to identify brain injury makes it less time consuming & would not require a trained EEG specialist to be present, 3) faster & can be done at bedside	1) Difficult to detect new vs old strokes, 2) cannot be used in pts taking certain drugs because it will alter the EEG reading, 3) sensitivity & specificity are not high enough to use this in absence of imaging	Human	Sensitivity for predicting stroke: 91.7%, sensitivity for all ISs: 90.3%, sensitivity for all HSs: 94.1%

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TABLE 2. Summary of studies, including diagnostic mechanism, benefit of method, limitations, and accuracy

Authors & Year	Mechanism	Time to Diagnosis	Size & Portability	Benefits Compared w/ Standard Imaging	Potential Limitations	Model Used for Testing	Accuracy in Detection
Mobashsher et al., 2016 ¹⁴	Microwave	NA	Portable device	1) Portable, 2) rapid diagnosis, 3) low cost, 4) noninvasive, 5) fast image processing	1) Quality of image can decrease if hemorrhage depth is increased so will require better statistical analysis, 2) need to scan from multiple perspectives depending on target size, 3) smaller targets: scattering from surrounding parts of brain can be stronger so signal-to-clutter ratio can decrease, 4) wide bandwidth subjects it to be affected by noise	Phantom head	NA
Brogan et al., 2017 ⁹	NIRS	2–15 mins	NA	1) Can be used as diagnostic aid when CT is unavailable, 2) can be used as triage tool	1) Subgaleal hematomas impede detection rates of intracranial pathology, 2) certain trauma pts may not be suitable for NIRS exam, 3) difficult to get to deep lesions	Human	Cross-study NPV of 0.9 & PPV of 0.77
Bashri et al., 2017 ²¹	Microwave	NA	NA	1) Real-time, 2) portable, 3) compact/wearable, 4) low cost	1) Accuracy of imaging system dependent on no. of antennas, which would mean device is less compact, 2) will most likely require machine learning algorithm as postprocessing technique to make up for transmission loss	Phantom head	Located blood clot through CDAS imaging technique
Kellner et al., 2018 ⁸	VIPS	<1 min	Portable, like a visor	1) Portable, 2) noninvasive, 3) rapid diagnosis, 4) minimal specialized training	1) Pts w/ intracranial implants, 2) metallic objects in hair, 3) sensitivity can be improved by having a prestroke baseline for each pt, but not possible in most cases, 4) unsure of cost of device	Human	Severe stroke vs small strokes: sensitivity 93%, specificity 92%, AUC 0.93; severe stroke vs all other pts: sensitivity 93%, specificity 87%, AUC 0.93; severe stroke vs other stroke pts: false neg 7%, false pos 8%
Thorpe et al., 2019 ²⁷	Ultrasound	NA	Portable ultrasound	1) Portable, 2) inexpensive	Requires a trained technician to reach results cited in ultrasound	Human	LVO pts separated from controls w/ avg AUC of 92%
Coli et al., 2019 ²²	Microwave	<5 mins	NA	1) Low cost, 2) rapid diagnosis, 3) portable, 4) can check for hemorrhage & confirm that it is not IS	1) Starting parameters of binary accumulative processing require large no. to attain accurate % change for reconstructed perimetry & mean reconstructed value, 2) will need specific processing protocol to detect IS; current model can rule out IS if it is an HS	Phantom head	NA

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TABLE 2. Summary of studies, including diagnostic mechanism, benefit of method, limitations, and accuracy

Authors & Year	Mechanism	Time to Diagnosis	Size & Portability	Benefits Compared w/ Standard Imaging	Potential Limitations	Model Used for Testing	Accuracy in Detection
Shreve et al., 2019 ¹³	EEG	3 mins	Portable EEG	1) Portable/bedside, 2) very fast	1) While EEG helps w/ diagnosing large acute ISs, data do not perform well in identifying acute cerebral ischemia, 2) no data on its usefulness in ICH, so still cannot be used in hemolysis decisions	Human	NA
Alqadami et al., 2020 ²⁰	Microwave	<1 min	24 × 45 × 4 mm ³	1) Low cost, 2) nonionizing, 3) rapid diagnosis, 4) portable, 5) flexible antenna compared w/ other options, 6) compact	1) Target locations inside imaging domain can be less accurate (shifts ~1 cm), 2) 32 max no. of antennas can be used to maximize accuracy in detection	Human	1) 155% fractional bandwidth (0.45–3.6 GHz), 2) sensing efficacy verified on 3D MRI-derived head model & homogeneous head phantom w/ different sizes of bleeding targets, 3) 22-element array better than 16-element array (possibly due to compactness of the antenna)
Cooley et al., 2021 ²⁹	Portable MRI	Faster than conventional MRI since transportation is not required	Portable, does not require cooling, lightweight (160–230 kg), can mount on cart or w/in ambulance	1) Portable, 2) low cost, 3) more accurate characterization than CT, 4) POC diagnostic method, 5) comparable w/ low-field MRI, 6) magnetic field variation shaped into built-in field gradient for image encoding, 7) reduced power requirements, 8) only around head so less confinement around body, 9) quiet operation/does not need ear plugs	1) Spatial resolution & sensitivity lower compared w/ high-field MRI, 2) experiments conducted in RF-shielded scanner suite (like traditional scanners) because EMI could not be fully eliminated in human imaging	Human	Nonlinearity/resulting error of readout gradient Gx 6.8% avg error & 46.6% max error in 17-cm circular ROI, nonlinear mapping of voxels in image causes geometric distortion using simple FFT reconstruction & variability in local field gradient leads to spatial varying image resolution
Gottlib et al., 2020 ¹⁰	EEG	10 mins	Portable (simple version of EEG)	1) Low cost, 2) portable, 3) outside hospital setting, 4) easier protocol/does not require well-trained staff, 5) rapid diagnosis, 6) indicative of ischemia like traditional EEG/rsBSI parameter, 7) change in EEG wave patterns occurs seconds after onset of stroke	1) Does not provide high-resolution info, 2) could not identify rsBSI score as cutoff for stroke pts, 3) noise & artifacts increase asymmetry level, so must be removed during data analysis	Human	NA
Guasch et al., 2020 ²⁵	Ultrasound	<10 mins	Portable ultrasound system/helmet	1) Low cost, 2) portable, 3) better soft-tissue contrast than CT, 4) easier protocol, 5) can help w/ earlier intervention	1) Computational efforts for image reconstruction (runtime & costs) but tech advancements are making it easier, 2) starting model of skull/absorption of signal through multiple layers to reach soft tissue	Phantom head & human	NA
Shahrestani et al., 2020 ¹²	ECD	2.43 mins	11.4-cm diameter	Localize hemorrhage quickly at bedside, leads to reduced time to treatment	Only demonstrated detection of HS	Phantom head	Accurate prediction of bleed location 16/16 (100%)

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TABLE 2. Summary of studies, including diagnostic mechanism, benefit of method, limitations, and accuracy

Authors & Year	Mechanism	Time to Diagnosis	Size & Portability	Benefits Compared w/ Standard Imaging	Potential Limitations	Model Used for Testing	Accuracy in Detection
Sheth et al., 2021 ²⁸	Portable MRI	Faster than conventional MRI since no transportation required	1) No cryogenics, 2) uses single standard power outlet, 3) maneuverable w/in ICU room, 4) self-contained motor	1) Portable/bedside, avoid risks involved in transporting pt to imaging suite (e.g., displacement of endotracheal tube, pts w/ infectious disease), 2) no need to remove ferromagnetic equipment in hospital room (e.g., gas tanks, ventilators) because low-field, 3) cloud-based imaging viewer	1) Low-field, 2) study limitations: single-center design, small no.	Human	COVID-19–neg pts (n = 30), neuroimaging findings in 29 cases (97%); COVID-19–pos pts (n = 20); all 11 pts who had conventional imaging w/ agreeable findings
Wilkinson et al., 2020 ²⁴	EEG	11 mins	Portable EEG	1) Portable, 2) potentially faster time to diagnosis	1) Not very accurate in determining small & large strokes w/in stroke group, 2) pts tested an avg 3.7 days post-stroke onset, which changes EEG readings	Human	Severity classification has accuracy of 0.36 & sensitivity for controls & small, moderate, & large strokes of 0.67, 0, 0.33, & 0, respectively; classification for stroke vs control is 0.67 accuracy, w/ sensitivity of 0.75 & specificity of 0.33; classification of moderate & large strokes vs small strokes & controls has accuracy of 0.76, w/ sensitivity of 0.63 & specificity of 0.86

Avg = average; CDAS = confocal delay-and-sum; EMI = electromagnetic interference; FFT = fast Fourier transform; HS = hemorrhagic stroke; info = information; IS = ischemic stroke; LVO = large-vessel occlusion; MCA = middle cerebral artery; NA = not available; neg = negative; NPV = negative predictive value; POC = point of care; pos = positive; PPV = positive predictive value; ROI = region of interest; rsBSI = revised brain symmetry index; tech = technological.

TABLE 3. Overview of stroke diagnostic technology included in this systematic review

Name of Technology	Description of Technology	Potential to Differentiate IS vs HS	Potential to Differentiate Stroke From Stroke Mimics	Potential to Detect LVO Stroke
Microwave	Measuring microwave scattering due to the dielectric contrast of different tissue types; usually used in a helmet-like device w/ antennas	Yes	Unknown	No
EEG	Using brain electrical activity to detect acute stroke	Yes	Not determined (specificity of 50.4% to stroke mimic in Michelson et al. ²³)	Unknown
Ultrasonography	Using ultrasound tomography to provide a 3D image of brain to diagnose acute stroke	No	Unknown	Yes
NIRS	Detects absorption of 805-nm wavelength, which is sensitive to blood vol	No	No	No
Portable MRI	Portable, low-field MRI to detect acute stroke	Yes	Yes	Yes
VIPS	Uses array of low-energy radio waves to detect bio-impedance of different tissue type & fluid properties	Unknown	Yes	Yes
ECD	Measures changes in electrical conductivity in the brain by creating microtesla magnetic fields	Yes	Unknown	Unknown

"Unknown" is used in instances in which the comparison had not been studied or had not been well reported on. "Not determined" is used in instances in which a comparison had been reported but did not have definitive results.

time normally associated with placing numerous leads on the head. Furthermore, if MRI is indicated, all magnetic leads must be taken off of the patient, which requires additional time. Additional limitations include poor spatial resolution and that small infarcts or hemorrhages may not be detected using this method.

Stroke Diagnosis Using Ultrasonography

Ultrasound diagnosis of stroke is a nonionizing technique that is currently being investigated by several groups.^{25–27} The primary limitation of this technique is the need for ultrasound transducer materials to minimize signal attenuation. Even with appropriate transduction materials, the density of the skull contributes to significant signal attenuation, and the temporal bone window is frequently used for intracranial ultrasound applications.²⁶ Even when implementing these findings, heavy computation is critical in accurately utilizing ultrasound for stroke diagnosis. Thorpe et al. demonstrated the calculation of a velocity curvature index from cerebral blood flow velocity using a transcranial Doppler probe.²⁷ This method yielded a maximum area under the receiver operating characteristic curve (AUC) of 0.94, which represents one of the highest metrics of device performance reported in the contemporary stroke diagnostic device literature.

Stroke Diagnosis Using NIRS

The FDA has approved the use of NIRS for detection of hemorrhagic stroke.^{9,15} Nonionizing NIRS to determine absorption of a 805-nm wavelength, which is sensitive to blood volume and not blood oxygen saturation.¹⁵ While this technology allows for rapid and compact scanning and has a cross-study sensitivity of 78%, specificity of 90%, positive predictive value of 77%, and negative predictive value of 90%, it has several major limitations.⁹ First, NIRS is unable to detect ischemic stroke and can only detect

hemorrhagic stroke > 3.5 mL. Furthermore, NIRS can only detect hematomas within the most superficial 2.5 cm of the head. As such, this method is not helpful for detecting deeper intracerebral hemorrhage (ICH) (such as some basal ganglia ICHs) and cannot yet distinguish between stroke subtypes to facilitate treatment. Additionally, the NIRS device is only probed at 8 unique points on the head and is not indicated for continuous scanning.

Stroke Diagnosis Using Portable MRI

Aside from novel diagnostic technologies, significant advances have taken place with regard to portable MRI scanners. Both Sheth et al. and Cooley et al. described these portable advancements, which boast many of the benefits of traditional MRI, including accurate neuroimaging and millimeter resolution.^{28,29} However, portable MRI scanners have several limitations compared with the other stroke diagnostic devices, including much larger sizes, increased power requirements, and increased device costs, limiting widespread availability.

Stroke Diagnosis Using VIPS

Another nonionizing stroke diagnostic technique is VIPS, which uses bioimpedance asymmetry scores to predict large-vessel occlusions.⁸ While the VIPS device is portable, noninvasive, and easy to use and has a sensitivity of 93% and specificity of 92% for large-vessel stroke, it has not yet been shown to work effectively for differentiation of ischemic and hemorrhagic stroke. In addition, VIPS devices are extremely sensitive to metal (e.g., metallic implants, metal objects worn in the hair), and the presence of metal can significantly disrupt the signal.

Stroke Diagnosis Using ECD

ECD sensors represent a nonionizing stroke diagnostic

technology.¹² These sensors are 11 cm in diameter and operate by creating microtesla-level magnetic fields capable of detecting changes in electrical conductivity within the brain, with ischemia having reduced conductivity and hemorrhage having increased conductivity. Prior studies have demonstrated a scanning depth of 5 cm into the brain, with accurate (100% detection) image production of hemorrhagic stroke within 2.43 minutes.¹² However, current limits of hemorrhage detection have been reported to be 25 mL, and it has been shown to also be sensitive to the presence of metal objects.

Discussion

The present systematic review describes contemporary and evolving stroke diagnostic technologies, their proposed benefits and limitations, and current accuracy in diagnosis. Following our comprehensive review of the literature, we identified 7 diagnostic avenues that are currently being investigated or preliminarily implemented for the assessment of stroke. The primary benefit of next-generation stroke technology centers around portability. All of the studies included in this study emphasized the need for portable stroke-sensing capabilities to facilitate triage and save time compared with CT or MRI. Furthermore, rapid prehospital diagnosis (compared with traditional imaging) was emphasized as a potential benefit in all studies. A wide variety of limitations was also discussed for each diagnostic method. Most notably, scanning depth into the brain and the detection of submillimeter lesions require further investigation. In addition, VIPS and ECD sensors were highly sensitive to the presence of metal, which may be present as a medical implant or within patient clothing.

Recent technological advances have allowed for the development of technologies for stroke detection and have also allowed for the modification of preexisting diagnostic devices for stroke applications. Technologies such as ultrasonography and EEG are being retrofitted for stroke applications thanks to recent computational advancements, including finite element modeling and machine learning.^{24,30} One major benefit of the utilization of preexisting diagnostic tools for stroke diagnostics is the well-understood risks and benefits associated with the technology. Such a thorough understanding also greatly reduces the difficulty of obtaining FDA approval, allowing for a shortened timeline to market. Notable medical devices that accurately predicted stroke in our review included EEG-based diagnosis with a maximum sensitivity of 91.7% for predicting a stroke,²³ microwave-based diagnosis with an AUC of 0.88 for differentiating ischemic stroke and ICH,¹¹ ultrasound with an AUC of 0.92,²⁷ VIPS with an AUC of 0.93,⁸ and portable MRI with a diagnostic accuracy similar to that of traditional MRI.^{28,29}

In addition, current technologies require further innovation to accurately classify stroke subtypes while achieving acceptable scanning depths and volume sensitivity. As previously mentioned, FDA-approved NIRS methods are currently indicated only for suspected hemorrhagic stroke and cannot distinguish ischemic and hemorrhagic stroke subtypes.^{9,15} Furthermore, the moderate sensitivity of NIRS, volume limits, and detection range prevent

it from being useful in cases of suspected deep or small ICHs.^{9,15} Similarly, microwave-based methods and EEG have also been described to have a limited ability for detection of small hematomas, which prevents their use for high-accuracy stroke subtyping and for the guidance of thrombolytic administration.^{10,11,13,14,24} The technology that shows the greatest potential promise for the detection and classification of stroke subtypes is currently portable MRI, which essentially operates as a miniaturized compact version of traditional MRI. However, these devices are much more expensive and much larger than comparable next-generation stroke diagnostic technologies.^{28,29} Further research on VIPS and ECD methods for stroke detection are necessary to fully understand their capabilities in ischemic and hemorrhagic stroke detection and classification.⁸

With the hope of further improving the detection of stroke, biomarker approaches are also being investigated but remain outside of the scope of this review. One of the best biomarker diagnostic performances described in the literature was achieved when using apolipoprotein A1-unique peptide as a biomarker for acute ischemic stroke, with an AUC of 0.975, a sensitivity of 90.63%, and a specificity of 97.14%.³¹ Similarly, Tao et al. conducted a study with the second largest AUC of 0.879, which was achieved by combining lipoprotein-associated phospholipase A2, serum amyloid A, and fibrinogen as diagnostic biomarkers for acute cerebral infarction.³² However, among all of the blood-based biomarker diagnostic tests, one major problem remains: access to a laboratory for the analysis of blood components. This is a huge limitation, and laboratory processing times may take several additional hours depending on the assay required for diagnosis (e.g., enzyme-linked immunosorbent assay).

Limitations

There are several limitations to this study. First, many of the technologies described in this article are exploratory, and additional multicenter randomized controlled studies are necessary to fully confirm the efficacy of these stroke diagnostic methodologies. Second, significant heterogeneity existed within each novel diagnostic subgroup discussed in our review. This is likely due to the fact that optimal protocols have not yet been established because of the experimental nature of current investigations. Third, several of the devices discussed herein were specific for either ischemic or hemorrhagic stroke, and significant innovation is still required to differentiate the two subtypes.

Conclusions

As technology and computational resources have advanced, several next-generation medical devices have emerged that show promise in facilitating stroke diagnosis. These improvements include reduced diagnostic times, increased device compactness allowing for portable diagnosis, and reduced device costs. As additional data continue to emerge regarding these novel methods, it is imperative to reexamine the current stroke diagnostic paradigm and updated guidelines for diagnosis and management appropriately. Overall, additional studies are necessary to thoroughly investigate the benefits and limitations of emerging

stroke diagnostic technologies with the hope of improving stroke management and reducing rates of mortality and morbidity associated with patient transport or imaging availability.

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Disclosures

Dr. Mack: direct stock ownership in Integra, Cerebrotech, and Rebound Therapeutics.

Author Contributions

Conception and design: Shahrestani. Acquisition of data: Shahrestani, Wishart, Han. Analysis and interpretation of data: Shahrestani, Wishart, Han. Drafting the article: Shahrestani. Critically revising the article: Shahrestani, Strickland, Bakhsheshian, Mack, Toga, Sanossian, Tai. Reviewed submitted version of manuscript: Shahrestani, Strickland, Bakhsheshian, Mack, Toga, Sanossian, Tai. Administrative/technical/material support: Zada, Tai. Study supervision: Zada, Tai.

Supplemental Information

Videos

Video Abstract. <https://vimeo.com/557536887>.

Correspondence

Gabriel Zada: Keck School of Medicine, University of Southern California, Los Angeles, CA. gabriel.zada@med.usc.edu.