MRI Biomarkers in Acute Ischemic Stroke: A Conceptual Framework and Historical Analysis

Chelsea S. Kidwell, MD

Over the past 2 decades, advanced multimodal imaging has offered much promise for stroke investigators and clinicians, particularly those interested in using imaging to optimize and extend the time window for acute ischemic stroke therapies. Multimodal imaging has many potential applications in the acute stroke setting, such as the following: (1) to confirm the diagnosis of acute cerebral ischemia and exclude contraindications to treatment (eg, acute blood because of hemorrhagic transformation [HT]); (2) to select patients likely to benefit or not benefit from therapies (eg, by characterizing the extent of core irreversibly injured tissue, salvageable penumbra, or markers of high risk for HT); and (3) to serve as a surrogate or auxiliary outcome measure to test putative treatments.

However, the promise of advanced multimodal imaging as a selection modality to optimize efficacy and safety of new treatments for stroke and also as a surrogate end point to test interventions has yet to be fully realized. Both of these applications use neuroimaging as a biomarker. A critical analysis of both the successes and missteps of studies performed to date, including translation of animal models to human studies, can provide valuable lessons that can be applied to the design of future studies. Applying current definitions and criteria for biomarkers to stroke neuroimaging research helps provide a conceptual framework for this analysis.

The National Institutes of Health Biomarkers Definitions Working Group defines a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.1 Biomarkers (Table 1 shows types, definitions, and examples) can be used as a diagnostic tool, a prognostic tool, a predictive tool (for predicting response to an intervention), or a substitute for a clinical outcome to measure the response to an intervention (surrogate end point). Biomarkers must be biologically plausible and show statistically appropriate performance characteristics. Prognostic biomarkers must correlate with clinical outcomes irrespective of treatment. Predictive biomarkers must be able to predict response to therapy. Finally, surrogate end points must additionally show responsiveness to therapeutic interventions. Thus, surrogate end points are a subset of biomarkers intended to substitute for a clinical end point, which are reasonably likely, based on epidemiological, therapeutic, pathophysiological, or other evidence, to predict clinical benefit (or harm or lack of either).1 A valid surrogate end point must demonstrate both accuracy (correlation with clinical end point) and precision (reproducibility). Further, surrogate end point evaluation includes analytic validation, qualification, and utilization analyses.2 The acute stroke imaging field is rife with studies of imaging biomarkers in acute stroke; however, the field has lagged in clearly defining the types of biomarkers and properly evaluating and validating them.

In acute stroke neuroimaging, most attention has been recently devoted to using imaging biomarkers either as a prediction tool (for treatment selection) or as a surrogate end point (eg, attenuation of lesion growth). Imaging selection biomarkers can be used in acute stroke to optimize inclusion/exclusion criteria by focusing enrollment of patients with the target disease state and excluding those unlikely to benefit or even at risk for worse outcomes. In this case, evaluation of the utility of these biomarkers requires comparison to the gold standard definition of the biomarker itself along with demonstration that the biomarker predicts the probability of response to an intervention. Examples of putative imaging inclusion biomarkers designed to optimize efficacy are penumbral imaging, a target vessel occlusion, or a persistent perfusion deficit. Examples of putative imaging exclusion criteria to optimize both safety and efficacy are presence of a large volume of core irreversibly injured tissue or markers of high risk for HT (eg, blood–brain barrier disruption).

In contrast, surrogate end points in acute stroke neuroimaging studies are designed to demonstrate a beneficial effect of a treatment (such as thrombolysis) on an imaging outcome (eg, attenuation of lesion growth) that correlates with (and is therefore a substitute for) a clinical outcome. The use of surrogate end points in all fields of clinical research has held enormous appeal because they have the potential to identify effective treatments with smaller sample sizes. Examples of surrogate end points in acute stroke neuroimaging treatments trials include vessel recanalization, tissue reperfusion, and attenuation of lesion growth.

However, the literature provides many examples of potential pitfalls of biomarkers in clinical research in other fields. Much work has been performed to define the various types of biomarkers and how they should be evaluated. Previous reports have examined the potential merits and limitations of the use of surrogate end points in stroke.3–5 This article...
provides a conceptual framework for using current definitions and approaches to all types of biomarkers in the field of acute stroke magnetic resonance imaging (MRI), including a critical review of the evidence supporting imaging biomarkers for selection and surrogate endpoints. Although this review focuses on MRI, many of the concepts discussed apply to the multimodal computed tomography approach as well.

**Brief Historical Overview, Definitions, and Gold Standards**

The ischemic penumbra was first defined by Astrup et al in an animal model (baboon) of focal ischemia based on cerebral blood flow thresholds that define core, penumbra, and benign oligemia.\(^6\) Subsequent animal studies and translational research with positron emission tomography (PET) began to provide even further insights into the dynamic pathophysiology of acute ischemic stroke.\(^5\) Importantly, in humans, PET studies suggested that a subset of patients have prolonged time windows of salvageable tissue.\(^6\)–\(^11\) Moreover, single photon emission computed tomography studies reported that the volumes of hypoperfused tissue predict stroke outcome.\(^12,13\)

However, because PET is not feasible in the acute stroke clinical setting, using imaging to define individual pathophysiology and extend the time window for treatment seemed out of reach until the introduction of first diffusion–perfusion MRI and then multimodal computed tomography in the 1990s. These new multimodal advanced imaging techniques thus offered opportunities to explore, advance, and optimize acute stroke imaging therapies. There was an early recognition that multimodal MRI had the potential to not only optimize approaches to patient selection for acute stroke therapies (eg, penumbral selection hypothesis) but also serve as a useful surrogate end point to detect signals of treatment effects in small sample sizes. In translating the concepts of acute stroke pathophysiology from both animal studies and human PET or single photon emission computed tomography studies to multimodal imaging biomarkers, it is useful to critically evaluate the supporting evidence for the various types of biomarkers. For this purpose, operational

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**Table 1. Neuroimaging Biomarkers in Stroke: Definitions and Review of Magnetic Resonance Imaging Biomarkers Studied to Date**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prognostic Biomarker</th>
<th>Prediction (Selection) Biomarker</th>
<th>Surrogate End Point</th>
</tr>
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<tr>
<td></td>
<td>Requires Biological Plausibility and Adequate Performance Characteristics (Sensitivity, Specificity, Reproducibility)</td>
<td>Must Correlate with Clinical Outcome</td>
<td>Must Predict Probability of Response to Intervention</td>
</tr>
<tr>
<td>Ischemic injury</td>
<td>Final infarct volume (eg, FLAIR, T2-weighted sequences)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>DWI lesion volume (including measures of large core)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Change in lesion growth</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hemodynamic compromise</td>
<td>Perfusion deficit</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vessel status</td>
<td>Large vessel occlusion on MRA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Penumbral imaging</td>
<td>Diffusion–perfusion mismatch</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Clinical–diffusion mismatch</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>DWI-positive, FLAIR-negative</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>DWI-MRA mismatch</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>Hemorrhagic transformation on gradient echo imaging</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Blood–brain barrier disruption</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>DWI/ADC volume and severity</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

FLAIR indicates fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; ADC, apparent diffusion and NA; Not available.

* indicates that there is substantial support in the literature; ± indicates there is only weak or limited support in the literature.

*Time dependency.
† Change in lesion growth.
‡ Change in lesion growth or recanalization.
definitions of the ischemic core (tissue that is irreversibly injured despite early reperfusion), ischemia penumbra (tissue that is at risk for infarction unless perfusion is restored), and benign oligemia (tissue with low blood flow but not at risk for infarction) are most useful in evaluating MRI biomarkers (Figure).

Despite the absence to date of definitive studies proving the penumbral imaging selection hypothesis, there have been a series of important studies and findings that support the rationale and potential success of these approaches.14,15 Initial studies of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) MRI in acute ischemic stroke demonstrated the natural history and evolution of ischemia over time, with the diffusion lesions growing over time, particularly in patients with diffusion–perfusion mismatch.16–18 Moreover, the initial lesion volumes correlated well with clinical outcome stroke scales.19–21 Of particular interest were studies demonstrating that in humans, mismatch was present up to 24 hours or more in some patients.22,23 However, a number of studies attempting to identify apparent diffusion coefficient or perfusion thresholds corresponding to core or penumbra met with only modest success.22,24–28

These initial observational studies were followed by several pivotal studies suggesting that patients treated with thrombolytic therapy followed by successful recanalization had smaller infarcts, less lesion growth, and improved clinical outcome. Based on these initial studies, a number of neuroprotective and thrombolytic trials or studies were designed and conducted using MRI biomarkers for selection and surrogate end points. Despite the negative neuroprotective studies, important findings have emerged regarding the role of MRI biomarkers in acute stroke from the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) and EchoPlanar Imaging Thrombolysis Evaluation Trial (EPITHET) studies.14,15 Both studies tested the diffusion–perfusion mismatch hypothesis for selecting patients for treatment with intravenous tissue plasminogen activator up to 6 hours from onset. EPITHET additionally explored lesion growth as a surrogate end point for treatment efficacy.

Animal Studies

Unlike most other imaging modalities, MRI is an ideal imaging modality for translational research in acute stroke because it is readily available and accessible in both the laboratory and the acute clinical setting. Moreover, multimodal MRI can noninvasively provide serial information on the degree of ischemic injury (DWI or apparent diffusion coefficient sequences), hemodynamic compromise (PWI), and HT (gradient echo).29 Animal models of acute focal ischemic stroke using MRI techniques not only have provided important insights into the natural history and pathophysiology of ischemic stroke but also have laid the groundwork for human studies.30,31 Animal models of focal ischemic stroke first demonstrated that diffusion and perfusion changes can be visualized within minutes of ischemia and represent tissue bioenergetic compromise.32,33 It was also first noted in animal models that the perfusion deficit was larger than and surrounded a more densely ischemic region of core infarct in both temporary and permanent middle cerebral artery occlusion models.

**Figure.** Operational definitions of ischemic regions and approaches to understand characteristics of each region in human studies. To characterize the imaging features of core, patients undergoing successful recanalization must be studied. To characterize the imaging features of the penumbra (compared with benign oligemia), patients without successful recanalization must be studied.
Most importantly, these studies showed that early reperfusion (either through a transient occlusion model or with thrombolytics) or treatment with neuroprotective agents had the potential to attenuate lesion growth. It was additionally first observed in animal models that early reperfusion could reverse the diffusion and apparent diffusion coefficient lesion. However, complicating these findings were studies demonstrating that initial reversal of ischemic lesions could be followed by later secondary injury. Finally, MRI animal models supported previous studies suggesting that not only do the thresholds for ischemia change over time but also there are likely tissue and regional specific variations.

**Human Studies**

**Ischemic Injury**

Infarct volumes as measured by MRI, particularly on subacute or chronic fluid-attenuated inversion recovery, T2-weighted sequences, and T1-weighted sequences, have strong biological plausibility (supported by animal literature) as a measure of irreversible ischemic injury compared with pathologically proven completed infarcts. As prognostic biomarkers, final infarct volumes show modest correlation with clinical outcome scales, particularly when lacunar and posterior circulation infarcts are excluded. Recent studies have suggested that final infarct volume can be measured as early as 24 hours on DWI, which correlates strongly with the day 90 volume measured on fluid-attenuation inversion recovery sequences.

Although there is support for the role of final infarct volume serving as a surrogate or auxiliary endpoint for stroke therapies (particularly when using a measure of change from baseline within an individual), caution must be used for a number of reasons. First, final infarct volume does not meet the strictest criteria of a surrogate endpoint because it is clear that final infarct volume is unlikely to capture the full effect of the treatment on the clinical end point. Baseline DWI lesion volumes also have been suggested as a measure of the ischemic core (irreversibly injured tissue), and this concept is an integral notion of the mismatch model for defining penumbra (as discussed). Despite the simplicity and appeal of this approach, both animal and human studies have demonstrated that DWI lesions can reverse with early reperfusion and that a portion of the DWI lesion is penumbral tissue. Although there is some controversy regarding the clinical significance of this phenomenon, several systematic reviews have strongly concluded that the visible DWI lesion is not an accurate surrogate marker for the infarct core. Thus, the biological plausibility of DWI lesion as core is not fully supported.

Despite these concerns, there is a growing body of literature supporting the utility of using the presence of a large region of presumed ischemic core as a prediction biomarker (eg, imaging selection exclusion criteria) for acute therapies. Yoo et al reported that DWI lesion volume >70 mL predicted poor clinical outcome. In the DEFUSE study, a malignant profile predicting poor outcome was defined as a DWI volume >100 mL (or a PWI volume >100 mL with Tmax >8 seconds). It should be noted that the concept of a large core as a strong predictor of poor outcome is supported by studies using alternative imaging techniques to define core.

The most promising surrogate endpoint for acute stroke studies is change in lesion growth (or attenuation of lesion growth with treatment) from acute imaging (baseline DWI volume) to a following time point (most commonly fluid-attenuated inversion recovery). Both animal models and early observational studies in thrombolysis-treated patients have shown that early reperfusion is associated with both attenuated lesion growth and that attenuated lesion growth, in turn, is associated with improved clinical outcome. In the EPITHET study, tissue plasminogen activator treatment was associated with lower infarct growth compared with placebo (in mismatch patients). Unfortunately, there were too few non mismatch patients to test the mismatch selection hypothesis. However, as has been noted in previous articles, both measures of final infarct volume or attenuation of infarct growth are prone to other pitfalls common to surrogate end points, including loss of data in patients unable to undergo follow-up imaging (eg, because of death and poor outcome).

**Hemodynamic Compromise**

PWI in acute stroke is most commonly used with the first-pass bolus contrast tracking technique. As a biomarker of ischemic stroke, the presence of a perfusion deficit not only has strong biological plausibility supported by animal literature but also has relatively high specificity. However, the presence of a PWI deficit may have relatively low sensitivity, particularly in the setting of smaller infarcts or at later time windows when spontaneous vessel recanalization may occur. When present, the extent and severity of the perfusion deficit are useful prognostic biomarkers with studies suggesting strong correlations both with final infarct volumes and acute stroke scale scores and long-term functional outcome measures.

The utility of magnetic resonance perfusion measures as a prediction biomarker of response to treatment by itself seems to be limited in its current state of technological advancement for a number of reasons. As has been discussed in the literature at length, lack of standardization of perfusion image acquisition, postprocessing, and analysis approaches limits generalizability of findings. In addition, magnetic resonance perfusion imaging in common practice provides only relative measures of hemodynamic compromise, not absolute cerebral blood flow measures or other advanced imaging measures to quantify presence of penumbra (such as oxygen extraction fraction). As such, the utility of a magnetic resonance perfusion deficit by itself as a prediction biomarker is likely limited to narrow time windows. Alternatively, data from the pooled DEFUSE-EPITHET studies suggest that a PWI threshold (Tmax >8 seconds) of ~100mL identifies patients likely to have poor outcomes (including HT).

There is, however, support for perfusion imaging as a surrogate end point for reperfusion therapies in acute stroke. Here the distinction between reperfusion (measure on PWI) vs recanalization (visualized on magnetic resonance angiography [MRA], see discussion) is important. Reperfusion provides a more accurate surrogate outcome than recanalization because of the occurrence of distal emboli, the no-reflow phenomenon, and the potential for adequate reperfusion from collateral flow even without recanalization. In the EPITHET study, reperfusion measured on PWI was shown to be a better surrogate marker of clinical outcomes independent of
recanalization as measured by MRA at days 3 to 5. In the small phase II tenecteplase vs alteplase study, the tenecteplase groups had greater rates of reperfusion at 24 hours on PWI and improved clinical outcomes. However, the utility of reperfusion as a useful surrogate end point is likely limited by time (duration of penumbra) and likelihood of spontaneous recanalization and therefore reperfusion.

Alternative approaches to perfusion imaging, including arterial spin label imaging, offer promise in acute ischemic stroke; however, further work is needed to demonstrate their accuracy and feasibility in this setting.

Vessel Status
A proximal large vessel occlusion, visualized on either contrast-enhanced or time-of-flight MRA, has proven biological plausibility as a biomarker for acute stroke therapies. For acute stroke thrombolytic or embolectomy therapies, the presence of a visible vessel occlusion on baseline imaging has the advantage of ensuring the patient has the target disease. In the EPITHET trial, the treatment effect of tissue plasminogen activator vs placebo was greater in patients with a baseline arterial occlusion. In fact, presence of a target vessel occlusion has been proposed as a critical inclusion criteria for trials of reperfusion therapies. Moreover, there is a fairly extensive body of literature addressing performance characteristics compared with the diagnostic gold standard of catheter angiography, with sensitivity and specificity ranging from 70% to 100%. However, MRA as currently available does not show adequate performance characteristics to serve as a biomarker for distal vessel occlusions.

A number of studies have shown that vessel occlusion visualized on MRA is a modest prognostic biomarker and has potential as a prediction biomarker. Similarly, vessel recanalization visualized from the pretreatment to the posttreatment time point is a useful surrogate end point for reperfusion studies, particularly in early time windows. Vessel recanalization correlates both with attenuated infarct growth and improved functional outcome. As with reperfusion, at later time points, the value of recanalization is likely dependent on the initial presence and subsequent salvage of viable penumbral tissue. Because of the common occurrence of spontaneous recanalization, it has been suggested that repeat imaging after treatment should be performed within the first 24 hours to optimize the utility of these measures as surrogates.

Penumbral Imaging
Although a number of approaches to identify salvageable penumbral tissue have been proposed, the most widely embraced to date has been diffusion–perfusion mismatch. The original definition used in a large number of studies was based on a visual assessment of mismatch, requiring that the perfusion lesion volume be 20% greater than the initial diffusion lesion volume. As noted previously, this definition was problematic for a number of reasons. From a historic standpoint, it is a notable lesson that a large number of neuroprotective trials, and even some reperfusion studies, were designed using this definition for selecting patients despite lack of validation and a growing body of literature recognizing the limitations of the approach.

As discussed, the biological plausibility that the DWI lesion is core irreversibly injured tissue is weak. Perhaps even more problematic is the assumption that the entire perfusion deficit includes at-risk tissue. Both the animal literature and a significant number of studies in humans clearly show that a portion of the visual perfusion deficit likely represented benign oligemia. The DEFUSE study has now shown that an optimal Tmax threshold of 4 to 6 seconds can be used to better-define the outer rim of the penumbra. The choice of 20% as a clinically meaningful percent mismatch also was not based on biological plausibility, but rather the smallest difference detectable by the human eye. However, the reliability of a visual assessment of mismatch has been disputed. For very large affected territories, as in a complete middle cerebral artery occlusion, this would equate to a very small rim of perfusion deficit surrounding a core DWI infarct of >300 mL. An additional important finding from the DEFUSE study was that a mismatch ratio of 160% optimally identified favorable clinical response.

Finally, the biological plausibility of mismatch as a biomarker for penumbra has been further disputed by a series of elegant MRI-PET studies showing that mismatch overestimates the penumbra. Even using a time to peak threshold of 4 seconds to define the outer rim of the perfusion deficit, these studies suggested that the mismatch region did not correlate with the region of elevated oxygen extraction fraction. Other mismatch definitions also have been proposed including clinical DWI mismatch and DWI/MRA mismatch. A number of studies have suggested that clinical DWI mismatch performs less well than DWI-PWI mismatch. Several studies have suggested that the MRI profile of DWI-positive but fluid-attenuated inversion recovery-negative is a marker for patients likely to be in a time window in which treatment is safe and effective, which may provide an important role in selecting patients with unknown onset times. In the DEFUSE study, MRA-DWI mismatch seemed to identify patients likely to benefit from treatment.

Despite these limitations, both the DEFUSE and EPITHET studies have shown that mismatch, particularly in its modified form, may serve as a useful predictive biomarker to select patients more likely to respond to reperfusion therapies. In DEFUSE, early reperfusion was associated with a favorable clinical response in mismatch patients, and patients without mismatch did not seem to benefit from early reperfusion. In EPITHET, mismatch patients treated with tissue plasminogen activator compared with placebo not only had attenuated lesion growth but also had significantly increased rates of reperfusion. Moreover, reperfusion significantly correlated with both growth attenuation and improved clinical outcomes. The DEFUSE-2 multicenter study results had been presented in abstract presentations at the time of this submission. This study used an automated mismatch analysis program for determining MRI patterns in a prospective, consecutive cohort of patients who were scheduled to undergo endovascular therapy. The study provided confirmation of the concepts demonstrated in DEFUSE and EPITHET: target mismatch patients who achieve early reperfusion therapy have less infarct growth and
more favorable clinical outcomes, and no association between reperfusion and favorable outcomes or infarct growth was present in patients without target mismatch.\(^6\) Unfortunately, none of these studies was able to definitively prove penumbral imaging selection (or mismatch hypothesis) because of lack of controls (DEFUSE) or insufficient numbers of nonpenumbral patients (EPITHET).

An important opportunity for optimizing the MRI-defined regions of core, penumbra, and oligemia is to study the characteristics of patients undergoing successful recanalization to assess the core and patients without successful recanalization (to differentiate core from penumbra) (Figure). The penumbral imaging selection hypothesis will be most definitively proven in a trial or trials that demonstrate that) treated patients with penumbral imaging selection have improved clinical outcomes compared with nonpenumbral-treated patients and that treated patients with penumbral imaging selection have improved outcomes compared with untreated patients with a penumbral pattern. One approach to achieve both these goals is a randomized controlled trial, with stratification by penumbral pattern to ensure sufficient number of patients in each group is available to test the hypotheses. Fast, automated postprocessing software packages are now available for incorporation into clinical trials to facilitate rapid and accurate measurement of imaging selection biomarkers.\(^70,71\) Proving the utility of the penumbral imaging hypothesis or even other biomarker selection criteria does not require evaluation or validation of the surrogate end points as long as it is demonstrated that the selection criteria improve outcomes compared with no imaging selection. However, ideally, the penumbral selection biomarkers would also show, as an intermediate step, validation as pathophysiologically relevant surrogate end points as well.

### Hemorrhagic Transformation

HT, visualized on gradient echo MRI sequences, is a biomarker of potentially poor outcome. Gradient echo is significantly more sensitive to HT than computed tomography or other MRI sequences and has proven biological plausibility.\(^72\) Rating scales incorporating the extent of hemorrhage along with measures of neurological deterioration have shown that the presence of HT,\(^73\) particularly when considered “symptomatic ICH,” is predictive of poor functional outcome. However, even “asymptomatic HT” seems to be a predictor of poor outcome; therefore, HT seems to be a useful surrogate end point for toxic or harmful treatment effects in reperfusion studies.\(^74\)

A number of baseline imaging biomarkers that are predictive of HT also have been proposed. These include the volume and fusion coefficient, cerebral blood volume, or \(T_{\text{max}}\),\(^50,75-79\) as well as biomarkers of blood–brain permeability.\(^77,80\) Although promising, none of these has been tested in large cohorts and data regarding performance characteristics are suboptimal.

### Conclusions

MRI-based neuroimaging biomarkers hold much promise, particularly in their role as predictive biomarkers to select patients most likely to benefit from therapy, as well as surrogate outcome measures to test putative acute stroke therapies. However, as we work our way through the tasks outlined in the acute stroke imaging research road map,\(^49\) important additional work needs to be performed to better-define, evaluate, and validate these imaging measures as true biomarkers. Future trials, and the research field in general, would benefit from development of a consensus panel or task force evaluation of stroke imaging biomarkers, including an approach to measuring statistical validity, evidentiary qualification, and utilization analysis.\(^2\)

The literature to date speaks to the complexity of human stroke pathophysiology–penumbral imaging for selection for acute stroke therapies is not as simple as diffusion–perfusion mismatch. As such, a number of areas of particular importance for advancing the field include the following (Table 2): measures of regional vulnerability;\(^81\) approaches to further optimize the diffusion–perfusion mismatch–defined penumbra, or alternative approaches beyond mismatch to more accurately identify the penumbra with MRI;\(^82\) approaches that incorporate a time variable into modeling and prediction (or clearly show the measures are independent of time); consideration of incomplete infarction and measures of secondary or late injury;\(^82\) approaches to validate biomarkers across imaging modalities (eg, computed tomography and MRI);\(^83\) and the use of combination biomarkers for patient selection/prediction (small core, low risk of HT, visible occlusion, presence of substantial penumbral tissue). This conceptual framework for understanding neuroimaging biomarkers in stroke also can be applied to other conditions, including intracerebral and subarachnoid hemorrhage.

Current clinical trials are underway that have the potential to definitively prove the neuroimaging selection hypothesis for the treatment of acute ischemic stroke, including the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) and Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) studies.\(^71,83\) Whether these trials are positive or negative, harmonization of definitions and consensus panels are needed to provide evidence-based assessment of the status and role of neuroimaging biomarkers in stroke.

### Acknowledgments

The author thanks Courtney Hsieh for her assistance in figure development.

### Sources of Funding

This manuscript is supported by grant P50 NS044378 from the National Institutes of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH).

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**Table 2. Areas Requiring Further Research and Biomarker Validation**

<table>
<thead>
<tr>
<th>1) Regional vulnerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>2) Refined definitions of penumbra (mismatch or alternative approaches)</td>
</tr>
<tr>
<td>3) Approaches that incorporate a time variable into modeling and prediction (or that clearly show the measures are independent of time)</td>
</tr>
<tr>
<td>4) Incomplete infarction</td>
</tr>
<tr>
<td>5) Secondary injury</td>
</tr>
<tr>
<td>6) Validation of biomarkers across imaging modalities (eg, CT and MRI)</td>
</tr>
<tr>
<td>7) Combination biomarkers for patient selection/prediction</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; MRI, magnetic resonance imaging.
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**Key Words:** biomarker ■ diffusion-weighted imaging ■ infarct ■ ischemic stroke ■ magnetic resonance imaging ■ neuroimaging ■ penumbra
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Stroke. published online November 6, 2012;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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