Heterogeneity of Association Between MTHFR and Stroke Among European Regions: Additional Population Studies Are Needed in Italy

To the Editor:
The recent meta-analysis of Cronin et al\(^1\) examined the association between the MTHFR C677T polymorphism, the strongest genetic determinant of moderate hyperhomocysteinemia, and ischemic stroke. These authors considered 31 studies, including 15 from Europe, and concluded for the existence of an overall weak and dose allele-dependent association; in the European area, they reported a lack of association between the MTHFR C677T polymorphism and ischemic stroke in Northern and Central Europe, whereas the MTHFR C677T polymorphism was surprisingly a significant risk factor for ischemic stroke in Italy. The same authors\(^2\) suggested that it was important to investigate whether this finding was attributable to population differences in T allele frequency, folate status, or other genetic or environmental influences. In fact, the frequency of MTHFR 677T allele is higher in Italy than in Central and Northern Europe, and the same gradient is observed for the dietary intake and status of folate.\(^3\) Therefore, the significant association observed by Cronin et al\(^1\) in Italy should be regarded as paradoxical if one considers that adequate folate dietary intake neutralizes the phenotypic influence of MTHFR on homocysteine.\(^2\) In fact, 2 of the 4 Italian populations that were included in the meta-analysis of Cronin et al\(^1\) were different for age and cause of stroke from those recruited in the other areas of Europe; this makes the paradox reported by Cronin et al questionable. Pezzini et al\(^3\) found a significant association of MTHFR 677TT with patients with spontaneous cervical artery dissection (CAD), a very particular cause of stroke, but not with those with non-CAD ischemic stroke, whereas Gallai et al\(^4\) found no association in younger patients with spontaneous CAD. A third study found no association between 677TT genotype and stroke,\(^5\) whereas in another study, Margaglione et al\(^6\) found only a weak association with premature stroke (age <50), after multivariate adjustment (\(P=0.0486\)). We have evaluated the association between MTHFR 677TT 677TT polymorphism and ischemic cerebrovascular disease in 131 patients from Southern Italy (Sicily) with a mean age of 76.2 years (51.9% males), compared with 118 sex- and age-matched controls (mean age 75.9 years, \(P=0.6032, 50.8\% \text{ males, } P=0.8672\). The 677T allele frequency was comparable in both groups (patients: 0.439 [95% CI, 0.380 to 0.499], controls: 0.432 [95% CI, 0.371 to 0.496]; \(P=0.8798\)) and no difference of the 677TT genotype frequency was observed (patients: 0.229 [95% CI, 0.165 to 0.308], controls: 0.169 [95% CI, 0.112 to 0.247]; \(P=0.2418\)). In our opinion, the small number of studies on the association between homocysteine or MTHFR and stroke needs to be increased, taking into consideration other nutritional and genetic determinants of homocysteine, folate and vitamin B12 in particular, before a definitive conclusion based on meta-analyses can be reached. This will be required for discussing the beneficial role of folate supplementation. Indeed, if folate intake in Europe does explain the heterogeneity of the associations, folic acid as a preventive intervention would be unlikely to have any influence in the regions where there is no MTHFR-vascular disease association, as recently suggested by Lewis et al for coronary artery disease.\(^7\)

Response:
We thank Dr Bosco and colleagues for their interest in our study. Although subgroup analyses of meta-analyses of stroke risk associated with genetic polymorphisms may yield useful hypotheses-generating information for future studies, we again caution that such analyses should be considered exploratory and that the lower numbers within individual subgroups may lead to loss of power. As outlined in our original publication, our subgroup analyses further included studies which reported the association of MTHFR TT genotype only when compared with a combined CT and CC genotype control group, from which allele-specific information could not be gleaned for the overall allele-dose analysis. In addition to those 4 studies outlined above, our Italian group further included a population from Soriente et al.\(^8\) In total, there were 523 cases and 1507 controls from Italy. Of these cases, only 50 (9.5%) had spontaneous cervical artery dissection as the underlying stroke mechanism. When these are excluded,
the risk estimate for ischemic stroke associated with the MTHFR TT genotype in the Italian subgroup is 1.24 (95% CI, 0.96 to 1.61), which is consistent with our findings in the overall group. We agree that there is a need for further study in individual racial and ethnic subgroups.

We further suggest that future analyses of stroke risk associated with the 677T allele should detail their findings in the context of stroke mechanism and serum homocysteine and folate levels. Because of few reports of folate levels and stroke subtype, it was not possible from available data to fully examine their influence on individual populations under study. Our overall findings in almost 15,000 subjects suggest a modest elevation of risk for MTHFR T allele homozygotes and heterozygotes. We agree that large prospective population-based studies and clinical trials in homocysteine-lowering therapies are needed to definitively resolve the relationships between 677T allele, homocysteine, and vascular risk. Pending the availability of such data, meta-analyses remain a useful, albeit imperfect, approach to addressing some of the limitations of smaller retrospective studies. We await the results of ongoing trials with interest.

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There Is More to it Than: the Greater the Infarction Volume, the More Probable Is a Malignant MCA Infarction

To the Editor:

In Stroke, we read with great interest the original article by Serena et al.1 on prediction of malignant middle cerebral artery (MCA) infarction. As a group working experimentally and clinically on malignant MCA infarction,2–4 we would like to comment on their competent study on molecular blood-brain barrier (BBB) disruption markers in patients who developed a malignant MCA infarction, because their work establishes a new point of view in the understanding of this life-threatening disease.

The approach of Serena and colleagues to detect matrix metalloproteinases (MMPs) and basal lamina decomposition products like cellular fibronectin in plasma of patients allows a quite precise prediction of malignant MCA infarction.1 Cerebral ischemia leads to an up-regulation of MMPs, which degrade elements of the extracellular matrix and of the basal lamina.5,6 BBB disruption may result from this process because the basal lamina is part of the blood-brain barrier system. Thus, substances involved in this process are of substantial interest not only for diagnostic purposes but also for investigations of the mechanisms resulting in malignant infarction and associated complications like hemorrhagic transformation.7–9 Recently, studies using various imaging techniques have emphasized that the size of the initial infarct volume10–12 and possibly the intensity of blood-flow reduction12 is a good predictor of malignant brain edema formation. We should recognize, however, that in individual cases presented in these studies, a similar size of infarction resulted in completely different clinical courses highlighting the fact that a simple monocausal relationship does not exist for the development of malignant MCA infarction and that inter- or even intra-individual variations need further mechanistic explanations.

High levels of MMPs and of related substrates were thought to play a key role for such secondary deterioration,8 and in this respect, the work of Serena and colleagues is a promising step. For a more comprehensive understanding of the pathophysiology of malignant MCA infarction, however, we think that direct, simultaneous measurements in extracellular fluid, cerebrospinal fluid and plasma are needed. In particular, the analysis of extracellular fluid would provide information about the extracellular matrix as the relevant location where MMPs generate their enzymatic activity. Furthermore, MMP-9 is produced by astrocytes as well as endothelial cells, and both glial and endothelial MMP-9 are thought to be responsible for BBB damage.13,14 Combination with microdialysis might provide the chance to get simultaneous information at the parenchymal and vascular side of the basal lamina.

We need longitudinal information on MMPs and related substrates. It is possible that processes at the parenchymal and at the vascular side of the basal lamina follow different time scales. Thus, the origin of substrate alterations detected in plasma remains unclear. The comparison with alterations in the extracellular fluid detected by cerebral microdialysis13,15 might help here, too. More importantly, longitudinal information on extracellular fluid and plasma concentration would also offer the chance to detect slower courses of malignant transformation in individual patients and thus provide the chance for treatment options like hemicraniectomy in these individuals. In this context, complementary translational research with animal models of malignant stroke would be valuable because we could compare with preschismic baseline levels of relevant substances.

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Response:
We are grateful to Drs Bosche, Graf, Dohmen and Hamann for the interest shown in our article. We agree that further studies focusing on both the comparison of molecular markers obtained simultaneously in extracellular brain tissue by microdialysis and peripheral blood samples as well as longitudinally obtained data regarding matrix metalloproteinases (MMPs) and related substrates are needed. We supply some information concerning this second point.

As in the studies cited by the authors, we too found that similar infarct volume resulted in very different clinical courses and so agree that better predictors of malignant MCA (m-MCA) infarction are needed. The analysis of extracellular fluid by microdialysis in experimental studies together with plasma samples would provide additional and useful information in clinical practice, particularly considering that microdialysis is not a suitable technique in clinical practice and could only be conducted in animal models or, possibly, after a hemicraniectomy has been performed with a prior decision, which rather defeats the object. Unfortunately, the study of cerebrospinal fluid before hemicraniectomy is not recommended in patients with massive brain infarction because of the risk of herniation.

Temporal profile of MMP-9 and its substrate c-Fn in the whole population with acute ischemic stroke of <12 hours evolution (upper graphs) and with massive MCA infarction (lower graphs) divided in those whose finale did or did not develop an m-MCA infarction.
We agree too in the need for longitudinal studies of MMPs and related substrates, such as cellular fibronectin (c-Fn), because the application of these results may well increase the precision with which we are able to select patients, particularly in cases of delayed malignant brain infarction. In our study we focused on blood samples taken at admission because this is the most relevant sample in identifying patients at risk of subsequent m-MCA infarction. As commented in our article, the blood samples were part of a prospective register aimed at evaluating serum markers of early and late clinical course in acute ischemic stroke. In this register we take blood samples at admission (mean time from stroke onset to blood sample: 2.85 ± 2.06 hours), 24 hours and 72 hours from stroke onset. In the Figure it is possible to see the longitudinal MMP-9 and c-Fn profiles in blood samples in the whole group of patients with acute ischemic stroke. Similar temporal profiles were found in patients with and without m-MCA infarction although higher concentrations of these molecules were observed in m-MCA patients. We agree that the parenchymal and vascular sides of the basal lamina may present different patterns and that data obtained from animal models would be of interest and might be applicable in humans. However, what is sought for clinical practice is an accurate early marker of m-MCA infarction, which acts to indicate hemi-craniectomy, and it seems that plasma samples are sufficiently accurate and precocious as to make this possible although it should be stressed that our data were obtained from a post hoc analysis and so should be considered as hypothesis generating only and requiring confirmation in a large-scale prospective study.

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Intra-arterial Thrombolysis in Late Pregnancy
To the Editor:
Johnson et al injected a limited amount of recombinant tissue plasminogen activator (r-TPA) in the middle cerebral artery of a 37-week pregnant woman with left acute ischemic stroke.1 The middle cerebral artery did not reopen. On the final angiogram, an efficient collateral circulation through posterior cerebral artery, not seen on the preoperative angiogram, filled the peripheral branches of the occluded middle cerebral artery. The patient rapidly improved, and no adverse effects of the procedure were observed.

We congratulate the authors for rapid diagnosis, excellent therapeutic approach and good final results, but we deeply disagree with the interpretation of angiographic pictures. Figure 1 (preoperative) and Figure 2A (postoperative) express exactly the same pattern of collateral circulation toward peripheral middle cerebral artery, the sole difference being the phase, early and late arterial, respectively. In effect, some thin branches of middle cerebral artery filled by leptomeningeal collaterals are already seen in Figure 1. In other words, collateral circulation may be similar pre- and postoperatively. In Figure 2B the main branches of the anterior cerebral artery are still injected, whereas posterior cerebral artery is not. This is the typical angiographic pattern of a posterior cerebral artery filled both from anterior and posterior circulation: the pressure wave of the contrast injection in carotid artery partially fills the posterior cerebral artery. Once the pressure wave of the injection is past, contrast is rapidly washed out from fresh blood of posterior circulation. Visualization of the posterior cerebral artery depends on the pressure of the injection and on the position of the catheter. The alternative hypothesis suggested by Johnson et al of an asymptomatic thrombus occluding posterior communicans artery at its origin, dissolved by 15 mg of r-TPA injected in the middle cerebral artery, seems less realistic. Improvement may be explained by natural history of the middle cerebral artery occlusion, frequently going toward rapid improvement with limited basal ganglia infarctions,2 possibly helped by the systemic action of r-TPA. Anyway, the behavior of the authors was absolutely correct, because it was based on the clinical and not on the angiographic improvement. In similar cases a mechanical embolotomy may represent a less risky alternative.

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Response:
I want to thank Drs Bergui and Bradac for their interest in our article and their kind words regarding our management. I am pleased to report the patient and her child continue to do well.

The writers suggest that the patient’s clinical improvement may have been an example of the natural history of resolving middle cerebral artery (MCA) occlusion with residual basal

![Figure 1. Angiogram. Right common carotid artery (RCCA) arterial phase. Lateral. Prethrombolysis RCCA angiogram shows nonfilling of the PCOM and nonfilling of the parietal and temporal MCA branches.](image-url)
ganglia infarction. They disagree with our interpretation that improved collateral circulation to the MCA territory accounted for the clinical improvement. These writers offer a valid criticism because the few images published do not clearly depict this change in circulation.

During the thrombolysis itself, we observed the first appearance of the posterior communicating artery (PCOM) and posterior cerebral artery (PCA), and, with that, we saw improved collateral circulation to the MCA via PCA-MCA leptomeningeal collaterals (Figures 1 and 2). The prethrombolysis image (Figure 1) shows nonfilling of the PCOM, with nonfilling of the parietal and temporal branches of the MCA. The postthrombolysis image (Figure 2), at comparable angiographic phase, using similar injection parameters, shows the first filling of the PCA with concurrent improved filling of additional parietal portions of the MCA territory.

These more complete images demonstrate that the differences in MCA collateral filling result from the improved PCA circulation, not from the differences in angiographic phase as suggested by the writers. One can never know whether the treatments given result directly in patient improvement, assist the patient in the natural process of healing, or occur contemporaneously with, but coincident to, spontaneous healing. We can only hope our efforts did contribute to the good outcome for this patient and her child.

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Formal Dysphagia Screening Protocols
Prevent Pneumonia

To the Editor:

Hinchey and the Stroke Practice Improvement Network Investigators1 are to be commended for managing a major multi-site collaborative effort that has compiled a dataset demonstrating current practice in 15 institutions. However, this report is attended by all the usual limitations of this sort of study—dependence on routine documentation rather than evidence of actual practice, in some cases retrospective data extraction, pooling of data from diverse population groups, and an endeavor to identify significant factors among a host of variables which may potentially explain subgroup differences in outcomes.

In this instance, these problems are reflected in significantly different age and ethnicity profiles between clusters of sites, poor completion of key data fields, limited inter-rater reliability of data extraction for crucial variables, and presentation of selected information. Particular problems for this study included limited capture of stroke severity data, very broad definitions of what constitutes dysphagia screening, no information whether screening was performed before oral intake commenced in 25% of patients, and no data regarding duration for which patients were kept nil orally. There is also no consideration of the composite nature of the screened and nonscreened groups; both will have contained a mix of dysphagic and nondysphagic patients, and screening nondysphagic patients is unlikely to have affected pneumonia rates. Although many of these difficulties are acknowledged by the authors, they nonetheless claim a causal relationship, in the title and text, between use of dysphagia screening and reduced aspiration rates. This disregards their comparison of sites according to levels of guideline compliance (ie, a package of “best practice” care management). Given their reportage of only 1 of their 4 selected “quality indicators”, we have no idea of other, potentially equally significant discrepant aspects of care.

This study has much to commend it as a means to support local practice development, but its contribution to the body of knowledge is as further corroboration of the merits of adherence to evidence-based guidelines. It is neither unique in this field, (see for example Duncan et al12) nor this area (eg, Perry and McLaren13). What it does not do is demonstrate that formal dysphagia screening reduces incidence of pneumonia; there are many other aspects of care within guideline-compliant management that may contribute to this. Dysphagia screening is an essential yet not sole contributor to this outcome, but this study does nothing to unpack what other key components may be.

Once again, we have another study that shows much of current practice as substandard (for example, only 6 of 11 hospitals with Stroke Units had formal screening protocols), that indicates that we could achieve better outcomes for patients, including by use of dysphagia screening, but without fully investigating what may be required to accomplish this.

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Publishing Rehabilitation Randomized Controlled Trials

To the Editor:

The Stroke Rehabilitation Evidence-Based Review (SREBR) is the most comprehensive and current review of the stroke rehabilitation literature. The website is www.ebrsr.com. Our systematic review found 452 randomized controlled trials (RCTs) of interventions directly related to stroke rehabilitation. We have listed the 10 journals with the most published RCTs in the area of stroke rehabilitation (Table). Stroke has the greatest number of RCTs directly related to stroke rehabilitation.

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Journals Publishing RCTs in Stroke Rehabilitation

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Response:

We are delighted that Stroke leads in publishing randomized clinical trials in rehabilitation. This reaffirms our commitment of being a comprehensive stroke journal where the best in every discipline is published.

We continue to look forward to receiving the highest quality manuscripts, enabling Stroke to become the stroke journal of choice.

Vladimir Hachinski, MD, DSc
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Cataract Surgery After Acute Stroke: Maybe More than a Coincidence

To the Editor:

Cataract and stroke are 2 common pathologies in the elderly population. The need of cataract surgery in the UK approximates 200 000 a year, and >2.4 million people aged over 65 experienced cataracts with visual impairment in 1 eye or 2. This number increases by 1.1 million over a 5-year period. About 5% of patients undertaking cataract surgery reported a past history of stroke. Most stroke patients experience various levels of functional impairment which may, on the one hand, limit them from having cataract surgery, but, on the other hand, they may have a stronger drive to improve their visual acuity after stroke.

Oxford Radcliffe Hospital (ORH) Trust is the only general hospital providing acute stroke care, so the majority of patients in Oxfordshire contracting acute stroke would be sent to ORH for treatment. A retrospective chart survey of acute stroke inpatients in ORH Trust in 2003 to 2004 was done to explore the relationship between stroke and cataract surgery. In 2003, 735 acute stroke inpatient records (mean age = 77.3 ± 13.4 years, 47.9% males) were sorted by ICD-10 (I619, I639, I64X) and were followed through 2004 with the mean follow-up of 377.8 days. At discharge, 213 (28.9%) died at the stroke events, 281 (53.8%) went back home with care package, 15 returned to nursing homes (2.9%), and 226 (43.3%) were transferred for intermediate care. In 2004, 20 patients (3.8%) died, mostly because of infectious complications and recurrent cardiovascular events. Among the 522 stroke survivors, 136 (26.4%) of them were readmitted, and 11 cataract surgeries were performed during the follow-up period. Four hundred and sixteen stroke survivors from 2003 to 2004 were aged over 64. Patients undertaking cataract surgery after stroke were aged over 64 (median age = 77 years, range: 65 to 87 years), and none of them had been transferred to any form of intermediate care, implying that they perhaps recovered better from stroke events. In 1999 to 2000, ~164 000 cataract surgeries were performed for patients aged over 64 in England and Wales, and the cataract surgery rate of people aged over 64 was 1.9% in England and Wales. Cataract surgery rate in stroke survivors aged over 64 was 2.6% (11/416) in our study, which was higher than the national survey.

Is this discovery merely a coincidence between common pathology in the elderly? Maybe yes and maybe no. Hu et al reported that cataract extraction surgery was positively related to coronary heart diseases, and oxidative damages were considered the cause of both conditions. In addition, does head CT scans done during acute stroke events predispose cataract? Previous studies indicated that radiation exposure (diagnostic X-ray and CT scan) was not related to cataract in the middle-aged and the elderly. It is still premature to conclude a causal relationship between stroke and cataract surgery. A large-scaled longitudinal study is needed to ascertain this phenomenon. However, from the patient’s perspective, a stroke survivor with relatively preserved functional status may have a stronger drive to enhance their visual acuity. And, from clinician’s perspective, cataract with visual impairment should be treated more aggressively in order to prevent falls after a stroke. This may be a coincidence following a larger-scale investigation; the attempt to explore the need for stroke survivors should continue.

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Response:

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Potential Role for TCD-Directed Antiplatelet Agents in Symptomatic Carotid Artery Dissection

To the Editor:

We read with interest the debate regarding the role of anticoagulation in extracranial arterial dissection.1,2 We agree with Norris1 that artery to artery embolism is the most likely cause of stroke, and also agree with Lyrer2 that there is no evidence supporting anticoagulation for extracranial internal carotid artery dissection (CAD). Donnan and Davis3 make a most important contribution when they differentiate between the use of antithrombotic agents and antplatelet agents in CAD.

The commonest mechanism of stroke in carotid artery dissection is hypothesized to be artery to artery embolism.1 If this hypothesis is correct, then the situation would appear to be analogous to transient ischemic attacks arising from a critical internal carotid artery stenosis. Transcranial Doppler (TCD)-directed intravenous antiplatelet agents have been successful in treating these patients4,5 both before and after elective surgery. In further support of this hypothesis, we have recently reported a 45-year-old patient who was successfully treated with TCD-directed antiplatelet agents6 for recurrent focal deficits associated with an embolizing subintimal CAD.

Converging lines of evidence suggest that embolization from large arteries can cause focal cerebral symptoms and can be treated in the short-term with TCD-directed antiplatelet agents.4 TCD can rapidly and noninvasively assist both in identifying those patients at higher risk of a subsequent neurological event, and in assessing the efficacy of interventions.5 TCD emboli detection appears to offer an important advance, enabling the optimal integration of both medical therapy and the timing of any surgical intervention, in patients with symptomatic large-vessel disease. We advocate TCD interrogation of the middle cerebral artery for microemboli in symptomatic CAD, particularly where there are fluctuating neurological signs. TCD-directed antiplatelet agents could then be used to control cerebral microemboli and symptoms.7 Elective surgical or endovascular intervention can then be considered where appropriate.

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Magnetic Resonance Direct Thrombus Imaging in Moderate Carotid Artery Stenosis

To the Editor:

Wasserman et al1 present a proof-of-concept case elegantly demonstrating that high-resolution MRI of carotid plaque can identify a lesion that was highly likely to be causing cerebrovascular symptoms even though it was not causing significant stenosis of the carotid lumen. The authors also acknowledge that acquiring high-resolution MR images is time-consuming and requires the injection of contrast.

We too are interested in using MR techniques to find features of carotid artery plaque related to its biological behavior, rather than simply the degree of stenosis caused by it. We have explored magnetic resonance direct thrombus imaging (MRDTI) on the basis that thrombus associated with plaque is likely to be important in disease progression or to the crucial final step before plaques give rise to cerebrovascular symptoms.2 MRDTI takes only 5.3 minutes to acquire, and no contrast is required, making it potentially more easy to use than high-resolution MRI. MRDTI is sensitive and specific for complicated plaque in symptomatic patients with >70% stenosis coming to carotid endarterectomy.3 We are currently undertaking a longitudinal study of MRDTI in symptomatic patients with lesser degrees of carotid stenosis who, in our center, are not routinely offered carotid endarterectomy. We present the following case from our series which illustrates how this technique, like high-resolution MRI, can be clinically valuable.

Mr G was a 68-year-old man who had 2 episodes of loss of power affecting his right arm in September 2002. Duplex ultrasound (undertaken 10 days after the event) showed 30% to 50% stenosis of the right internal carotid artery. He was managed medically and commenced on an antiplatelet, a statin and an angiotensin-converting enzyme inhibitor. MRDTI was positive in the right internal carotid artery (Figure). In March 2004, he developed sudden weakness of the left arm and leg. An MRI scan the same day showed a stenosis of 60% to 70%, and the MRDTI was again positive in the right carotid artery.
He successfully underwent endarterectomy and has had no further symptoms to date. Histology of the endarterectomy specimen demonstrated a ruptured plaque with intraplaque hemorrhage.

We postulate that MRDTI of his carotid artery plaque identified symptomatic disease, even though the degree of intraluminal stenosis was below our usual threshold for surgery. MRDTI provides a feasible alternative to high-resolution MRI for this purpose, although we note that the findings of longitudinal studies such as ours are needed.

**Acknowledgments**

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Formal Dysphagia Screening Protocols Prevent Pneumonia
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