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# Special Report: MEG and MSI for the Purpose of Presurgical Localization of Epileptic Lesions—A Challenge for Technology Evaluation

## Executive Summary

### Background

This Special Report examines the use of magnetoencephalography (MEG) and/or magnetic source imaging (MSI) to provide additional diagnostic information that improves the management and outcomes of patients who are being evaluated for neurosurgical treatment of epilepsy. MEG/MSI would be used to characterize the location of the epileptic zone for resection. No other uses of MEG/MSI are considered in this Report. In this Report, the general term “MEG” will be used for simplicity and consistency.

However, most clinical studies combine MEG information with magnetic resonance imaging (MRI) images to form what is called magnetic source imaging (MSI) when providing anatomic localization of epileptogenic lesions or functionally important cortical regions.

### Objective

The objective of this Special Report is to present the particular challenges that this diagnostic technology presents in terms of evaluating the evidence to determine its potential benefit. Without a thorough presentation of the manner in which MEG is used in the evaluation of patients, it is difficult to determine whether the technology is beneficial. Various problems such as ascertainment biases, patient dropouts, and imperfect reference standards crop up in the published studies evaluating MEG, making it more difficult to assess them. To some extent, these difficulties may be inherent in the clinical setting in which MEG is used.

### Search Strategy

A MEDLINE® search (via PubMed) was performed through September 2008 using keywords “MEG,” “magnetoencephalography,” “MSI,” “magnetic source imaging,” “epilepsy OR seizure,” and “surgery.” The electronic search was limited to English-language studies of human subjects. Review articles and other systematic reviews provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search.

There is a lack of studies that comprehensively allow the determination of benefit of MEG. Due to selection and ascertainment biases, and lack of reference standards, studies of diagnostic performance are biased. Thus the literature was selected to be representative of the types of studies evaluating MEG. This Special Report is meant to explain the diagnostic issues of MEG, rather than to comprehensively review studies.



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## Main Results and Conclusions

Assessment of diagnostic technologies used for the purpose of localizing surgical sites that may relieve seizures is fraught with difficulty. Fundamentally, the disease is not fully understood to the point that there is completely solid knowledge as to what factors result in a surgical cure. Surgical cures can occur in the context of a positive or negative noninvasive test of any kind. Surgical cure can occur when findings on the intracranial electroencephalogram (IC-EEG) are negative, but other imaging tests point to a region that may cause seizures. If it is understood that IC-EEG is a rather imperfect reference standard, then it is understandable that tests that have an imperfect correlation to IC-EEG may be viewed by some as providing equivalent or better information than IC-EEG, at times.

The diagnostic workup of patients includes consideration of IC-EEG, an invasive procedure that carries risks of complications. Many patients apparently drop out of the diagnostic workup before having this test, meaning that there is an inherent ascertainment bias in comparing this test to other possibly complementary or substitute tests. Studies that do not take this into account are difficult to evaluate, and studies may not be comparable due to differing unobserved patients. Evaluation of the correlations between IC-EEG and other tests is also made difficult by the inherent nonindependence of IC-EEG and the preceding workup.

By what standard, then, should a diagnostic technology such as MEG, when used to localize seizure locus, be held to in order to determine whether it is effective or not? Are randomized, controlled trials possible comparing ultimate outcomes of patients entering the diagnostic workup, one arm utilizing MEG and another arm not utilizing MEG? Are there epilepsy centers in the country that do not have or believe in MEG, that could enroll patients in an observational study comparing their outcomes to an otherwise similar epilepsy center that does utilize MEG? Given the difficulties of evaluating MEG strictly as a diagnostic test (due to ascertainment biases and lack of an independent reference standard), perhaps MEG needs to be viewed as part of the therapeutic process, in which the ultimate comparison is “MEG-guided surgical decision-making” versus “non-MEG-guided surgical decision-making.”

Lacking this type of true comparative information on health outcomes, is it possible to make a case for the effectiveness of MEG using data generated from clinical practice, essentially case series data? One study suggests that even with optimistic assumptions regarding the unobserved patients, it is likely that neither the sensitivity nor specificity of MEG is sufficiently high to bypass IC-EEG in patients either proceeding to surgery or stopping the workup. This would end the case for MEG if IC-EEG, despite its imperfections, were a mandatory part of the workup for seizure surgery. However, surgery can be successful without a positive IC-EEG in the experience of some researchers and in some patients without IC-EEG at all.

The argument that MEG improves the diagnostic yield of IC-EEG is often made, but it is difficult to identify studies that can support this argument. Studies that compare IC-EEG to MEG do not inform this particular question. On the other hand, given the gravity of this particular situation, there are some possible arguments to be made on behalf of MEG. Given that current decision-making regarding who should receive surgery and what type of surgery is done with some uncertainty and lack of a true reference standard, an additional piece of information that is known to correlate with seizure focus could be arguably of some value in making difficult decisions. The diagnostic test is easy to perform and noninvasive. Also, IC-EEG and surgery are extremely invasive procedures that do not always provide diagnostic information. Information from MEG might influence a patient's decision to undergo the risks of further testing or surgery if the outcome can be slightly better estimated. However, given that one possible outcome of use of MEG may result in avoidance of tests and procedures that may benefit the patient, it is not possible to rule out harm from use of the test. The net effect of the use of MEG on patient outcomes for this indication remains to be determined.

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The Special Report format is used to review this technology because, as will be demonstrated, the quality of the studies does not meet the usual standards for evaluating diagnostic tests. Analyses of diagnostic performance of MEG have been derived from retrospective case series, which generally have inherent ascertainment biases and incomplete accounting of all patients. Thus, it is difficult to informally or formally extrapolate or model comprehensively patient outcomes. At least some of the difficulty may be inherent in this clinical situation, where certain tests and treatments are avoided because of possible morbidity to patients.

## Background

### Epilepsy

Epilepsy encompasses a wide variety of conditions associated with seizures and is estimated to affect approximately 2 million people in the U.S. These patients are treated with antiepileptic drugs to control seizure activity; however, approximately 20–25%, or 400,000–500,000 patients continue to have seizures despite medical management (Engel 1996; Aldrich et al. 2001). In the U.S., it is estimated that epilepsy surgery could benefit about 100,000 patients with medically refractory epilepsy with about 5,000 new candidates for surgical treatment each year (Ebersole et al. 1995). Interest in surgical treatment of epilepsy increased during the late 1980s and 1990s, but in the early 1990s, only an estimated 2,000 to 2,500 operations for seizures were being performed annually (Ebersole et al. 1995).

Much of the growing interest in surgical treatment for epilepsy has been supported by technical developments and advances in video electroencephalographic (V-EEG) monitoring and neuroimaging techniques, as well as by improvements in surgical technique and improved understanding of underlying pathophysiology (Engel 1996).

The most common site of focal origin for seizures in adults is the mesial temporal lobe. This is often associated with atrophy or sclerosis in the hippocampus, and outcomes after surgical resection are good in approximately 80% of cases (Moore et al. 2002; Benbadis 2001; Engel 1996). Such patients have specific lesions visible with MRI, such as small hamartomas, low-grade tumors, subtle areas of gliosis, and focal atrophy. When these types of lesions are confirmed as the source of epileptic activity using scalp V-EEG, patients with these findings are referred to surgery with very good results (Aldrich et al. 2001). These types of patients are not the patients in whom MEG is being considered as clinically useful. MEG and the other noninvasive tests, and invasive intracranial EEG (IC-EEG) are generally reserved for so-called nonlesional epilepsy.

Although freedom from seizures is the desired outcome of surgery, studies have also assessed other outcomes such as freedom from antiepileptic drugs, long-term mortality, psychosocial outcomes, and neuropsychological outcomes (Tellez-Zenteno et al. 2007). However, many of these studies may not be generalizable to the clinical situation for which MEG is indicated, so the outcomes of these other studies may not apply. Tellez-Zenteno et al. (2007) reviewed 15 studies and showed that 20% of patients were free from medication after surgery. Eleven studies that evaluated long-term psychosocial outcomes showed mostly favorable outcomes following surgery. Several studies have attempted to determine whether epilepsy surgery improves long-term mortality, by comparing to the general population or to medically treated control groups. Several of these studies (Tellez-Zenteno et al. 2007) demonstrate lower mortality among patients achieving freedom from seizures after surgery. In the section of the review evaluating neuropsychological outcomes, 5 studies evaluating intelligence consistently reported no long-term postsurgical worsening in intelligence scores (Tellez-Zenteno et al. 2007). Several of the studies showed memory declines among considerable proportions of patients, however. It is difficult to tell whether the findings from these studies can be applied to the patients in which MEG would be applied.

There are multiple classification systems used to describe different types of seizures and seizure disorders (Benbadis 2001), although a complete discussion of these systems is beyond the scope of this Report. Surgical treatment of seizures is most frequently applied to partial (or focal or localization-related) seizure disorders and the most frequent operation, anterior temporal lobectomy, involves resection of mesial temporal lobe structures (including the amygdala and hippocampus) (Engel 1996). However, newer surgical techniques to treat focal lesions in primary functional cortical locations have been developed such as lesionectomy or “multiple subpial transections, which sever intracortical connections in a way that prevents the spread of epilepsy and still preserves the columnar structure necessary to maintain normal cortical function” (Engel 1996).

### **Magnetoencephalography and Magnetic Source Imaging**

Magnetoencephalography (MEG) is a noninvasive diagnostic tool that measures extracranial magnetic fields spontaneously produced within the brain when electrical current flows along neurons. The MEG device is a purely passive recording device and does not deliver energy into the patient. The output display of MEG appears as a set of waveforms, analogous to an electroencephalogram (EEG). However, there are several differences in the information obtained from MEG and EEG resulting from differences in the physical principles of electrical and magnetic fields that will be discussed in more detail. The information from MEG recordings must be mathematically modeled to localize a source of epileptic activity that would be consistent with the patterns observed. Unlike the mathematical processing involved in creating a CT or MRI image, the data do not contain sufficient information to fully resolve the equations, so numerous constraining assumptions are required. MEG information and MRI information are co-registered using a set of fiducial markers placed during each examination. Thus, MEG information in some ways might be more similar to a risk score or a loading factor (in discriminant analysis), albeit with spatial information, than an imaging test such as MRI or CT.

In this Report, the term “MEG” will generally be used for simplicity and consistency; however, it is acknowledged that most clinical studies combine MEG information with MRI images (i.e., MSI) when providing anatomic localization of epileptogenic lesions or functionally important cortical regions.

The magnetic field associated with a single neuron is too small to detect extracranially; however, the summation of about a million synchronously activated neurons can be detected using very sensitive biomagnetometer systems that rely on superconducting quantum interference device (SQUID) technology (Otsubo and Snead 2001). Also, because the magnetic fields being emitted from the brain are so weak, MEG systems must be designed to screen out the earth’s magnetic field and environmental magnetic noise, which is about 100,000 times stronger than magnetic signals appearing as epileptiform spikes.

The orientation of an electrical current and its associated magnetic field is described by the “right hand rule,” which states that an electrical current flowing in the direction of an extended thumb is associated with a circular magnetic field flowing in the direction of the curled fingers at 90 degrees to the direction of the thumb. When the neuronal current from a group of neurons is oriented tangentially to the brain surface, then the magnetic field exits and re-enters the head, allowing external detection. However, radially oriented currents produce magnetic fields that do not exit the head and, thus, cannot be detected by a MEG system (Ebersole 1999).

Early MEG systems contained only a limited number of detector channels covering only small portions of the head and, thus, examination times were long in order to cover the whole head (Ebersole et al. 1995). Current MEG technology provides simultaneous recording over the whole head using approximately 140 to 300 channels, and some machines have the capability to simultaneously record both MEG and EEG signals.

MEG has a technical advantage over EEG in that magnetic fields measured by MEG are less subject to distortion by intervening tissues (e.g., scalp, skull, cerebrospinal fluid, and brain) than are electrical fields measured by surface EEG. This results in better spatial localization of epileptic foci detected by MEG as compared with surface EEG, which can produce “smeared” and distorted signals (Baumgartner 2000b). MEG signals are thought to arise from intracellular current flow; whereas, EEG electrical currents are produced by extracellular current flow (Gallen et al. 1995). However, MEG has some limitations as well, since magnetic fields generated deep within the brain tissues (e.g., in the medial temporal lobe) decay rapidly over distance and may be less likely to be detected at the surface compared with electrical fields (Shigeto et al. 2002; Zijlmans et al. 2002).

Furthermore, MEG is not sensitive for detecting magnetic dipoles that are radially oriented, and, thus, some lesions may be relative blind spots for detecting epileptic foci with MEG (Ebersole 1999). Therefore, surface EEG and MEG are often considered complementary technologies for noninvasive localization of epileptic foci, and some commercially available MEG systems are capable of performing simultaneous EEG and MEG acquisition (Zijlmans et al. 2002).

Most MEG and many EEG evaluations are performed during the interictal state, that is, between seizures. Measurements of interictal brain spike activity is thought to reflect activity from an underlying “irritative zone” rather than the epileptogenic seizure origin itself (Ebersole 1995). Thus, actual measurement of brain spike activity during ictal events may also be of interest in localizing seizure foci; however, the movement associated with a seizure may present challenges for MEG assessment. Nonetheless, anecdotal reports of ictal MEG results have been reported in the literature (Shiraishi et al. 2001).

Initial validity of MEG as a method to localize seizure activity in general comes from several types of studies (Knowlton 2006). Studies using implanted dipoles were used to generate the mathematical models, which were then used to demonstrate capability to localize the dipoles. Studies with simultaneous invasive EEG and MEG show concordance of localization of epileptic activity. Other studies have studied MEG in patients with lesions visualized with other methods that are clearly the single focal cause of a given patient’s seizures. In such patients invasive EEG monitoring has confirmed the location of the seizures. In such studies the MEG findings have been shown to be concordant with the location of the tumors and malformations (Knowlton 2006). However, these types of studies, which demonstrate capability of MEG to locate known sources, do not demonstrate the capability of MEG to assist in the localization of unknown sources, nor do they demonstrate that MEG improves health outcomes.

#### **Other Noninvasive Tests Used to Evaluate Seizure Focus**

Initial evaluation of patients with a chronic recurrent seizure disorder aims to identify treatable causes such as structural lesions amenable to surgical resection (e.g., brain tumors, cerebrovascular arteriovenous malformations, or cavernous malformations). Clinical evaluation of observable seizure characteristics may help to localize the seizure origin. In addition, a variety of noninvasive diagnostic tests may be used to help localize the putative seizure focus using electrophysiologic and/or imaging methods, and a consensus using all information available is sought.

All patients generally undergo MRI and V-EEG. When lesions are seen on MRI that are

classically associated with seizures, and V-EEG provides sufficient supporting information to confirm that the lesion is responsible for seizures, patients may undergo surgery without further workup. These patients would be classified as having lesional epilepsy. In a series of patients having V-EEG and MRI reported by Knowlton (personal communication, 2008), 95 of 264 patients were sufficiently localized with these two tests to proceed directly to surgery without further testing. A few additional patients did not go further in the diagnostic workup, and the rest were referred for additional testing. In addition to MEG, patients can undergo FDG-PET and/or ictal SPECT.

### **FDG-PET**

According to Knowlton (2006), after MRI and V-EEG, FDG-PET is the most established functional imaging test. FDG-PET identifies areas of decreased metabolism in the brain. The actual cause of hypometabolism in and near epileptogenic foci in the brain, however, is not clear. When used in patients with known mesial temporal lobe epilepsy, FDG-PET has been shown to be 80–90% sensitive.

A problem with FDG-PET is its lack of specificity in delineating the exact location and extent of the epileptogenic zone. When positive, the area of hypometabolism identified may extend over a much larger area than the lesion itself. Therefore, FDG-PET may not be a reliable guide to determine the exact location and extent of surgical resection.

### **Ictal SPECT**

This test assesses regional cerebral blood flow during seizures. Labeled isotopes are injected into the patient as quickly as possible after onset of a seizure, and regional blood flow is assessed. Such regional blood flow changes may provide precise localization not possible with other techniques. Ictal SPECT findings have been shown to correlate with surgical outcomes in several studies (Knowlton 2006).

The limitations of ictal SPECT lay mainly with the logistics of a successful procedure, which require great resources to detect a seizure, infuse labeled isotopes, and image the patient.

### **Invasive Testing: Intracranial EEG**

Invasive intracranial interictal and ictal video EEG (IC-EEG) is considered the gold standard diagnostic test for patients with nonlesional epilepsy. It is a highly invasive procedure

involving surgical implantation of electrodes, and several days of hospital observation. (Ebersole et al. 1995). Various methods of intracranial electrical monitoring include stereotactically implanted depth electrodes, implanted strip electrodes, and implanted grids that require craniotomy and may be placed subdurally (Aldrich et al. 2001). Implanted electrodes can be used for chronic monitoring and may also be used during intraoperative evaluation, and this type of monitoring is often referred to as electrocorticography (ECoG). Morbidity associated with implanted electrodes includes risk of hematoma, which is highest for depth electrodes and estimated to be 1%. There is also a very small risk of infection associated with electrode wires extending through the skin.

Implanted electrodes may be used to detect interictal and ictal spike activity to localize epileptic foci. However, these electrodes may also be used to perform functional mapping of language-related cortex. To do this, electrical current is passed between two electrodes, and if language function is arrested, then “the underlying cortex is considered eloquent for language and spared at the time of resection” (Aldrich et al. 2001). Positive results are easier to interpret than negative results (i.e., when no language arrest is detected) and current strength may be increased.

Although IC-EEG is considered a gold standard of sorts, there are a few complicating issues in considering it as such. First, it is not an “independent” reference standard in the usual sense of a diagnostic standard. The results of prior diagnostic tests are taken into account in the decision as to where and how to place the electrodes. This is done to hopefully improve the yield of the IC-EEG to increase the probability of finding an epileptic focus and more precisely localizing it. Thus, the result of the IC-EEG is intrinsically “unblinded” with respect to the tests that contributed information prior to its performance, even if interpretation is technically blinded.

Because there is no pathologic method of determining whether a certain region of the brain, in fact, contains the epileptic focus, there is no “true” reference standard in this particular clinical situation. The hypothetical reference standard is identification of a specific lesion or area that, if removed, would cure a patient’s epilepsy. Surgical cure rates give some indication about better or worse diagnostic

reference standards, but the fact that surgery does not cure seizures in all of even the classical MRI-localized lesional epilepsy cases, and that one cannot know whether such a lesion even might exist in a patient who never comes to surgery, means that there will be some degree of incomplete ascertainment of all possible epileptogenic lesions. Many studies have tried to approach this issue by using surgical outcome, cured and not-cured, as the equivalent of diseased and nondiseased status to calculate sensitivity and specificity of different diagnostic tests.

**FDA Status.** MEG machines are classified by the U.S. Food and Drug Administration (FDA) as Class II devices, which require special controls only and do not require Premarket Application (PMA) submission but do require 510(k) clearance. MEG products have been manufactured by several different companies and a number of models have been cleared for marketing through the FDA 510(k) process. Software algorithms that analyze the MEG information and create single equivalent current dipole images have also been cleared by the FDA.

Examples of products that have received 510(k) clearance include:

- Magnes® 3600 Whole Head Magnetoencephalography (MEG) (Biomagnetic Technologies, Inc., San Diego, CA – currently known as 4-D Neuroimaging), cleared December 3, 1999.
- Magnes® 2500 Whole Head Biomagnetometer (Biomagnetic Technologies, Inc., San Diego, CA – currently known as 4-D Neuroimaging), cleared May 7, 1997.
- Magnes® II Biomagnetometer (Biomagnetic Technologies, Inc., San Diego, CA – currently known as 4-D Neuroimaging), cleared May 16, 1996.
- CTF Whole-Cortex MEG System (K971329) (CTF Systems, British Columbia, Canada), cleared November 20, 1997.

The indication for use statement for the Magnes® 3600 Whole Head MEG system reads: “The Magnes 3600 WH MEG is intended for use in diagnostic procedures that require the measurement and display of extracranial magnetic fields and information about the electrical activity in the brain as inferred from those fields.”

### Other Technology Assessment Documents

The Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC) published an Assessment of MEG for the indication of seizure localization in 2005 (Vol. 18, No. 6). The indication of mapping functional areas of the brain was also assessed at that time. The TEC Assessment included 13 studies evaluating a total of 359 subjects. The studies included varied greatly with respect to inclusion criteria, outcomes, and analysis. Some studies showed that MEG results correlated with IC-EEG. Most of the studies had small sample sizes and incomplete reporting of results. There was also substantial variability in study design and patient populations that made comparison across studies difficult. MEG did not meet TEC criteria for localization of seizure foci or for presurgical functional mapping.

The Ontario Health Technology Advisory Committee published an assessment of functional brain imaging in 2006, of which MEG for the indication of seizure localization was included (OHTAC 2006). This review selected 6 studies that compared the results of IC-EEG to MEG. In some analyses the area of the surgical resection was correlated to MEG and IC-EEG. In some studies, IC-EEG and MEG were correlated with surgical outcomes. The review concluded that it is difficult to draw conclusions regarding the effectiveness of MEG due to limitations in the evidence, and that studies were mostly small, case series with heterogeneous samples.

## Methods

### Search Methods

A MEDLINE® search (via PubMed) was performed through September 2008 using keywords “MEG,” “magnetoencephalography,” “MSI,” “magnetic source imaging,” “epilepsy OR seizure,” and “surgery.” The electronic search was limited to English-language studies of human subjects. Review articles and other systematic reviews provided background information. The bibliographies of retrieved articles were consulted to identify references that may have been overlooked by the electronic search.

### Study Selection

There is a lack of studies that comprehensively allow the determination of benefit of MEG. Due to selection and ascertainment biases, and lack

of reference standards, studies of diagnostic performance are biased. Thus the literature was selected to be representative of the types of studies evaluating MEG. This Special Report is meant to explain the diagnostic issues of MEG, rather than to comprehensively review studies.

#### **Medical Advisory Panel Review**

This Special Report was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on September 16, 2008. In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Special Report.

#### **Model of the Diagnostic Process in Nonlesional Epilepsy**

Most of the studies and reviews of MEG lack clear focus as to how MEG improves health outcomes in patients in comparison to diagnostic strategies that do not use MEG. Although MEG appears to correlate with other methods of localizing seizures, and MEG findings appear to correlate with surgical outcomes, it is usually not made explicitly clear how MEG fits into the diagnostic process to improve patient outcomes.

This section of the Report proposes a model of conceptualizing the use of MEG in the evaluation of seizure patients. This model allows a more complete accounting of the health outcome states associated with the use of MEG, and reveals the shortcomings of the currently available data. Because most of the studies of MEG analyze data that was obtained during the course of patient care rather than controlled clinical trials, it is important to understand the sequence of care and the flow of patients through this sequence of care. The model proposed may lack some of the subtleties introduced by particular findings on particular tests, and for specific epileptic areas of the brain. The only studies found that actually followed patients through this process with relatively complete enumeration of all the clinical pathways are the papers of Knowlton et al. (2008a, 2008b).

The Figure shows the sequence of events for patients who might consider undergoing MEG for evaluation of potential surgical treatment of intractable seizures. The initial population of patients are all potential candidates for evaluation with MEG. In the studies by Knowlton et al. (2008a, 2008b), these were patients who were all referred for scalp V-EEG monitoring, who had nonlocalizing or insufficiently localizing MRI studies (nonlesional epilepsy). Absent from this pool of patients are patients with lesional epilepsy, sufficiently localized with MRI and V-EEG to go directly to surgery (pathway above the horizontal dotted line in the Figure).

In addition to MEG, other noninvasive tests at this point include FDG-PET and ictal SPECT. After the noninvasive tests, a decision is made whether to proceed to IC-EEG. Many patients do not proceed to invasive EEG. In one of Knowlton's studies (2008a), 72 of 160 patients proceeded to have invasive EEG. Whether to proceed to invasive EEG appears to be an individualized decision based on the all the results of prior tests up to that point.

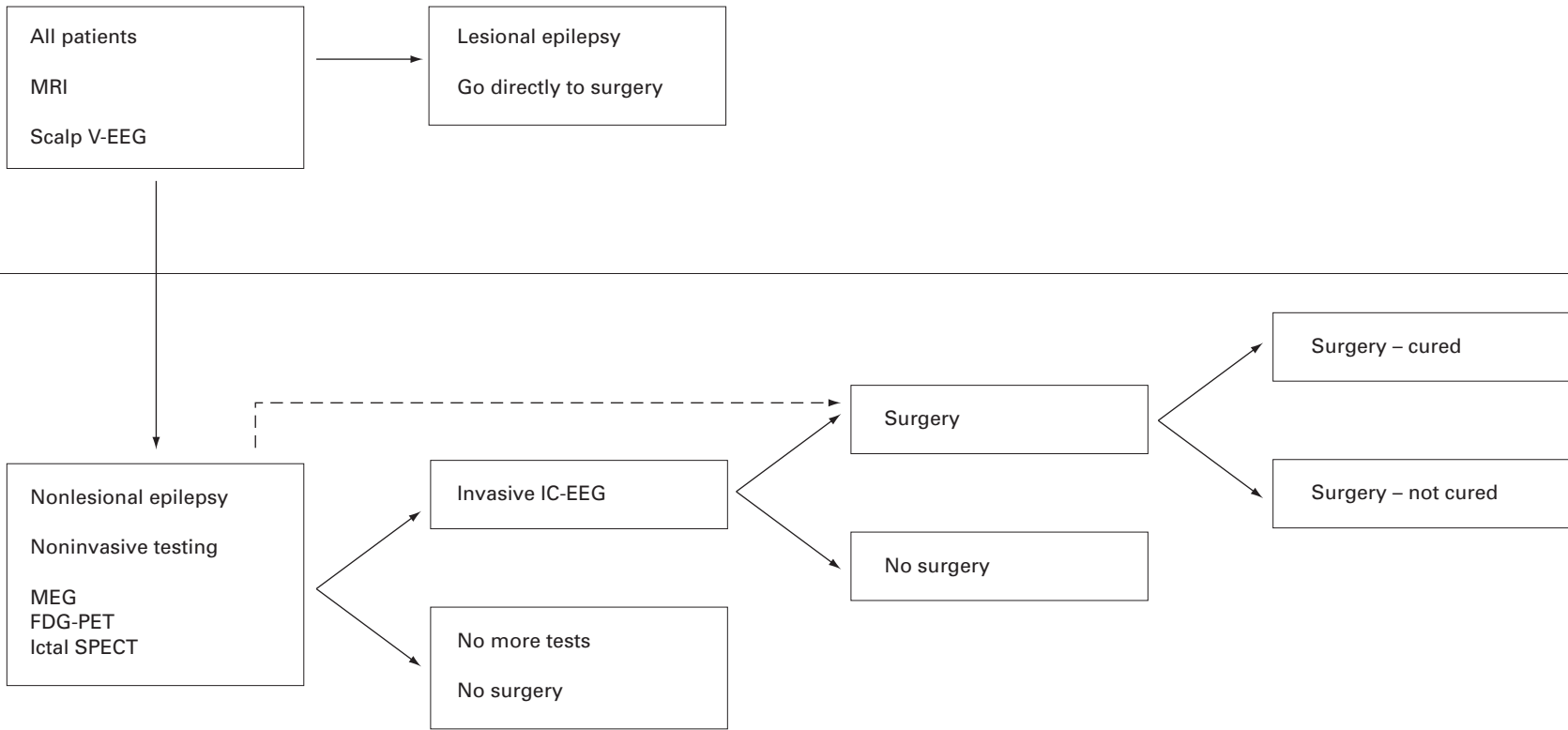
After invasive EEG, patients either proceed to surgery or not. A "positive" IC-EEG is not always necessary in order to proceed to surgery. Also, some patients proceed to surgery based on positive non-invasive tests without IC-EEG (Knowlton 2008 personal communication). The decision to proceed to surgery appears to be based not on strict decision rules, but on the strength and consistency of findings that indicate the possibility of removing the part of the brain causing seizures.

#### **Complete Accounting of Final Health States Affected by Use of MEG**

If we imagine this model of medical management exists in two forms, one that includes availability of MEG and one that does not include MEG, even with all the individualized decisions that are made at various points in the process to perform certain tests, alter the technique of other test, and whether to proceed further in the workup, we could imagine different numbers of patients ending up with different outcomes.

When we visualize the whole population of patients whose outcomes could be affected by MEG, we can then more clearly identify the health outcome states that might be affected by the availability of MEG. Table 1 shows one simple method of qualitatively ranking the

**Figure.** Diagram of Diagnostic Workup in Seizure Patients Initiating Workup for Possible Surgery



possible health outcome states of patients going through this diagnostic and therapeutic process. The groups of patients are ordered from worst health state to best health state. Assume that the average health status of subjects who are in each state includes the probability of complications due to procedures undergone. IC-EEG incurs some morbidity to patients, but less than surgery. Patients who underwent IC-EEG and surgery without benefit have the worst average health state. Noncurative surgery has a worse health state than IC-EEG without proceeding to surgery. Noninvasive tests are considered to have no effect on health status. Surgery that cures or reduces the morbidity of seizures results in better health status. Although it appears that currently IC-EEG is generally performed before surgery (even if its results are sometimes overruled), a proposed benefit of MEG is the possible avoidance of invasive EEG (if several noninvasive tests are concordant for a surgically amenable lesion). Thus this health state will be included in this table, but labeled with an asterisk.

When we see the range of possible health outcomes, the complexity of trying to understand the health impact of MEG becomes clearer. Depending on whether a “positive” or “negative” MEG is used as information to maintain or deselect a patient on the pathway to surgery, and whether the test result is used before and/or after invasive testing to make decisions, MEG could affect the numbers of patients in several of the different health states. Also, none of the tests appear to be used in a strict algorithmic fashion, but weigh into the decision at a specific point.

Ideally, with rigorously measured observational comparisons or a randomized clinical trial, where one set of patients had MEG and another set of patients did not have MEG, all health outcomes could be measured and averaged over the total number of persons. A simplified version of this outcome, which ignores the morbidity of failed surgery and invasive tests, would be the number of surgical cures divided by the total number of patients initiating the diagnostic process. Note that this is different than the surgical success rate, which is the number of surgical cures divided by the number of patients undergoing surgery. If MEG allows identification of a larger number of persons who undergo surgery with equivalent (or possibly even slightly lower) surgical success rates, it would produce a higher number of cures in the total diagnostic population.

#### Using Limited Perspectives to Assess the Utility of MEG

We currently lack such comparative data using the appropriate denominators for calculating overall health outcomes in the diagnostic population of interest. Because patients drop out of the diagnostic process before having IC-EEG, there is probable ascertainment bias in evaluating the diagnostic performance of any of the noninvasive tests in comparison to each other, to IC-EEG, or correlations with surgical outcome. Such biases would depend on the propensity of the physician to weight differentially positive or negative noninvasive tests of different types in deciding to continue to pursue localization with IC-EEG. Rosanski et al. (1983) in a classic study, showed that the diagnostic characteristics of a test appear

**Table 1.** Relative Health Outcomes of Patients Undergoing Diagnostic Workup for Surgical Treatment of Nonlesional Epilepsy

Health Outcome	Procedures Undergone and Surgical Outcome
Improved	*Noninvasive workup, surgery, cured Noninvasive workup, IC-EEG, surgery, cured
Neutral	Noninvasive workup, no surgery
Slightly worse off	Noninvasive workup, IC-EEG, no surgery
Worse off	*Noninvasive workup, surgery, no benefit Noninvasive workup, IC-EEG, surgery, no benefit

Noninvasive workup consists of MEG, FDG-PET, ictal SPECT

\*uncommon pathway in current practice

to worsen over time as it begins to be trusted, with both pretest referral bias and post-test referral bias leading to the appearance of poorer diagnostic characteristics.

The propensity to pursue surgery after the complete battery of noninvasive tests and IC-EEG might also depend on the physician's prior belief, and thus affect the correlation between specific tests and surgical success rates.

Another way to make the argument for the utility of MEG relies on examining a specific aspect of the diagnostic path, with the critical assumption that everything else on the path is constant regardless of the result of MEG. Under these limited circumstances, it may be possible to infer a benefit from MEG using information from diagnostic performance characteristics.

For example, avoidance of a negative IC-EEG would be an unequivocal benefit. Such a patient would not be a surgical candidate and would be spared the morbidity of the procedure. In this example, a negative MEG would have 100% predictive value for nonlocalizing IC-EEG. Assuming all else is equal, with this use of MEG there would be slightly more persons undergoing only a noninvasive workup and no surgery, and slightly fewer persons undergoing invasive EEG without surgery.

Another example would be if MEG can preclude the need for invasive EEG in a patient who has a surgically amenable epileptic area. In this scenario, the same number of patients would undergo surgery and be cured, but with fewer invasive EEGs being done. Here, a positive MEG has 100% positive predictive value for a localizing invasive EEG.

If MEG improves the success rate of surgery, by providing supplemental information regarding the extent and location of surgery, this would increase the number of persons cured by surgery and decrease the number of persons not cured by surgery. However, this particular outcome can probably not be inferred by any associations observed in case series data in which all patients underwent MEG and such information was utilized.

There are probably other such scenarios where limiting the perspective to one branch of the diagnostic and therapeutic process, assuming the others are unaffected, could produce a result where a given diagnostic capability of MEG would be considered an unequivocal benefit.

Regarding the first two scenarios mentioned above, a test that has both 100% positive and negative predictive values in relation to IC-EEG would essentially be a perfect test, perfectly correlated with IC-EEG. It would be near impossible for a diagnostic test to have both 100% positive and negative predictive values at the same cut point, but a test like MEG could be interpreted in different ways for different purposes, i.e., to be "strongly positive" based on certain findings for the purpose of having a high positive predictive value, or as contributing to a composite result of several tests that indicate a "strongly positive" result. Different thresholds and composite results could be used that have a high negative predictive value.

There are several potential problems with this approach. One problem is that when the positive or negative predictive values are good, but not near definitively close to 100%, then by following the decision rule some patients would conceivably be harmed or not cured, and thus the tradeoffs inherent in most decision analysis problems would occur. A less than 100% predictive value for predicting a negative IC-EEG might eliminate some patients who could be cured with surgery, and a less than 100% predictive value for predicting a positive IC-EEG might result in lower surgical success rates.

Also, the predictive values may very well depend on the spectrum of patients studied—the various pretesting, inclusions, and exclusions that have been already performed to get to the population studied. MEG itself may have been used in an earlier step in the diagnostic process to define the population studied retrospectively with MEG at a later step. It may be hard to know what type of patients are included in any particular study. Depending on how much a particular diagnostic test is weighted in deciding to go further on in the diagnostic process, its diagnostic characteristics will be distorted, and comparisons to other diagnostic tests will be biased in such a study population.

## Surveying the Current Literature on MEG

A MEDLINE® search (via PubMed) and review of bibliographies of recent review articles and technology assessments showed that there are no randomized clinical trials of MEG, nor could studies be identified that resemble cohort studies that try to ascertain patient outcomes of patients who have undergone MEG versus patients who have not undergone MEG.

In examining other studies cited in the prior TEC Assessment, review articles, and other technology assessment documents, it is clear that attempts to discern associations between MEG and other noninvasive tests, IC-EEG, or surgical results are rife with problems of ascertainment bias due to patients dropping out of the diagnostic workup before having IC-EEG. Thus, it is problematic to attempt to define a relevant subset of the vast literature on MEG that stands out from the rest of the studies as being better evidence than other studies. Missing information from the studies regarding the full diagnostic population makes analysis of potential biases difficult or impossible. For example, even if we assume that patients who did not proceed to having IC-EEG would have had negative IC-EEG (based on the decision not to pursue the test), not knowing the results of MEG on those patients makes it impossible to calculate the specificity of MEG, because any positive MEG results would contribute to the number of false positives.

In order to better elucidate the problem of missing patients and the types of analyses that are performed with case series data, the data from a recently published pair of studies (Knowlton et al. 2008a, 2008b) will be presented in detail. These two papers are exemplary relative to other studies in terms of keeping track of most patients and describing their initial characteristics. The findings of these papers appear to be consistent with many other studies, but are much more transparent regarding the whole diagnostic population. Only numbers available from the published manuscript will be presented.

### Studies of Knowlton et al. (2008a and 2008b)

Knowlton et al. enrolled 160 patients who had diagnostic workups for intractable seizures. They underwent a standard workup with MRI and V-EEG. Those with normal MRI or

insufficiently localized MRI findings entered the study. Of the 160 patients, 72 proceeded to IC-EEG. All 72 of these patients had MEG, 60 of them had FDG-PET, and 35 had ictal SPECT. Twenty-seven patients had all three noninvasive tests. The results of noninvasive tests and reasons for not proceeding to IC-EEG are not reported. It is likely that some patients dropped out because of several negative noninvasive tests, but some patients proceeded to IC-EEG despite having all three tests negative. This can be inferred by 72% sensitivity using criteria of at least one positive noninvasive test of three, indicating that some positive localizations occurred among patients with all negative tests.

Of 72 patients having IC-EEG, 54 had positive studies, 18 had nonlocalized ictal patterns, and 5 studies were nondiagnostic in that no seizures were captured during the recording sessions. Sensitivity, specificity, and predictive values were calculated for the three noninvasive tests, using IC-EEG as the reference standard. Combinations of the noninvasive tests to increase sensitivity or specificity were also evaluated among patients who had both or all three noninvasive tests.

Under certain assumptions of the unaccounted for data among the patients that did not proceed to IC-EEG, the calculations of sensitivity and specificity may be approximately valid, at least relative to each other. If we assume that patients who did not proceed to IC-EEG were “true negatives” who would have been negative on IC-EEG had they had the test, then the sensitivity calculations are roughly correct. If we assume that all patients with at least one positive noninvasive test received IC-EEG, then the specificity calculations are conservatively biased, because of missing numbers of patients who would be IC-EEG negative and have negative noninvasive tests. If some patients with positive noninvasive tests did not receive IC-EEG, then the specificity calculations are probably biased upward.

Table 2 shows the results of sensitivity, specificity, and predictive values for each of the noninvasive tests and combinations of the tests, based on the 72 patients who had IC-EEG. A range of values is shown for several of the values because the values were calculated several times for different subsets of the data (different combinations of patients that had 1 or 2 of the 3, or all 3 noninvasive tests).

**Table 2.** Summary of Results of Knowlton et al.: Diagnostic Performance of Noninvasive Tests to Predict IC-EEG Localization (2008a)

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
MEG	58–64	75–87	89–94	39–43
FDG-PET	22–40	53–63	57–71	24–26
Ictal SPECT	39–48	44–50	58–71	27–32
<b>Test alternatives</b>				
MEG or PET	80	40	80	40
MEG and PET	16	87	78	26
MEG or iSPECT	80	40	77	44
MEG and iSPECT	24	90	86	32
MEG or PET or iSPECT	72	22	65	29
MEG and PET and iSPECT	6	89	50	32

In general, requiring 2 tests to be both positive will likely decrease sensitivity but increase specificity, and requiring either test to be positive will increase sensitivity but decrease specificity. A high sensitivity would generally cause a high negative predictive value, which would be of use in predicting patients who are likely to have a negative IC-EEG. A high specificity would generally cause a high positive predictive value, which would be of use in predicting patients who would have a positive IC-EEG (and possibly be able to go directly to surgery).

In general, the only numbers that approach values that are clinically promising are the positive predictive value of MEG, by itself and possibly in some “AND” combinations. Because the “AND” combinations were only analyzed on subsets of the patients, the expected pattern of a higher positive predictive value was not always observed. The less than 100% positive predictive value means that some patients with positive MEG do not have a positive IC-EEG, and thus some may not be surgical candidates. If IC-EEG positivity were necessary in order to have a successful surgery, then using a positive MEG to bypass the need for IC-EEG would result in some unnecessary surgeries.

None of the negative predictive values were remotely close to a useful value for possibly using MEG or any of the noninvasive tests to eliminate unnecessary IC-EEG. However, caution is advised in making these conclusions from these calculations because they depend on

critical assumptions about the unobserved test results in those that did not proceed to IC-EEG.

In an accompanying paper, Knowlton et al. (2008b) assess the correlation between noninvasive test results and surgical outcomes. Out of the 72 patients who had IC-EEG, 62 proceeded with surgical resection. Note that from the prior paper, 54 patients had positive IC-EEG. Thus, there are 8 patients that proceeded to surgery despite a negative or non-diagnostic IC-EEG. Not counted in either paper are a number of patients of the original 160 who proceeded to surgery after noninvasive tests but without IC-EEG (personal communication, Knowlton 2008).

62 patients with prior IC-EEG who had surgery, 61% had Engel class I outcome, free of disabling seizures, and 16% had Engel class II outcome, rare disabling seizures. The study presents various analyses correlating the results of the noninvasive tests to surgical outcome, comparing Engel class I to all other outcomes. The usual manner of presenting associations in terms of sensitivity and specificity is difficult to understand, so the results are re-represented in terms of success rate for a given result of a test in Table 3. The paper also presents odds ratios, but these are not intuitively understandable because, given the high rate of outcome, odds ratios are not close estimates of relative risk. The PPV of the test is the surgical success rate in those with a positive test, and 1-NPV is the surgical success rate of

**Table 3.** Surgical Success Rates by Noninvasive Test Results, Recalculated from Knowlton et al. (2008b)

Test Result Subgroup (size of subgroup)	Surgical Success Rate (Engel Class I)
All patients (62)	61%
MEG positive (31)	78%
MEG negative (31)	49%
PET positive (24)	83%
PET negative (27)	46%
iSPECT positive (14)	62%
iSPECT negative (20)	38%

those with a negative test. Numbers of patients vary for each result because not all patients had all noninvasive tests.

Embedded in these results are 7 patients who had surgery despite nonlocalizing IC-EEG. These patients are reported anecdotally in the first paper (Knowlton et al. 2008a). Three of these 7 (42%) had Engel class I outcome. None of these patients apparently had a positive MEG, but had a positive PET or ictal SPECT, or both. Apparently the strength of these positive findings and the rest of the clinical context was convincing enough for surgery to be done despite a negative IC-EEG.

The results show that the positive noninvasive tests are associated with higher surgical success rates. The magnitudes of the difference are not very striking in terms of predicting the extremes of success or failure, but could conceivably affect patient or physician decision making regarding the risks and benefits of surgery.

Recall that not all patients had every test except for MEG, and the decision to pursue further testing may very well have been due to ambiguous, negative, or nondiagnostic findings of a prior test. Numbers of patients who had multiple or all three tests were very small, so results based on combinations of tests would be very uncertain. Thus the associations between PET and ictal SPECT and outcome could be affected by unknown selection biases.

It is uncertain whether association of testing and surgical outcome like this have any clinical value beyond prognosis. For patients who surgeons have selected to be surgical candidates,

a prediction of outcome would be extremely useful if it predicted a high probability of surgical failure, and that the patients should therefore not be a surgical candidate. However, no noninvasive test predicts such a low surgical failure rate that would preclude surgery.

Other studies of MEG present similar types of data as the Knowlton study, but without complete disclosure of patients dropping out of the diagnostic process or without analysis of other diagnostic procedures. Without accounting for these drop-outs and the reasons for these drop-outs, associations between diagnostic tests and associations between diagnostic tests and outcomes are probably irreparably biased.

#### **Other Types of Studies of MEG**

**Correlation of Surgical Resection, MEG Localization, and Surgical Outcome.** Many studies have examined the degree to which the surgical resection and the MEG localization overlap, and whether this is a predictor of outcomes. Lau et al. (2008) performed a meta-analysis of 17 studies of MEG in which it was possible to extract data from the studies regarding whether the surgical resection area coincided with the MEG-defined area, and surgical outcome as defined as Engel class I versus other classes. Included in these studies are many studies cited in prominent review articles and technology assessments.

The analysis is somewhat unusual in terms of performing rather unintuitive calculations of sensitivity and specificity. In this meta-analysis, sensitivity is defined as the proportion of patients with seizure-free outcomes whose MEG localization coincided with the surgical resection area. Specificity is defined as

the proportion of patients who were surgical failures whose MEG localization was not within the surgical resection area (Table 4).

Although a somewhat unorthodox way to express the association between resection of the MEG localization and surgical outcome, a way to understand sensitivity in this context is the proportion of all cures that are achieved with resection of the MEG-localized areas. Specificity is the proportion of non-cures that occur when the MEG localized areas are not resected. A more intuitive calculation would have been to calculate predictive values, which would translate to the cure rate if the MEG localized area is resected or not. Unfortunately, it is not possible to calculate the predictive values from the information presented in the paper.

Studies were often quite varied in defining and reporting sensitivity and specificity. The mean “sensitivity” was 0.84, meaning that of the total number of cured patients, 14% occurred despite the MEG-localized area not being resected. The mean “specificity” was 0.52, meaning that among 48% of patients not cured, the MEG-localized region was resected.

This meta-analysis shows that resection of the MEG-localized region is associated with surgical cure. However, it is an imperfect predictor of surgical success. This result does not really address the question as to whether MEG contributed original information to improve the probability of cure versus absence of MEG information. Patients in all these studies underwent many different types of tests to characterize the presence and location of surgical resection. Patients who underwent resections that did not include the MEG-localized area must have had other tests indicating a different area as being the most likely cause of seizures. Surgical cure rates in themselves may not be accurate surrogate outcome measures for the health outcomes associated with MEG, if use

of MEG leads to differing surgery rates in the original diagnostic population. Thus this particular analysis of a rather large body of studies is probably uninformative regarding whether MEG is overall beneficial or not.

#### Miscellaneous Cited Studies

##### Studies Rating the Clinical Utility of MEG.

Other studies cited in other reviews and technology assessments are more difficult to characterize in terms of how they contribute to knowledge regarding efficacy of MEG. The study by Stefan et al. (2003) is a retrospective review of 455 patients who underwent MEG. The principal analysis in this study is a comparison between epilepsy focus estimates based on a consensus of all other noninvasive and invasive tests (including IC-EEG) and MEG. The comparison was coded into 5 categories and applied to 104 patients who underwent surgery during the later part of their study. Results of this comparison in relation to 5 categories of comparison to the rest of the workup are shown in Table 5.

It is difficult to determine on what basis the codes indicating a benefit from MEG (codes 2 and 3) are given. Surgical outcomes were not tabulated in this study. It does not appear to be possible to determine from these data whether MEG improved surgical outcomes beyond what they would have without MEG, nor whether MEG contributed to the decision to have surgery.

**Comparisons of V-EEG and MEG.** Other studies make claims of clinical utility without assessing actual patient outcomes. Pataria et al. (2004) compared MEG to noninvasive V-EEG in determining which test correlated better with the actual resection site. In this study, 113 patients who ultimately underwent surgery were evaluated prospectively. Surgical resections were performed apparently without knowledge of MEG results, but with additional

**Table 4.** Definitions for Sensitivity and Specificity, from Lau et al. 2008

	Surgical Outcome	
	Seizure-free	Not Seizure-free
Resection-MEG concordant	A	B
Resection-MEG discordant	C	D

Sensitivity =  $A/(A+C)$   
Specificity =  $D/(B+D)$

**Table 5.** Classification of Utility of MEG Findings in Patients Undergoing Surgery, from Stefan et al. (2003)

Category of MEG Result	Percentage (total n=104)
Code -2 disagreement with rest of workup	2%
Code -1 no contribution to workup	10%
Code 1 agreement	54%
Code 2 additional information	24%
Code 3 influence upon neurosurgical procedure	11%

noninvasive tests such as PET, ictal SPECT, and IC-EEG. V-EEG results correlated with the surgical resection site in 40% of patients, whereas MEG results correlated with the surgical resection site in 72.5%. Without patient outcomes, it is impossible to know whether the correlation would contribute to improved outcomes. The data simply demonstrates that MEG results correlate with the other additional tests used to make the final decision regarding resection location, and not whether it could have contributed information to meaningfully change the diagnostic workup or outcome of patients.

As in many studies of MEG, the study only includes patients who had surgery, not accounting for the results of any patients who did not go on to have surgery. There may have been positive V-EEG or positive MEG studies among these patients not having surgery.

Another study by Paulini et al. (2007) compared V-EEG findings and MEG findings in 105 consecutive patients who ultimately had surgery. Again there is the absence of data in patients who did not undergo surgery. MEG was non-diagnostic (no spikes recorded) in 52 of 105 patients. In the rest of the 73 patients, MEG showed localization to one anatomical lobe in 60/73 (82%). Ictal V-EEG localized in one lobe in 66 patients, and interictal V-EEG localized in one lobe in 59 patients. Among the 25 patients who had no clear localization identified with V-EEG, MEG identified the resection lobe in 11, of whom 6 were seizure-free after their surgery.

The implication from both of these studies is that MEG finds resection areas that V-EEG does not; therefore, it is useful, according to the authors. However, a nonlocalizing V-EEG is not the end of the diagnostic path, as patients can go on to receive other noninvasive tests and IC-EEG. Thus a comparison of V-EEG and MEG

may not provide useful information regarding the utility of MEG.

## Discussion

Assessment of diagnostic technologies used for the purpose of localizing surgical sites that may relieve seizures is fraught with difficulty. Fundamentally, the disease is not fully understood to the point that there is completely solid knowledge as to what factors result in a surgical cure. Surgical cures can occur in the context of a positive or negative noninvasive test of any kind. Surgical cure can occur when findings on the IC-EEG are negative, but other imaging tests point to a region that may cause seizures. If it is understood that IC-EEG is a rather imperfect reference standard, then it is understandable that tests that have an imperfect correlation to IC-EEG may be viewed by some as providing equivalent or better information than IC-EEG at times.

The diagnostic workup of patients includes consideration of IC-EEG, an invasive procedure that carries risks of complications. Many patients apparently drop out of the diagnostic workup before having this test, meaning that there is an inherent ascertainment bias in comparing this test to other possibly complementary or substitute tests. Studies that do not take this into account are difficult to evaluate, and studies may not be comparable due to differing unobserved patients. Evaluation of the correlations between IC-EEG and other tests is also made difficult by the inherent nonindependence of IC-EEG and the preceding workup.

By what standard, then, should a diagnostic technology such as MEG, when used to localize seizure locus, be held to in order to determine

whether it is effective or not? Are randomized, controlled trials possible comparing ultimate outcomes of patients entering the diagnostic workup, one arm utilizing MEG and another arm not utilizing MEG? Are there epilepsy centers in the country that do not have or believe in MEG, that could enroll patients in an observational study comparing their outcomes to an otherwise similar epilepsy center that does utilize MEG? Given the difficulties of evaluating MEG strictly as a diagnostic test (due to ascertainment biases and lack of an independent reference standard), perhaps MEG needs to be viewed as part of the therapeutic process, in which the ultimate comparison is “MEG-guided surgical decision-making” versus “non-MEG-guided surgical decision-making.”

Lacking this type of true comparative information on health outcomes, is it possible to make a case for the effectiveness of MEG using data generated from clinical practice, essentially case series data? The data from the study of Knowlton et al. (2008a) suggests that even with optimistic assumptions regarding the unobserved patients, it is likely that neither the sensitivity nor specificity of MEG is sufficiently high to bypass IC-EEG in patients either proceeding to surgery or stopping the workup. This would end the case for MEG if IC-EEG, despite its imperfections, were a mandatory part of the workup for seizure surgery. However, surgery can be successful without

a positive IC-EEG in the study of Knowlton and in patients without IC-EEG at all (personal communication, Knowlton 2008).

The argument that MEG improves the diagnostic yield of IC-EEG is often made, but it is difficult to identify studies that can support this argument. Studies that compare IC-EEG to MEG do not inform this particular question. On the other hand, given the gravity of this particular situation, there are some possible arguments to be made on behalf of MEG. Given that current decision making regarding who should receive surgery and what type of surgery is done with some uncertainty and lack of a true reference standard, an additional piece of information which is known to correlate with seizure focus could be arguably of some value in making difficult decisions. The diagnostic test is easy to perform and noninvasive. Also, IC-EEG and surgery are extremely invasive procedures that do not always provide diagnostic information. Information from MEG might influence a patient’s decision to undergo the risks of further testing or surgery if the outcome can be slightly better estimated. However, given that one possible outcome of use of MEG may result in avoidance of tests and procedures that may benefit the patient, it is not possible to rule out harm from use of the test. The net effect of the use of MEG on patient outcomes for this indication remains to be determined.

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