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Imaging in StrokeNet: Realizing the Potential of Big Data

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Albers: Consultant to iSchemaView, Covidien, Lundbeck; equity interest in iSchemaView.

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Introduction

Imaging of stroke and neurovascular disorders has profoundly enhanced clinical practice and related research during the last 40 years since the introduction of CT, MRI and PET enabled mapping of the brain. Various imaging techniques have been developed to study stroke pathophysiology and inform medical decision-making in prevention, prehospital care, acute monitoring of revascularization, during the subacute ICU course and recovery settings. The technology to acquire such imaging with sophisticated scanners, software for rapid post-processing, analysis, computer vision methods and telemedicine platforms to instantly beam such information around the world now warrant reconsideration of the potential of stroke imaging in the era of big data.

These dramatic changes in neuroimaging and the vast potential to catapult stroke care depend on large-scale, multi-institutional research initiatives to establish their role. These initiatives would require that the current infrastructure and philosophy of translational research must be modernized to incorporate such advances. In this position paper, we describe the historical context, conceptual framework, current issues, logical analyses for strategic planning and the proposed aims of future stroke imaging initiatives to advance data science with the recently established NIH StrokeNet.¹ The StrokeNet consists of 25 regional stroke center hubs each associated with a group of spoke hospitals that are capable of conducting stroke research. The network will be responsible for conducting future multicenter NIH stroke trials and represents an ideal setting to capture large volumes of invaluable neuroimaging data.

Our perspective contrasts with the limited translational research use of imaging in most prior stroke trials, recognizing a unique opportunity to maximize data science and leverage this landmark NIH investment to transform stroke trials of prevention, acute treatment and recovery. The tools already exist for widespread acquisition and transmission of image data, systematic real-time extraction of discrete imaging variables, enabling creation of an enduring and valuable resource for future research, education and clinical uses. We outline three innovative specific aims that focus on establishing the dedicated infrastructure, archival process and centralized core laboratory function to provide a foundation for stroke imaging studies that fully realize the potential of big data.

Historical Context

During the last decade, we have witnessed a convergence of three simultaneous evolutions in biomedical research related to stroke and neurovascular disorders. Stroke imaging, large-

scale development of stroke research networks and the modernization of medicine and neuroscience with large datasets are now capable of intersecting with related, yet potentially divergent, trajectories.

Stroke and Neurovascular Imaging

The approval of intravenous tissue plasminogen activator for thrombolysis prompted the use of non-contrast CT to primarily rule out hemorrhage before treatment, as early ischemic changes were generally deemed inconsequential. The development of noninvasive angiography, perfusion imaging with CT and MRI techniques and parenchymal MRI sequences such as diffusion-weighted imaging (DWI) subsequently provided clinicians with enhanced ability to rapidly diagnose and treat acute stroke.² The use of these multimodal CT and MRI protocols rapidly increased, augmenting our knowledge within a few short years regarding stroke pathophysiology. In the early 2000s, stroke trials started to embed such imaging as screening tools and secondary outcome measures for novel drugs and then devices. Even while stroke trials struggled to establish new treatments, advanced image analyses often yielded new insight.³ For example, the DEFUSE trialists demonstrated that specific patterns of evolving ischemic injury could be used to predict subsequent clinical outcomes after revascularization.^{4, 5}

Several trials using imaging as a screening/selection criterion provided mixed, positive and negative results. Some concluded that “imaging has failed us” and that the imaging-based trials did not demonstrate the need for such “costly” diagnostic tests. The lack of central coordinated and standardized collection of the image data from these different trials limited pooled analysis of these data, which represents a huge opportunity loss considering the significant funding invested to perform imaging in these trials. Because of their large sample sizes, such pooled analyses could have significantly contributed to the field of stroke by potentially explaining what worked in the positive trials and what did not work in the negative trials. The STIR/VISTA Collaboration has established the utility of an image repository, but this effort has been limited by the reluctance to share and the non-standardized mechanisms for image data submission.⁶

StrokeNet

The organization of stroke research networks more than a decade ago with the establishment of seven Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS) centers provided the momentum to systematically study several of the most critical translational research questions in acute stroke. Imaging played a central role in several of these phase II studies. The relatively small size of these translational studies, however, limited conclusions regarding the impact of imaging. As SPOTRIAS ended, the NIH StrokeNet replaced the SPOTRIAS program to expand the geographical reach to 25 regional centers to cultivate larger stroke trials intended for novel therapies and biomarkers related not just to acute stroke, but also towards recovery and prevention. Imaging was implicitly considered, yet a mechanism does not currently exist to support the role of imaging beyond data capture for individual trials. The Imaging Work Group was established to advise the StrokeNet regarding the use of imaging in new proposals for the network. During these early stages of the NIH StrokeNet, several proposed studies and related discussions have

underscored the need for a dedicated imaging infrastructure, related funding and active data collection that extends beyond novel imaging techniques to leverage the routine imaging studies acquired in participants enrolled in NIH-funded stroke trials.

Big Data

At the same time, big data has emerged at the forefront of biomedical research in refining precision medicine, studying the human brain and maximizing the utility of imaging across various neurological disorders. The Alzheimer's Disease Neuroimaging Initiative (ADNI) demonstrated the potential of large-scale imaging analyses to study longitudinal changes in brain disorders, utilizing many routine MRI techniques.^{7, 8} Against this backdrop, the NIH established imaging registries in many neurological disorders far less common than stroke, funded the Human Connectome Project, emphasized the impact of Big Data 2 Knowledge funding opportunities and then celebrated the BRAIN initiative as one of the most important biomedical research accomplishments that will utilize imaging to revolutionize the study of neuroscience, bolstered by specific hypotheses and goals.^{9, 10} This overwhelming constellation of research activity has yet to address imaging of stroke and related cerebrovascular disorders. Several years ago, comments were solicited regarding data sharing for imaging in neurological and psychiatric disorders and most recently, the NIH has established a formal policy for sharing of genomic data. The Cancer Genome Atlas (TCGA) has a glioma imaging arm that was funded by NCI.¹¹ NINDS is funding the FITBIR repository for traumatic brain injury data including imaging. Data sharing for stroke imaging remains uncoordinated, even within NIH-funded studies. The NIH Common Data Elements (CDE) Project uses content standards that enable clinical investigators to systematically collect, analyze, and share data across the research community.¹² The CDE Project includes numerous imaging variables, yet these parameters are not necessarily required nor are source image datasets collected.¹² Furthermore, the infrastructure has never been established to support the maintenance of image datasets beyond the conclusion of a trial. Despite these limitations, stroke survivors and individuals at risk now store such vital imaging studies of their brain and vasculature on their portable devices or in the Internet cloud through HIPAA-secure mechanisms.

Conceptual Framework

Certain concepts related to stroke imaging have been erroneously perpetuated, leading to confusion and threatening future progress.

Stroke imaging serves a triple role as diagnostic tool, potential guide to best therapeutic approach and an outcome biomarker in individuals with cerebrovascular disease, from those at risk for brain ischemia or hemorrhage to those who have suffered an acute event. The vast information provided as a snapshot of the vessels, perfusion and lesions in the brain may be utilized beyond its use to answer a go-no go decision about treatment. The multiple dimensions and serial imaging may discern critical variables such as collateral circulation and expected clinical outcomes over extended time periods. Stroke trials often focus solely on the investigational treatment without considering individual baseline pathophysiology that may impact therapeutic response. There is now a concrete opportunity to establish precision medicine in stroke or individualized approaches by leveraging the big data

contained within imaging studies. For instance, variable degrees of collateral status in proximal middle cerebral artery occlusion may radically influence the response to endovascular therapy for acute ischemic stroke.¹³ Imaging also provides insights into neural state after stroke that cannot be gleaned from bedside exam. For example, an image-based measure of corticospinal tract injury predicts motor recovery better than total infarct volume or baseline behavior.¹⁴ Imaging provides extensive data about these interactions between novel treatments and baseline pathophysiology. Such variability in baseline imaging is an important consideration in medical decision-making and selection for clinical trials, yet imaging is often blamed as solely a cause of added delay and cost. Feasibility of standardized image acquisition is often cited as an impediment, but can be easily implemented even across different proprietary equipment. Anonymization and transmission of image data are easily achieved nowadays. Furthermore, serial imaging is routinely acquired in clinical practice yet rarely funded in stroke trials. In addition to comparing subjects or groups of participants, focusing on the relevant measures of individual patients serving as internal controls for the longitudinal impact of alternative treatments over time, may usefully expand the concept of controls in stroke trials. Finally, the utility of big data in stroke imaging cannot be realized by solely mandating local collection of imaging variables or by massive storage in a repository, as *data flow and the continuous, systematic, standardized and timely extraction of CDE imaging variables is essential.*

Current Issues

Since the implementation of the StrokeNet Imaging Work Group, several examples have underscored the need for a concerted focus on imaging beyond the current mechanisms and infrastructure available. For studies that do not have a primary imaging hypothesis, the question often arises as to whether image data should be centrally collected, processed and stored. The need for data collection, development and utilization of case report forms (CRF) is often questioned despite the fact that imaging variables are an integral part of the NINDS CDEs. Unlike other CDEs that focus on clinical variables or other measures, the imaging CDEs are often removed due to the apparent complexity of implementing proper expertise, cost and infrastructure for imaging review. Even when imaging variables may be considered for inclusion, the collection of source image files is seen as overly complex. There exists an arbitrary distinction between study-related imaging and routinely acquired imaging that is principally defined by the funding source for the imaging study. From this perspective, imaging is handled unlike any other types of data, as it would be incongruous to refrain from collecting other data elements that are obtained as part of the clinical routine. Why should routinely acquired imaging studies with extensive detail regarding stroke pathophysiology be removed from data collection in a person enrolled in an NIH-funded trial? The broad array of imaging studies acquired per routine clinical practice should be used to better inform trials on the value of serial imaging and to validate specific hypotheses. Variables such as final infarct volume would be readily compared across trials. Similarly, why should serial ASPECTS scoring only be collected when designated in a trial CRF? In the current format, only the designated imaging variables are listed and collected in the CRF, locked into the final dataset and the image files discarded, thereby preventing any further investigation, reliability testing or subsequent validation. Acquisition and storage of source

image data will allow for more precise standardized processing of known derived measures, as well as re-derivation of new measurements defined in the future. Techniques such as anonymization ensure that this can be done in a HIPAA-compliant manner.

The subsidiary role of imaging relative to therapeutic interventions fosters the conclusion that imaging is irrelevant if primary analyses of the investigational treatment are shown to be positive or negative. Paradoxically, the potential impact of novel therapies is often best understood with imaging surveillance. Routine imaging studies are not often included in CRF, because they are not study-related and also because they are seen as too rudimentary; yet sophisticated imaging approaches are viewed as costly or impractical. Most commonly, the post hoc analyses of routinely acquired imaging reveal fundamental insight about the underlying stroke subtype or disorder. For example, retrospective analyses of routine imaging in WASID have demonstrated that the trial designated imaging variable of interest, percent stenosis, is less informative than collateral grade collected in post hoc analyses.¹⁵

The pace or timeframe of such imaging evaluations should also mirror the approach to other forms of data in a clinical trial. The imaging may be used to inform adaptive trial design and markedly reduce costs due to smaller sample sizes, more refined effect estimates and help in the design of better “proof-of-concept” phase 2b trials with imaging biomarkers as influential selection criteria and outcomes. Such an approach becomes reasonable when one considers recent endovascular therapy studies that utilized various imaging paradigms to achieve positive results with only a fraction of the expected sample sizes.^{16, 17}

The insightful information regarding pathophysiology derived from imaging has fueled a plethora of proposed ancillary imaging studies and subgroup analyses that represent a significant contribution to the stroke literature. Most recently, ancillary imaging has been embedded in the StrokeNet charge to evaluate novel biomarkers yet the focus remains on novel therapeutics, and there has yet to be an imaging biomarker ancillary study. Imaging biomarkers remain most closely aligned with routine practice and they may identify those individuals most at risk for disease progression or modification with informed interventions. Even the choice of endpoints in a stroke trial may be altered, as recurrent stroke may be less important than subsequent cognitive decline. These challenges are only amplified when StrokeNet trials address not just acute stroke, but recovery and prevention.

The digital nature of image data should be leveraged to maximize the information that can be extracted from NINDS-sponsored clinical trials, and the amount of knowledge that can be developed out of these trials. Historical examples include the use of stored images from the NINDS-tPA trials and PROACT-II where non-contrast CT and angiography provided subsequent further insight.^{18, 19} *Considering the number of patients and funds invested in these trials (especially those that involve imaging), maximal resource utilization depends on imaging in perpetuity that focuses both on investigational treatments and the underlying pathophysiology. This approach would make subsequent ancillary studies feasible at a much lower cost considering that the image data has already been collected and are easily accessible, similarly to the TCGA glioma and FITBIR TBI initiatives. Also, this strategy would create a valuable educational resource for subsequent generations of scientists.* The success of this approach is illustrated by how the centralized, expert TICI scoring in

endovascular studies led to the subsequent implementation of local TIC1 scoring as a measure of quality for comprehensive stroke center certification.

Strategic Imaging Plans

Strategic planning for topics like stroke imaging are often best informed by logical analyses and formal evaluation with introspective approaches like strengths-weaknesses-opportunities-threats (SWOT) analyses that allow structured planning. This planning method can identify both internal and external factors that are favorable and unfavorable for future development of stroke imaging in clinical research paradigms. Table 1 reveals the key elements of SWOT analyses related to imaging of stroke and neurovascular disorders. Only the most salient elements are outlined to facilitate strategic approaches to the current impasse described above. In brief, key strengths of stroke imaging hinge on the exquisite ability to depict dynamic neurovascular pathophysiology in vivo. In contrast, weaknesses often cited include limited availability or deployment, cost, and the one-dimensional nature of imaging outcome measures. Exciting opportunities exist for the application of stroke imaging in clinical research, although existing threats to the use of stroke imaging must be considered.

Constructive strategic planning for stroke imaging can link these strengths, weaknesses, opportunities and threats in the form of threats-opportunities-weaknesses- strengths (TOWS) analyses that map out the most logical avenues to approach next steps in the field. Although such pairings are critically dependent on the previous SWOT factors proposed, the TOWS analyses for imaging of stroke and neurovascular disorders (Table 2) provides a framework to address current issues delineated above and means to maximally realize the potential of stroke imaging.

Vision to Implement Stroke Imaging as Big Data

These strategic planning tools that outline both the current nature of stroke imaging approaches and a constructive path to efficiently overcome potential limitations underscore the need to focus on three specific aspects of data science relevant to imaging in StrokeNet. There is an overt need to establish a concerted infrastructure specifically devoted to stroke and neurovascular imaging data, an active archival process where data flows in real-time, and establishment of a centralized core laboratory that creates and maintains a resource for future data mining in education and research.

Infrastructure for Imaging Brains in Stroke

Dedicated infrastructure and support should be established to integrate trial and non-study related stroke imaging data with the clinical, genomic and other potential biomarkers. Such momentum would harmonize the stroke field with other areas of neuroscience where imaging has been at the forefront of big data initiatives. Although the tools are already available to collect large-scale image datasets across vast networks, currently there is no mechanism to support the individuals involved in image processing, expertise of centralized review and integration with other components of clinical trial design across various phases of stroke from prevention to acute treatment and recovery. The nature of stroke imaging

techniques, post-processing and resultant data are distinct from other neurological disorders, justifying the need for this novel initiative in StrokeNet. Routinely acquired image data should be included in central imaging datasets, along with the study-specific imaging. For instance, participant consent should include the collection and analysis of non-contrast CT scans, MRI scans and other routine clinical imaging studies to extract established imaging variables defined by the CDE. Novel imaging techniques would continue to be funded by the specific trials. Much like other forms of source data, imaging datasets can always be verified and may persist indefinitely due to their digital nature. Such infrastructure would ensure that imaging remains a vital biomarker in many stroke trials and addresses the unmet need of innumerable ancillary imaging studies that would otherwise go unfunded. This infrastructure would prompt implementation of a formal stroke imaging data sharing policy, in line with policies for other research areas and types of biomarkers. Funding and authorship roles would entice investigators to participate in this initiative. The rudimentary imaging techniques or tools and the expertise already exist, yet omission of this much-needed infrastructure and disregard of this impetus to develop more sophisticated analytical methods would relinquish the extensive value of imaging as big data.

Active Archiving – The Data Must Flow

Collection of imaging datasets in stroke trials is only the initial step, as extraction of imaging variables based on central reviewer expertise and automated processing is the critical element in a process where the data must flow in real time. Archive storage of source imaging and the systematic collection of the imaging CDE in sync with participant enrollment in a clinical trial is imperative. Prospective, blinded imaging analyses in parallel with subject recruitment allows for adaptive trial design, leveraging the imaging data rather than waiting years for locking of datasets, imaging analysis and resultant subgroup analyses that require yet another clinical trial. Ultra-fast transfer of data to a central server can also allow study investigators to view imaging at their study sites prior to patient enrollment, potentially avoiding enrollment of patients who do not meet imaging-related inclusion criteria.

Safety, efficacy and pivotal biomarker correlates are enabled in this model of parallel imaging trial designs. Furthermore, such an approach allows integration of patient level data across trials to focus on underlying pathophysiology in addition to the investigational treatment. For instance, trial selection criteria may attempt to reduce heterogeneity in stroke mechanisms yet concurrent trials may pool imaging data to focus on certain causes of stroke such as large artery intracranial atherosclerosis or alternatively, small vessel disease. Understanding such neurovascular disorders with routinely archived data variables would likely disclose pivotal imaging biomarkers such as white matter hyperintensities, silent brain infarcts, or cortical volumes and novel treatment opportunities rather than awaiting the next candidate therapy to emerge along the trial pipeline years later. The STAndards for ReportIng Vascular changes on nEuroimaging (STRIVE) initiative persuasively underscores the need to harvest detailed yet standardized neuroimaging characteristics.²⁰ Differentiating particular features of small vessel disease, as in the formative work of STRIVE, may modernize the clinical management of this incredibly common disorder. There are increasing data that neuroimaging measures have value as stratifying variables in the context

of stroke recovery where specific measures of brain injury or function markedly enhance the ability to classify subjects at baseline according to their likelihood of having a robust response to a proposed therapy.^{21, 22} Nested or embedded imaging analyses could disclose critical findings regarding the interaction of specific therapies with baseline pathophysiology. For instance, the relative benefit of endovascular therapy based on collateral status could be integrated into the analysis plan and examined by the DSMB during, rather than after trial completion.²³ Such added value or imaging insurance would enhance the investment of each NIH-funded trial in StrokeNet, without the need to pre-specify all of the myriad mechanisms that could be studied with imaging. The recent flurry of positive endovascular stroke therapy trials based on recruitment of only a fraction of the projected sample sizes, provides a great example of how stroke imaging may revolutionize research progress and reduces ultimate costs. Continuous support, however, is necessary to sustain the expertise and flow of data, including data collection, processing, storage, re-processing, and innovative statistical analyses to realize the full potential, as solely collecting imaging in data repositories does not achieve such goals.

Imaging in Perpetuity – Centralized Core as Unique Resource

Both central and local imaging readings are critical. Central expertise is essential in establishing novel parameters and systematic data collection, whereas local readings are most informative regarding ultimate generalizability. Establishment of this imaging architecture in a stroke trial network and the active archival process by expert reviewers adds layers or dimensions of potential data exploration and creates a unique resource for all aspects of stroke pathophysiology. Image datasets and extracted variables may be utilized indefinitely, if support is established. Such a centralized core laboratory may enhance education in imaging expertise by facilitating comparisons between local and central reviewers, as well as amongst a large spectrum of central reviewers from distinct backgrounds. Inter-rater reliability and ultimate generalizability of various image parameters or approaches could be explored in the form of pilot studies and subsequently extended, rather than each trial electing to start from scratch.^{6, 24} The use of local imaging readings could be enhanced by such an educational resource and novel imaging measures or parameters could also be piloted. Permeability imaging on older perfusion datasets and recognition of the spot sign in acute intracerebral hemorrhage could be tested in data accumulated years in the past. Multiple associations between imaging markers of underlying mechanisms could also be discerned without the need to conduct dedicated observational trials. Similarly, this resource or imaging data library could facilitate preliminary analyses and pilot testing of new post-processing or for future therapeutic research endeavors such as feasibility is currently tested in the Greater Cincinnati/Northern Kentucky Stroke Study.²⁵ The burgeoning field of neuroinformatics may disclose opportunities for cutting-edge techniques such as advanced computational modeling, machine learning and computer vision to delineate hidden and potentially influential patterns in this imaging data library. This will undoubtedly spawn nascent algorithms and software methods that emphasize the need for transdisciplinary efforts at the intersection of computational and mathematical sciences. Image data sharing would become a reality for future generations.

Undoubtedly, the extensive characteristics and complexity of efficiently integrating stroke imaging into an ideal data resource for clinical stroke research is a daunting task and alternative approaches likely exist. The envisioned multifaceted approach, however, overcomes many of the current limitations that threaten the potential yield of imaging as a critical data resource for understanding and treating various phases of stroke. This practical and logically outlined roadmap offers potential advantages and does not supplant imaging development or other observational imaging studies. Multiple imaging modalities may be incorporated in acute stroke, recovery and prevention, including the use of serial imaging outcomes at a fraction of the potential cost. The tools now exist to overcome the current limitations in translating the potential of stroke imaging data in StrokeNet, yet the dedicated architecture for centralized and expert data flow, preservation and integration must be established. These tangible products may leverage and maximize the utility of neuroimaging data in stroke therapy studies and enhance the long-term scientific investment of these NIH-funded trials.

Conclusions

A remarkable opportunity now exists to leverage the potential of stroke and neurovascular imaging within StrokeNet, establishing dedicated architecture of imaging experts, inaugurating an active process of data flow and CDE variable extraction and creation of a centralized core laboratory as a unique resource to fuel educational objectives and future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

SWOT analyses of current stroke and neurovascular imaging.

	Favorable	Unfavorable
Internal	<p>Strengths</p> <ul style="list-style-type: none"> - noninvasive imaging of cerebral vessels and perfusion providing insight into stroke pathophysiology - standardized imaging protocols - improved technology: rapid, becoming more simple to use - HIPAA-secure cloud technology 	<p>Weaknesses</p> <ul style="list-style-type: none"> - perceived complexity of imaging - potential delay caused by imaging - cost of imaging
External	<p>Opportunities</p> <ul style="list-style-type: none"> - need for biomarkers - imaging may inform medical decision making for stroke prevention, treatment selection and monitoring, rehabilitation tools already exist for widespread image acquisition, transmission and processing - StrokeNet initiative - stroke imaging CDEs - clinical practice often includes serial imaging - imaging may reduce costs through allowing smaller sample sizes - imaging may inform adaptive trial design 	<p>Threats</p> <ul style="list-style-type: none"> - contradictory results of image-guide acute stroke trials, with no central or standardized data collection and no pooled analysis - no dedicated imaging RFA and no significant, dedicated funding for imaging infrastructure in StrokeNet - no plans/funding for permanent repository of images beyond trials in StrokeNet - large computing or memory needs

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Table 2

TOWS analyses for constructive strategic planning on the future of stroke and neurovascular imaging.

	Opportunities	Threats
Strengths	S-O Strategies: <i>Infrastructure</i> - central collection of imaging data - imaging data sharing	S-T Strategies: <i>Centralized Core</i> - permanent repository of imaging data beyond life of trials
Weaknesses	W-O Strategies - opportunity cost of not investing in stroke imaging central collection and analysis	W-T Strategies: <i>Archiving Process</i> - continuous, systematic, standardized and timely extraction of stroke imaging CDEs