A Computerized Algorithm for Etiologic Classification of Ischemic Stroke
The Causative Classification of Stroke System

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Background and Purpose—The SSS-TOAST is an evidence-based classification algorithm for acute ischemic stroke designed to determine the most likely etiology in the presence of multiple competing mechanisms. In this article, we present an automated version of the SSS-TOAST, the Causative Classification System (CCS), to facilitate its utility in multicenter settings.

Methods—The CCS is a web-based system that consists of questionnaire-style classification scheme for ischemic stroke (http://ccs.martinos.org). Data entry is provided via checkboxes indicating results of clinical and diagnostic evaluations. The automated algorithm reports the stroke subtype and a description of the classification rationale. We evaluated the reliability of the system via assessment of 50 consecutive patients with ischemic stroke by 5 neurologists from 4 academic stroke centers.

Results—The kappa value for inter-examiner agreement was 0.86 (95% CI, 0.81 to 0.91) for the 5-item CCS (large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes), 0.85 (95% CI, 0.80 to 0.89) with the undetermined group broken into cryptogenic embolism, other cryptogenic, incomplete evaluation, and unclassified groups (8-item CCS), and 0.80 (95% CI, 0.76 to 0.83) for a 16-item breakdown in which diagnoses were stratified by the level of confidence. The intra-examiner reliability was 0.90 (0.75–1.00) for 5-item, 0.87 (0.73–1.00) for 8-item, and 0.86 (0.75–0.97) for 16-item CCS subtypes.

Conclusions—The web-based CCS allows rapid analysis of patient data with excellent intra- and inter-examiner reliability, suggesting a potential utility in improving the fidelity of stroke classification in multicenter trials or research databases in which accurate subtyping is critical. (Stroke. 2007;38;2979-2984.)

Key Words: classification cerebral infarct etiology

Etiologic stroke classification is an integral part of individual patient care and stroke research. Reliable classification of stroke, however, is a complex task because stroke is a heterogeneous disorder with multiple potential mechanisms. Advances in research methodology and diagnostic technology often allow identification of multiple competing causes in a given patient, making the determination of stroke etiology even more complex. Inter-rater agreement decreases when attempts are made to classify strokes with multiple mechanisms into specific etiologic classes in the absence of evidence-based strategies.1–5 This, in turn, severely detracts from the usefulness of research data regarding stroke subtypes. We have recently developed an evidence-based classification algorithm (SSS-TOAST) that harmonizes multiple aspects of the diagnostic stroke evaluation to identify the most likely mechanism of stroke, even when multiple potential causes exist.6 An initial evaluation of the SSS-TOAST in 50 patients has shown that the system can assign strokes with multiple competing mechanisms into a specific etiologic subtype without sacrificing high inter-rater agreement.6 In the

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Disclaimer: The automated CCS algorithm is freely available for academic use at http://ccs.martinos.org/. Massachusetts General Hospital has reserved licensing rights for the use of the CCS by for-profit entities.

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current study, we present an automated version of the SSS-TOAST system, the Causative Classification System (CCS), to improve its reliability and facilitate utility in multi-center settings.

Materials and Methods
Moving from the broad descriptive approach that was first outlined in the initial description of the SSS-TOAST classification to a computerized algorithm required that a number of minor ambiguities be resolved such that the web-based CCS application provides definitive answers to each possible situation. Consequently, the SSS-TOAST methodology was refined as described.

Etiologic Subtypes
The CCS incorporates clinical, epidemiological (quantitative primary stroke risk estimates), and diagnostic data to determine stroke subtype in 5 major categories (Table 1): large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes. The undetermined group is further divided into cryptogenic embolism, other cryptogenic, incomplete evaluation, and unclassified categories. In the CCS, each etiologic category is subdivided based on the weight of evidence as “evident,” “probable,” or “possible.” A mechanism is deemed “evident” only if the available data indicate that it is the sole potential mechanism conforming to 1 of the etiologic categories. When there are >1 “evident” stroke mechanisms, the system assigns a “probable” stroke mechanism based on specific characteristics that make one mechanism more probable than the others. In the absence of any “evident” cause, a search is made for “possible” mechanisms that carry a lower or less-well defined risk for stroke.

Criteria for Subtype Assignments
The CCS adopts the same criteria that were used to standardize subtype assignments in the SSS-TOAST system. Briefly, an “evident” mechanism is separated from a “possible” mechanism using an arbitrary 2% annual or 1-time primary stroke risk threshold. The criteria for “evident” mechanism in the CCS are summarized in Table 1.

A “possible” etiology in the CCS corresponds to mechanisms that have <2% annual or 1-time primary stroke risk. In addition, an “evident” mechanism is changed to “possible” if relevant etiological investigations are stopped when a positive test result for another etiology is obtained. An “evident” mechanism is also modified to “possible” in circumstances in which available brain imaging is not sensitive to pick up the expected abnormality given the duration of deficit, timing, and quality of imaging. The criteria that correspond to a “possible” mechanism are listed in Table 1.

The CCS assigns a “probable” mechanism only when there are multiple competing “evident” mechanisms, otherwise a single mechanism is declared “evident.” Because there is no gold standard to identify the cause in the presence of multiple competing etiologies, the CCS defines relationships to distinguish the most likely mechanism based on the presence of following criteria: the presence of a spatial relationship to link brain infarct to its vascular cause (for instance, multiple infarcts in both hemispheres and infective endocarditis, or demonstration of intraluminal thrombus as the source of embolism in arteries proximal to the infarct); the presence of a temporal relationship to tie brain infarct to a specific vascular event (for instance, acute stroke after acute arterial dissection, myocardial infarction, or endovascular procedure); a nonchronic occlusion or near-occlusive stenosis in arteries supplying the vascular territory relevant to the infarction is assigned probable when there are coexisting proximal sources of embolism; and the presence of a feature with positive likelihood ratio (the probability that a person with a given stroke subtype would have a particular clinical or imaging feature divided by the probability that a person with no such mechanism would have the same clinical or imaging features) is greater than or equal to an arbitrarily defined limit of 2 (Table 1).

Special Circumstances in Subtype Assignments
In circumstances in which there was absent primary risk data, inconsistent primary risk data, or no evidence-based diagnostic criteria for a given etiology, the subtype decision was left to the discretion of the treating physician in the SSS-TOAST system. As mentioned, to program the CCS algorithm, it was necessary to further categorize such items into more homogenous groups in the automated CCS system. Refinements were introduced in the current system, as described in the following paragraphs.

Other Causes
Disorders in this category are subdivided into 2 groups based on their relationship with the brain infarct in space and in time. Disorders that bear a clear and close temporal or spatial relationship with the acute infarct are listed in Table 2. When these disorders coexist with another evident cause (for which there is no probable criterion), a subtype is assigned as “probable other.” For instance, in a patient with atrial fibrillation and active cerebral vasculitis, the cause of stroke is classified as “probable vasculitis.” For disorders that do not bear temporal or spatial relationship, the subtype is assigned as “undetermined—unclassified” when they coexist with another evident cause (for which there is no probable criterion). For instance, in an acute stroke patient with Sneddon syndrome and ipsilateral carotid stenosis >50%, the stroke subtype is classified as “undetermined unclassified.” The final revision in this category concerned disorders that were considered as diagnoses of exclusion. These include “drug-induced” stroke and “migraine-related” stroke. Their coexistence with another evident cause does not reduce the level of confidence assigned to that evident mechanism. For instance, in a patient with history of cocaine use and left atrial myxoma, the CCS subtype is assigned as evident cardio-aortic embolism.

Incomplete Evaluation
The CCS requires that imaging of the brain, imaging of the cerebral vessels, and the evaluation of heart function be performed. Each of these investigations is specific for one evident subtype: brain imaging for evident small artery occlusion, vascular imaging for evident large artery atherosclerosis, and cardiac evaluation for evident cardio-aortic embolism. If the appropriate diagnostic studies were not performed despite the presence of a probable criterion for a given subtype, the CCS subtype is classified as “incomplete evaluation.” For instance, in a patient with multiple acute infarcts in both hemispheres (probable criterion for cardio-aortic embolism) but no cardiac evaluation, the CCS subtype is classified as incomplete evaluation even if diagnostic investigations reveal another evident cause.

Small Artery Occlusion
Small artery occlusion is unique in the stroke classification scheme because it is the only vascular cause that does not require demonstration of a vascular lesion. Instead, an evident mechanism requires the imaging proof of a single infarction within a territory supplied by a single penetrating artery originating from the proximal branches of the circle of Willis, basilar artery, or distal vertebral arteries. In situations in which a lacunar infarct presents with a classical syndrome but there is a coexisting alternative evident mechanism, the subtype is assigned as “probable small artery occlusion” instead of “undetermined—unclassified,” because the presence of a clinical lacunar syndrome and radiologic evidence of a typical lacunar infarct strongly indicates small artery occlusion secondary to intrinsic perforating artery disease as the underlying mechanism.7–12

Technical Features of the CCS Software
The CCS consists of a questionnaire-style classification scheme for ischemic stroke. The data entry is performed in 5 easy steps organized in checkboxes. These include results of clinical evaluation, imaging evaluation of the brain, imaging evaluation of the cerebral vasculature, cardiac evaluation, and evaluation for other causes of stroke. The CCS was implemented using standard computer languages used for content distribution and user interaction through the Internet: HyperText Markup Language (HTML), Cascading Style
<table>
<thead>
<tr>
<th>Stroke Mechanism</th>
<th>Level of Confidence</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large artery</td>
<td>Evident</td>
<td>1. Either occlusive or stenotic (&gt;50% diameter reduction or &lt;50% diameter reduction with plaque ulceration or thrombosis) vascular disease judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The absence of acute infarction in vascular territories other than the stenotic or occluded artery</td>
</tr>
<tr>
<td></td>
<td>Probable</td>
<td>1. History of ≥1 transient monocular blindness (TMB), TIA, or stroke from the territory of index artery affected by atherosclerosis within the last month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Evidence of near-occlusive stenosis or nonchronic complete occlusion judged to be caused by atherosclerosis in the clinically relevant extracranial or intracranial arteries (except for the vertebral arteries)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. The presence of ipsilateral and unilateral internal watershed infarctions or multiple, temporally separate, infarctions exclusively within the territory of the affected artery</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td>1. The presence of an atherosclerotic plaque protruding into the lumen and causing mild stenosis (&lt;50%) in the absence of any detectable plaque ulceration or thrombosis in a clinically relevant extracranial or intracranial artery and history of ≥2 TMB, TIA, or stroke from the territory of index artery affected by atherosclerosis, at least 1 event within the last month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Evidence for evident large artery atherosclerosis in the absence of complete diagnostic investigation for other mechanisms</td>
</tr>
<tr>
<td>Cardio-aortic</td>
<td>Evident</td>
<td>1. The presence of a high-risk cardiac source of cerebral embolism (see Table 3)</td>
</tr>
<tr>
<td>embolism</td>
<td>Probable</td>
<td>1. Evidence of systemic embolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The presence of multiple acute infarctions that have occurred closely related in time within both right and left anterior or both anterior and posterior circulations in the absence of occlusion or near-occlusive stenosis of all relevant vessels. Other diseases that can cause multifocal ischemic brain injury such as vasculitides, vasculopathies, and haemostatic or hemodynamic disturbances must not be present</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td>1. The presence of a cardiac condition with low or uncertain primary risk of cerebral embolism (see Table 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Evidence for evident cardio-aortic embolism in the absence of complete diagnostic investigation for other mechanisms</td>
</tr>
<tr>
<td>Small artery</td>
<td>Evident</td>
<td>1. Imaging evidence of a single and clinically relevant acute infarction &lt;20 mm in greatest diameter within the territory of basal or brainstem penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasoospasm, etc)</td>
</tr>
<tr>
<td>occlusion</td>
<td>Probable</td>
<td>1. The presence of stereotypic lacunar transient ischemic attacks within the past week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. The presence of a classical lacunar syndrome</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td>1. Presenting with a classical lacunar syndrome in the absence of imaging that is sensitive enough to detect small infarctions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Evidence for evident small artery occlusion in the absence of complete diagnostic investigation for other mechanisms</td>
</tr>
<tr>
<td>Other causes</td>
<td>Evident</td>
<td>1. The presence of a specific disease process that involves clinically appropriate brain arteries</td>
</tr>
<tr>
<td></td>
<td>Probable</td>
<td>1. A specific disease process that has occurred in clear and close temporal or spatial relationship to the onset of brain infarction such as arterial dissection, cardiac or arterial surgery, and cardiovascular interventions</td>
</tr>
<tr>
<td></td>
<td>Possible</td>
<td>1. Evidence for an evident other cause in the absence of complete diagnostic investigation for mechanisms listed above</td>
</tr>
<tr>
<td>Undetermined causes</td>
<td>Unknown</td>
<td>1. Angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal looking intracranial arteries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Imaging evidence of complete recanalization of previously occluded artery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. The presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Those not fulfilling the criteria for cryptogenic embolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. The absence of diagnostic tests that, under the examiner’s judgment, their presence would have been essential to uncover the underlying etiology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. The presence of &gt;1 evident mechanism in which there is either probable evidence for each, or no probable evidence to be able to establish a single cause</td>
</tr>
</tbody>
</table>

Cryptogenic embolism: 1. Imaging evidence of complete recanalization of previously occluded artery
2. The presence of multiple acute infarctions that have occurred closely related in time without detectable abnormality in the relevant vessels
3. Imaging evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal looking intracranial arteries

Other cryptogenic: 1. Those not fulfilling the criteria for cryptogenic embolism

Incomplete evaluation: 1. The absence of diagnostic tests that, under the examiner’s judgment, their presence would have been essential to uncover the underlying etiology

Unclassified: 1. The presence of >1 evident mechanism in which there is either probable evidence for each, or no probable evidence to be able to establish a single cause
Table 2. Disorders in the Other Causes Category

Abnormalities of thrombosis and hemostasis
Acute arterial dissection*
Acute disseminated intravascular coagulation*
Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy cerebral vasculitis*
Cerebral venous thrombosis*
Chronic arterial dissection
Clinically relevant aneurysm
Drug-induced stroke
Fibromuscular dysplasia
Heparin-induced thrombocytopenia type II*
Hyperviscosity syndromes
Hypoperfusion syndromes*
Iatrogenic causes*
Meningitis*
Migraine-induced stroke
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
Moyamoya disease
Primary antiphospholipid antibody syndrome
Primary infection of the arterial wall*
Segmental vasoconstriction or vasospasm*
Sickle cell disease
Sneddon syndrome
Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome*
Other

*Disorders that bear a clear and close temporal or spatial relationship with the acute infarct.

The Reliability of the CCS

To determine reproducibility of diagnoses per the CCS, the intra- and inter-examiner reliabilities were calculated by neurologists from 4 different NINDS - SPOTRIAS (Specialized Program of Translational Research in Acute Stroke) sites (Massachusetts General Hospital, UCLA, Columbia University, UCSD) who had not been involved in the design and development of the SSS-TOAST or the CCS, independently assessed 50 consecutive patients with acute ischemic stroke through reviews of abstracted data from medical records. Data abstraction was performed by 1 of the investigators who did not participate in the assessment process (E.M.A.). A manual was developed to guide the data abstraction process. This manual included official reports of brain imaging, vascular imaging, cardiac evaluation (EKG, echocardiography), and other specific laboratory tests. The manual also provided guiding for clinical features and neurological examination findings that were required for the CCS classification (Table 1). Each examiner was provided with a copy of the original publication describing the SSS-TOAST system and a 1-page summary of the operational aspects of the CCS. Examiners were asked to strictly apply all the rules specified in both the SSS-TOAST and CCS systems. Intra-examiner reliability was assessed by having 1 examiner categorize the same set of 50 patients on 2 separate occasions 5 months apart. The intra- and inter-examiner reliabilities were evaluated using the kappa statistic, according to the method described by Fleiss. A kappa of 1 indicates perfect agreement, whereas zero shows only chance agreement; in general, excellent agreement refers to values >0.80, whereas 0.61 to 0.80 indicates substantial agreement, and 0.41 to 0.60 indicates moderate agreement.

Results

The study population was composed of 26 male and 24 female patients with a mean age of 64 years (range, 36 to 86 years). There was history of hypertension in 32, diabetes mellitus in 17, coronary artery disease in 13, and atrial fibrillation in 12 of the 50 patients. Cerebral infarcts included the middle cerebral artery territory in 24, posterior cerebral artery in 7, brain stem in 7, posterior inferior cerebellar artery in 4, internal carotid artery in 3, and anterior cerebral artery in 1 patient. There were 4 other patients with infarcts in multiple arterial territories. Of the 50 patients, 43 had CT, 40 had CT angiography, 45 had MRI, 25 had MR angiography, 41 had transthoracic and/or transesophageal echocardiography, and 7 had vascular ultrasound studies. Diagnostic investigations revealed a high-risk cardiac emboli source in 14 (Table 3), a low-risk cardiac or aortic emboli source in 20 (Table 3), moderate to severe arterial stenosis or occlusion secondary to atherosclerosis in 14, lacunar infarct in 8, acute arterial dissection in 3, primary antiphospholipid syndrome in 2, angiographic moyamoya pattern in 1, and intracranial aneurysm in 1 patient. Diagnostic investigations did not reveal any etiology in 5 of the 50 patients.

The kappa value for inter-examiner agreement was 0.86 (95% CI, 0.81 to 0.91) for the 5 major CCS subtypes (large artery atherosclerosis, cardio-aortic embolism, small artery occlusion, other causes, and undetermined causes), 0.85 (95% CI, 0.80 to 0.89) when the undetermined group is further divided into cryptogenic embolism, other cryptogenic, incomplete evaluation, and unclassified groups (8-item CCS), and 0.80 (95% CI, 0.76 to 0.83) for the 16-item CCS in which the diagnoses were stratified by the level of confidence. The intra-examiner reliability was 0.90 (0.75–1.00) for 5-item, 0.87 (0.73–1.00) for 8-item, and 0.86 (0.75–0.97) for 16-item CCS subtypes.

Disagreement among examiners occurred in 12 of the 50 patients. In 8 of these 12 patients, the disagreement occurred because 1 examiner’s assignment differed from the other 4. Disagreements were attributable to examiners missing a critical data element presented in the abstraction sheets (8 patients), variation in interpretation of vascular imaging reports as to whether a vascular stenosis was caused by atherosclerosis or nonocclusive nonatherosclerotic stenosis (3 patients), and considering a prothrombotic factor as the underlying mechanism of stroke in a patient with another evident cause.
used original TOAST rules. The system was tested in 20 patients and revealed moderate inter-examiner reliability (kappa=0.68). In other studies of stroke classification, a high reliability could be attained only when the size of unclassified group was inflated to \( \approx 40\% \). It makes intuitive sense that there is a tight balance between inter-examiner reliability and the size of “unclassified” category. One can achieve a high reliability by assigning all patients with multiple mechanisms into the unclassified group, essentially a “wastebasket” bin. The CCS classifies patients into known etiologic categories without expanding the “unclassified” category and sacrificing reliability; the unclassified category was only 6% on average (range, 4% to 12%, depending on the examiner) in the present study. The combination of high reliability and a small “unclassified” category further supports the role of the CCS in multicenter stroke research.

Subjective interpretation of clinical data are an important source of variability in etiologic stroke classification. The SSS-TOAST system reduced this source by introducing a well-referenced, well-defined, and rule-based assignment. The CCS deals with another source of variability that comes from differences in interpretation of rules that standardize subtype assignments. The automated system eliminates this source of variability by providing a uniform language for data entry. The remaining variability is in large part caused by disparity in data abstraction and application of the abstracted data by the examiners. In the current study, the variability attributable to differences in data abstraction by examiners was reduced through the use of a standard manual that required extraction of official test reports, rather than abstractors’ or physicians’ interpretation of test results. The disparity in abstracted data application by examiners was minimized by introducing computer functions that prevented user from entering inconsistent data. These include automatic error checking and feedback functions, automatic enabling and disabling of dependent elements, and tool tips for more detailed explanations of certain terms and conditions. The current version of the CCS software offers a 5-patient training module based on abstracted information on clinical and diagnostic findings. During the evaluation of these training cases, the system intervenes with the user when critical information is missed or incorrectly entered. The training module aims to make users develop a sense to distinguish critical data for subtype assignments. We strongly recommend completing this module before starting to use the CCS (http://ccs.martinos.org).

Differences in interpretation of test results were a source of disagreement among examiners. The difficulty in distinguishing atherosclerosis from other causes of vascular stenosis appeared to be the leading cause of disagreement. This is a distinction that is difficult to make from abstracted test reports unless the reporting physician’s diagnosis is explicitly stated. The diagnosis requires individual physician’s primary assessment based on location, shape, and composition of stenosis, as well as coexisting changes in other vascular sites. We observed another source of disagreement that resulted from differences in examiners’ decision in assigning hereditary or acquired thrombophilias as an evident mechanism. Prothrombotic abnormalities such as factor-V Leiden,
activated protein C resistance, hyperfibrinogenemia, hyper-
homocystinemia, or positive antiphospholipid antibodies are 
very common but their link to stroke is unclear in adults. \(^{21–23}\)

Routine assignment of these abnormalities to an evident 
mechanism in an automated approach would obscure 
accountability of other coexisting cardiac or arterial abnormal-
ities as the cause of stroke. We advocate, along with others, 
that prothrombotic abnormalities should be considered as an 
evident cause of stroke only in patients with history of \(\geq 1\) 
unexplained thromboembolic events, in young stroke pa-
tients, in those with a family history of thrombosis, and in 
patients who have no other explanations for their stroke.\(^{21}\)

The CCS offers a number of features that ensure utility in 
clinical and research settings. It runs on almost any web 
browser and operating system. Its standalone application 
provides immediate feedback and does not depend on server 
availability or network connection. The resulting classifica-
tion is available at the end of the fill-in procedure. A printable 
summary page displays the stroke subtype along with all the 
data entered. This can be used for archiving purposes. In 
addition, it gives researchers an opportunity to have individ-
ual components of the stroke work-up so that they can 
reorganize the data according to the needs of their research.

The CCS fulfills an obvious need for an algorithmic 
classification system to establish a template that may serve as 
a common language in the field. It limits inter-examiner 
variability in interpretation of stroke-related characteristics, 
ensures uniformity in data entry, and thus uses an evidence-
based means of assigning cases to specific classes with 
excellent reliability. The CCS allows processing of vast 
amounts of patient data in a very short time frame with 
minimal level of inconsistency, suggesting a potential utility 
in multicenter stroke research, as well as in electronic 
archiving and billing systems.

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**Disclosures**

None.

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