1. Background and Objectives
A more refined endophenotype of bulbar ALS is needed to improve diagnostic and treatment specificity and to strengthen future efforts at identifying the genetic loci of ALS. Even more pressing is the need for sensitive outcome measures of bulbar performance for experimental drug trials. Unfortunately, the development of objective measures of bulbar involvement has been very slow, lagging behind those existing for detecting spinal involvement. Major obstacles have been the inaccessibility and complexity of the speech apparatus. Consequently, very little research has been conducted to elucidate the variable expression of bulbar ALS across individuals and the factors that affect speech decline in ALS.

In this investigation, we evaluate the neuromotor status of multiple speech subsystems in a group of individuals with ALS longitudinally. The specific aims of this preliminary investigation are to determine (1) the sensitivity of multiple measures of bulbar function to disease progression, (2) the relations between speech system and subsystem variables, and (3) the degree of individual variation in speech subsystem impairment.

2. Methods
Subjects: Our pilot group consists of 20 individuals with bulbar and spinal onset of ALS. They are being recorded every 3 months during their regular clinic visits.

Instrumentation: A motion tracking system (Optotrak, NDI); an aerodynamic measurement system (Biopac Inc.), JT-3D (BioResearch Associates Inc), high quality acoustic equipment for recording.

3. Preliminary Results
Analysis 1. Comparison across measures in their sensitivity to disease progression. For each subject, standardized slopes were fitted for each variable. Standardized slopes permitted the comparison across variables with different scales. Comparisons were made across variables to determine their level of sensitivity for detecting disease progression. Increase sensitivity is suggested by low, negative slope values.

Analysis 2. Relations between speech system and subsystem variables. Pairwise correlations were performed on all possible variables based on the standardized slopes obtained for each subject. Statistically significant (p < 0.05) correlations are denoted in blue.

Analysis 3. Individual variation in speech subsystem impairment. The standardized slope was computed for each subsystem level variable to determine differences among 4 subjects in speech subsystem decline.

4. Discussion
1. Performance variables differed considerably in their sensitivity to disease progression. In general, speech subsystem variables appeared to be more sensitive than system variables. Velopharyngeal performance was particularly sensitive to disease progression. These findings suggest that subsystem indicators of bulbar function can provide sensitive outcome measures for clinical trials.

2. Speech intelligibility and rate were strongly correlated with respiratory and velopharyngeal function, but not with speed of upper lip, lower lip and jaw movement. These findings suggest that poor respiratory support for speech is a primary contributing factor to the slowing of speech with disease progression. Orofacial movement speeds were not associated with system level or other subsystem level variables. This lack of association is most likely due to across subject differences in the speech subsystems that are affected.

3. Subjects varied considerably in which speech subsystems were most affected. All of the subjects, however, exhibited a decline in velopharyngeal function. Data from additional subjects are needed for identifying putative subtypes of bulbar ALS.

5. References