Table 1. Proposed criteria for neurophysiologic biomarkers

Psychometric properties of translational biomarkers
• Established substantial test-retest reliability (intraclass correlations > 0.8)
• Suitable for use as a repeated measure (i.e., no practice, maturation, instrumentation, testing or statistical regression effects)
Functional characteristics
• Early sensitivity to single- or limited "doses" of pharmacologic agents, cognitive training or other CNS interventions
• Consistent relationships to important domains of clinical, cognitive and/or psychosocial functioning in humans
Scalable for use in real-world multi-site global clinical trial settings
• Equipment should be low cost with identical interchangeable calibrated systems and components
• Measures are robust to variations in testers and testing environments
• Tests can be administered by non-specialists with appropriate training, certification, and centralized quality assurance and oversight
• Does not require special testing environments, suitable for valid use in varied multi-center settings
• Objective automated analysis methods that are amenable to centralized data processing blinded to group and conditions

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ADDITIONAL INFORMATION

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Sleep and EEG biomarkers as avenues toward new treatment approaches in Angelman syndrome

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Angelman syndrome (AS) is characterized by severe intellectual, speech and motor deficits [1]. The cause of AS is either disruption of the maternal ubiquitin-protein ligase E3A gene (*UBE3A*) (30%) or deletion of chromosome 15 at 15q11-q13 (70%). The deleted region includes *UBE3A* and *GABRB3*, *GABRA5*, and *GABRG3*, genes that encode the gamma-aminobutyric acid (GABA) type A receptor subunits β3, α5, and γ3. Several medical co-morbidities are associated with AS.

Sleep disturbance is a common medical co-morbidity, occurring in up to 80% of individuals with AS. Difficulty falling and staying asleep and reduced total sleep time are most common. The etiology of sleep disturbances in AS is multifactorial, involving genetic, co-morbid medical, and behavioral factors. Deletion of the *GABRB3-GABRA5-GABRG3* gene grouping, which occurs in most cases of AS, probably contributes to the high prevalence of sleep problems and co-morbid epilepsy [2]. Epilepsy occurs in 80–90% of individuals with AS and can contribute to sleep problems. In a study of sleep disturbances and epilepsy in 290 subjects with AS, disturbed sleep was described by caregivers of 58% of the sample [3]. Among these subjects, 79% had epilepsy, and 69% of those with both sleep problems and epilepsy had multiple seizure types. Subjects with epilepsy non-responsive to more than two antiepileptic drugs (AEDs) had more significant sleep disturbances than those successfully treated with up to two AEDs. From a behavioral standpoint, urinary

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incontinence overnight may cause mid-nocturnal awakenings, and agitation in response to separation from preferred caregivers may play a role in the disturbed sleep.

Recent studies are attempting to identify biomarkers of the pathophysiology of sleep disturbances in AS using EEG. In a retrospective study, den Bakker and colleagues [4] identified two quantitative readouts of dysregulated sleep composition in children with AS: increased gamma coherence and fewer sleep spindles. Increased long-range gamma-band coherence during sleep and wakefulness suggests that, despite reduced structural connectivity, there may be fewer inhibitory constraints on efferent projections in the brain of individuals with AS. Sleep spindles, which are reduced in several neurodevelopmental disorders, are important for memory consolidation and learning. Another group tested the hypothesis that genes other than *UBE3A* located on 15q11-q13 cause differences in pathophysiology between AS genotypes [5]. In children and adolescents with AS, they found that an abnormality in the delta-band EEG indexes *UBE3A*-related pathophysiology, while theta- and beta-band EEG abnormalities index contributions from other genes, most likely the *GABRB3-GABRA5-GABRG3* gene cluster.

Building upon the identification of biomarkers for disturbed sleep in AS, a Phase 2, 12-week randomized double-blind, placebo-controlled trial of gaboxadol (OV101), an extracellular delta-selective $GABA_A$ receptor agonist, was completed in 78 adults and adolescents [6]. At week 12, OV101 resulted in global improvement in significantly more subjects than did placebo. Sleep onset latency, overall sleep, and motor function were found to contribute to this global response.

Safe and potentially efficacious targeted therapies are being developed for interfering symptoms in AS. With continued progress, it is hoped that interventions will one day alter the course of this severe developmental disorder.

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