Quantitative Electroencephalography as a Diagnostic Aid for Attention-Deficit/Hyperactivity Disorder

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Based on review of available data, the Company considers quantitative electroencephalographic-based assessment of the theta/beta ratio as a diagnostic aid for attention deficit/hyperactivity disorder (ADHD) to be investigational.*

Background/Overview
Patients with ADHD may have alterations in their brain wave patterns that can be measured by quantitative electroencephalography (QEEG). A commercially available system, the Neuropsychiatric EEG-based ADHD Assessment Aid (NEBA™), measures the resting theta/beta ratio of the electroencephalogram. This technology is being evaluated to aid in the diagnosis of ADHD in adolescents and children for whom there is a clinical suspicion of ADHD.

Attention-deficit/hyperactivity disorder is a common disorder in children, adolescents, and adults defined by pervasive symptoms of inattention and/or hyperactivity-impulsivity, which lead to impairment in at least 2 domains of the work, school, or home environments. Stimulant medications reduce symptoms associated with ADHD, although there are concerns about the potential for overdiagnosis and overprescribing of medication. Presently, ADHD is diagnosed clinically by assessing behavioral symptoms and impairment via interviews and standard questionnaires. Diagnosis can be challenging, because the core symptoms are nonspecific. They may be present in other psychiatric disorders (eg, learning disabilities, conduct disorders, affective disorders) or result from environmental influences such as a lack of discipline. In addition, ADHD is a heterogeneous disorder with multiple subtypes, and frequently coexists with other psychiatric disorders.

There has been a substantial amount of research over the last several decades on whether electroencephalography (EEG)—derived brain wave patterns in patients with ADHD differ from those without ADHD. EEG patterns are typically categorized into 4 frequency ranges: delta (<4 Hz), theta (4-7 Hz), alpha (8-12 Hz), and beta (13-25 Hz). The largest focus of research on brain wave patterns in ADHD has been on whether there is increased theta wave activity and an increased theta/beta ratio in ADHD patients.

The NEBA system is a specific QEEG system that measures the resting theta/beta ratio of the EEG with an electrode located at the central midline position (referred to as position CZ in the international 10-20 EEG system). QEEG uses computer analysis with mathematical transformation from the time domain into the frequency domain (fast-Fourier transform) to determine the total power at each frequency. Relative power of the waveform can then be calculated in relation to the total power of the 4 frequency ranges. The NEBA
system uses proprietary cutoffs to generate an estimate of the likelihood of ADHD based on the resting theta/beta ratio.

It is proposed that the NEBA system can be used to confirm a clinical diagnosis or support further testing in children and adolescents with ADHD. The system is not intended to evaluate patients in whom the clinician’s diagnosis of ADHD is negative, and the system does not generate an interpretive report in this situation. It is also proposed that the clinician’s diagnostic impression plus the results generated by the NEBA system may reduce the potential for overdiagnosis of ADHD, and thereby reduce the risks of administering unnecessary pharmacologic therapy in the intended use population. In addition, as a result of research on EEG brain waves in ADHD, neurofeedback has been developed as a potential treatment for ADHD. This treatment employs principles of biofeedback using EEG brain wave activity and attempts to alter the brain wave patterns in beneficial ways.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

In 2011, the generic device Neuropsychiatric Interpretive Electroencephalograph Assessment Aid was granted a de novo 510(k) classification by the FDA (class II, special controls, product code: NCG). According to the FDA documentation, a neuropsychiatric interpretive electroencephalograph assessment aid is a device prescribed by a physician that uses a patient’s electroencephalogram (EEG) to provide an interpretation of the patient’s neuropsychiatric condition. In addition to the general controls, approval of these devices is subject to a number of special controls, including the following:

- Clinical performance testing must demonstrate the accuracy, precision, and reproducibility of the EEG-based interpretation, including any specified equivocal ones (cutoffs).
- Clinical performance testing must demonstrate the ability of the device to function as an assessment aid for the medical condition for which the device is indicated. Performance measures must demonstrate device performance characteristics per the intended use in the intended use environment. Performance measurements must include sensitivity, specificity, positive predictive value, and negative predictive value per the device intended use. Repeatability of measurement must be demonstrated using interclass correlation coefficients and illustrated by qualitative scatterplots.
- The device design must include safeguards to prevent use of the device as a stand-alone diagnostic.
- The labeling must bear all information required for the safe and effective use of the device.

In 2013, the Neuropsychiatric EEG-based Assessment Aid (NEBA; Lexicor Medical Technology, Augusta, GA) for ADHD was granted a de novo 510(k) classification by FDA. The device is indicated to measure the theta/beta ratio of the EEG at electrode CZ on patients 6 to 17 years of age, combined with a clinician’s evaluation, to aid in the diagnosis of ADHD (K112711). NEBA should only be used by a clinician as confirmatory support for a completed clinical evaluation or as support for the clinician’s decision to pursue further testing following a clinical evaluation. The device is not intended to be used as a stand-alone in the evaluation or diagnosis of ADHD.
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The Lexicor QEEG system is marketed as a diagnostic aid for ADHD. Lexicor Medical Technology provides an Internet analysis service of the QEEG, producing a DataLex report. Lexicor Medical Technology also developed the NEBA system. FDA Product Code: NCG.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source
This evidence review has been updated periodically with a review of the medical literature through a search of the MEDLINE database. The most recent literature update was performed through September 8, 2015.

Assessment of a diagnostic technology typically focuses on 3 categories of evidence: (1) technical performance (test-retest reliability or interrater reliability); (2) diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) in relevant populations of patients; and (3) demonstration that the diagnostic information can be used to improve patient outcomes. Subsequent use of a technology outside of the investigational setting may also be evaluated.

BCBSA TEC Assessment Overview
A Blue Cross and Blue Shield Association (BCBSA) Technology Evaluation Center (TEC) Assessment published in February 2014 evaluated the evidence related to the use of QEEG with the NEBA system in the diagnosis of ADHD. This evidence was submitted to the FDA in 2013 and subsequently published by Snyder et al (of NEBA Health) in 2015. The evidence related to the diagnostic accuracy of NEBA for the diagnosis of ADHD consisted of data submitted to FDA from 275 children and adolescents (6-18 years) who presented with attention and/or behavioral concerns to one of 13 clinics in the United States. The evidence related to the technical performance of NEBA for the diagnosis of ADHD included test-retest reliability of the NEBA theta/beta ratio for EEG data from 198 patients who had recordings on 2 different days. These studies are described in greater detail in the sections on technical performance and diagnostic accuracy. No studies were identified that assessed whether the reclassification of patients suspected of having ADHD, as reported to FDA, improves health outcomes.

Technical Performance
Data submitted to FDA for the NEBA system included test-retest reliability of the theta/beta ratio for EEG data from 198 patients who had recordings on 2 different days (~2.5 weeks apart on average). EEG data were collected for 10 minutes with patients seated in a chair with eyes open and fixed with attention to a point at eye level on the wall. Epochs (30 seconds in duration) with substantial artifact were screened out by EEG processing technicians at a central facility. Analysis of EEG data required at least 15 epochs of data with little to no artifact. There were 198 patients with 2 sessions of data out of the per protocol set of 275. The theta/beta cutoffs were revised prior to the blind break based on data from a prior study. The intraclass correlation coefficient of repeated NEBA theta/beta ratio was 0.83, which is considered to be high.
Diagnostic Accuracy

A number of studies have measured theta activity or the theta/beta ratio in children and adolescents with ADHD compared with nonaffected controls. The most commonly reported alteration in EEG is an increase in the theta/beta ratio. However, some studies have reported that other patterns (e.g., increased beta wave activity) are found in some patients, and several recent studies have found no significant difference in theta activity in a clinical versus nonclinical population.

A 2005 systematic review included 17 studies evaluating theta activity in children and adolescents with ADHD. Meta-analysis found a weighted mean effect size of 0.59 for an absolute increase in theta activity and a mean effect size of 0.91 for theta relative to total EEG activity. A 2006 systematic review by Snyder and Hall included 9 studies (N=1498) that used DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) criteria and screening tests in a clinical setting. Meta-analysis identified a mean increase of theta power of 32% and a pooled effect size of 3.08 for the theta/beta ratio in patients with ADHD compared with unaffected children, adolescents, and adults. It was noted that the included studies often had retrospectively defined limits and that an increase in the theta/beta ratio has also been identified in other conditions. A 2001 study by Monastra et al found a change in QEEG at CZ in a large study (N=469) of children and adolescents who were diagnosed with ADHD versus healthy controls, although this study used an attention index measured across 4 different tasks (eyes fixed, silent reading, listening, drawing).

Other studies find no significant difference in theta activity in a clinical population with ADHD. For example, in 2013, Liechti et al compared the theta/beta ratio in 32 children and 22 adults with ADHD versus healthy controls who were matched for age, gender, and IQ. Resting EEG was measured separately for the 3 midline electrodes (frontal [FZ], central [CZ], parietal [PZ]) and for frontal, central, and parietal regions. The study found a decrease in theta with age, but no consistent increase in theta or theta/beta ratio in patients with ADHD compared with controls. There was no evidence for a maturational lag in patients with ADHD. In 2012, Ogrim et al assessed differences in theta activity measured at CZ in 62 children and adolescents with a tentative diagnosis of ADHD compared with 39 sex- and age-matched controls. The overall accuracy at CZ was 63% for theta and 58% for the theta/beta ratio compared with non-affected controls. Elevations of theta were found in 25.8% of patients compared with 2.6% of controls. None of the EEG measures was statistically significant for discerning patients from controls. In other studies, subgroups of children with ADHD have been shown to have increased beta activity instead of decreased beta or increased theta/beta ratio. In a study of QEEG in combination with the Conners’ Continuous Performance Test and the Test of Variables of Attention in the diagnosis of ADHD in 157 children, 85 with and 72 without ADHD based on Diagnostic Interview Schedule for Children (Version IV), Kim et al reported that the ADHD group had significantly higher theta wave values in 13 positions, while for the theta/beta ratio, the ADHD group had higher values for only 1 position (right frontal lobe).

Sensitivity, Specificity, and Predictive Value of the Theta/Beta Ratio in the Diagnosis of ADHD

Data submitted to FDA regarding diagnostic accuracy of the NEBA system were from the multicenter study of 275 children and adolescents (6-18 years, described above) who presented with attention and/or behavioral concerns to one of 13 clinics in the United States. An additional 89 children and adolescents were recruited but did not complete the study, and, of these, 67 had incomplete EEG recordings. Diagnostic evaluation for ADHD and other disorders was conducted with clinical interview and rating scales that
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included behavior rating scales, IQ and achievement testing, and scales of severity and dysfunction. A consensus best-estimated diagnosis was determined by a multidisciplinary clinical team composed of a clinical psychologist, a neurodevelopmental pediatrician, and a child/adolescent psychiatrist. The clinical team had access to de-identified patient files, but did not interview patients or have access to the parent rating scales, features considered critical for a criterion standard diagnosis of ADHD. A separate group of investigators who were unaware of the clinical diagnosis collected the EEG data (NEBA system). When compared with the consensus diagnosis, NEBA had a sensitivity of 89%, specificity of 87%, positive predictive value (PPV) of 81% and negative predictive value (NPV) of 93% for adolescents (12-17 years). For children (6-11 years), NEBA had sensitivity of 79%, specificity of 97%, PPV of 96%, and NPV of 82%. The investigators calculated that the addition of NEBA to the clinician’s ADHD evaluation would have improved the clinician’s diagnostic accuracy from 61% to 88%. This calculation is based on the 275 patients who completed the protocol, rather than the intention-to-treat population. The results of this FDA-regulated study suggest that QEEG might be used to decrease the overdiagnosis of ADHD by identifying patients who may not have the disorder. Strengths of this study include its multicenter design and the reclassification analysis of data obtained from a blinded analysis. Limitations are lack of patient interview by the consensus team and lack of intention-to-treat analysis.

Snyder et al also reported the accuracy of the theta/beta ratio for diagnosis of ADHD in an industry-sponsored, investigator-blinded, multicenter study from 2008. Patients (N=159) ages 6 to 18 who had presented to 1 of 4 psychiatric and pediatric clinics with suspected attention and behavioral symptoms were evaluated in a standardized semi-structured manner according to DSM-IV criteria by a clinical team trained on the study instruments. Rating scales were distributed to parents and teachers and held in sealed envelopes until the blind was broken. EEG was collected separately by investigators, blinded to the clinical diagnosis, using a 19-electrode cap according to the 10-20 system with eyes open and eyes shut. A threshold of 1.5 SD of the theta/beta ratio from normative database values (according to age) at electrode CZ was used to determine ADHD versus non-ADHD. With a prevalence of ADHD of 61% based on clinical diagnosis, the theta/beta ratio had a sensitivity of 87%, specificity of 94%, PPV of 95%, and NPV of 82%. The rating scales provided sensitivity of 38% to 79% and specificity of 13% to 61%. Results from this study were used to set a new theta/beta threshold for analysis of data from the FDA-regulated study of the NEBA device.

Other studies have reported lower accuracy of QEEG in the diagnosis of ADHD. In the Kim study previously reported, on receiver operator curve analysis, QEEG theta wave amplitude showed low accuracy for the diagnosis of ADHD (56.4%), and the theta/beta wave amplitude did not significantly predict ADHD diagnosis. Sangal et al evaluated the discriminatory power of QEEG measurements during auditory and visual tasks requiring selective attention in 28 control children and 58 children with ADHD. Subjects with ADHD had significantly higher average theta/beta ratios (2.6 vs 2.25; p=0.007) and lower average beta-I amplitudes (3.66 vs 4.22, p=0.01). The average theta/beta ratio had sensitivity and specificity in diagnosing ADHD of 69% and 50%, respectively, while the theta/beta ratio at the CZ position had sensitivity and specificity of 69% and 43%, respectively.
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Section Summary: Diagnostic Accuracy
Patients with ADHD may have altered brain wave patterns on QEEG compared with patients without ADHD. While an increased theta/beta ratio is the most common alteration reported, not all studies have found this association, and some have reported other brain wave patterns in ADHD patients. A few studies have reported on the sensitivity and specificity of quantitative EEG compared with clinical diagnosis. In these studies, sensitivity ranged from 69% to 89% and specificity from 43% to 97%. However, a weakness of these studies is the lack of a true criterion standard for diagnosis of ADHD.

Effect on Clinical Outcomes
A proposed benefit of the NEBA system is a reduction in the overdiagnosis of ADHD, thereby lessening the risks of unnecessary pharmacologic therapy in children and adolescents. There were no published studies that directly reported on clinical outcomes, such as measures of disease activity and/or medication use. The pivotal FDA study reported reclassification of diagnosis following NEBA; this may be considered an indirect measure that may impact outcomes.

The evidence related to whether QEEG improves the clinical diagnosis of patients with suspected ADHD consists of the material submitted to FDA as part of the NEBA’s approval process, as previously described. The study included reclassification tables to demonstrate whether NEBA provides additional information beyond the clinician’s initial diagnosis, which are summarized in Table 1. Use of NEBA was consistent with the categorization of patients diagnosed with ADHD by both the initial clinical diagnosis and the consensus diagnosis. For example, 95 of 130 children and adolescents (73%) who were considered to have ADHD by the consensus diagnosis were classified as ADHD by both the clinician alone and NEBA. Reclassification was observed when using NEBA for patients diagnosed by clinician alone as ADHD and consensus as non-ADHD. For example, there were 145 children and adolescents who had a non-ADHD diagnosis by the consensus. Of the 145, 93 had received an initial clinical diagnosis of ADHD, but 85 (91%) were negative by NEBA.

Table 1: NEBA Reclassification of Patients With Consensus ADHD Diagnosis

<table>
<thead>
<tr>
<th>Consensus Diagnosis</th>
<th>Initial Clinical Diagnosis</th>
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<tbody>
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<tr>
<td>NEBA interpretation</td>
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</tr>
<tr>
<td></td>
<td>95 (81.9)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>11 (78.6)</td>
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</tr>
<tr>
<td></td>
<td>21 (18.1)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>3 (21.4)</td>
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<tr>
<td>Total</td>
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<td>14</td>
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<td></td>
<td>85 (91.4)</td>
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<td></td>
<td>51 (98.1)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>52</td>
</tr>
</tbody>
</table>

ADHD: attention deficit hyperactivity disorder; FDA: Food and Drug Administration; NEBA: Neuropsychiatric EEG-Based Assessment Aid; NEBA interpretation: NEBA results plus initial clinical diagnosis.

a The consensus diagnosis is assumed to be the reference standard (ie, correct). Two categories are included in the ADHD consensus diagnosis: diagnosed with ADHD or referred for more testing for the condition. Similarly, the “not ADHD” diagnosis included those diagnosed as not having ADHD or as needing more testing for other conditions.
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b The NEBA interpretation is a composite of both the initial clinical diagnosis and the NEBA results, like a dichotomized posttest probability. The performance measures are presumably calculated assuming that a negative NEBA result can override a positive initial clinical diagnosis, but in the FDA summary, it is stated that a negative diagnosis can only result from a negative initial clinical diagnosis (ie, the NEBA interpretation cannot override it).

Section Summary: Effect on Clinical Outcomes
Reclassification results from the pivotal trial suggest that NEBA may support an alternative diagnosis in patients initially suspected of having ADHD but not confirmed by consensus diagnosis. No studies were identified that address whether clinical outcomes are improved for patients with suspected ADHD who are reclassified by NEBA.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in September 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for QEEG in individuals who are suspected of having ADHD includes a number of studies on brain wave patterns, particularly the theta/beta ratio. Relevant outcomes are test accuracy, symptoms, functional outcomes, and medication use. Numerous studies have evaluated brain wave patterns with standard EEG equipment, and a pivotal trial was submitted to the FDA that measured the theta/beta ratio with the NEBA system. In the pivotal trial, the specificity and positive predictive value of QEEG was high. The reclassification analysis suggests that a negative NEBA might make ADHD less likely, although it is not clear from this study whether the consensus diagnosis was more accurate than the initial clinical diagnosis that included patient interview and parent rating scales. The larger body of evidence also raises questions about the utility of measuring the theta/beta ratio, because it has not been a consistent finding across studies. Given the uncertainty of an increase in the theta/beta ratio in patients with ADHD, additional study is needed to determine whether a low theta/beta ratio can identify children and adolescents who are unlikely to have ADHD. In addition, the effect of the test on patient outcomes would allow greater certainty regarding the usefulness of this test. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Quantitative Electroencephalography as a Diagnostic Aid for Attention-Deficit/Hyperactivity Disorder TEC Assessments. 2014; Volume 29, Tab 1

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Policy History
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12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. New Policy.
12/01/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 12/2017

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<td>ICD-10 Diagnosis</td>
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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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