INTRODUCTION
Osteoarthritis (OA) is the leading cause of disability in the United States. Non-operative management consisting of a physician prescribed rehabilitation regimen is a major component of treatment. Unfortunately, clinicians treating OA often have little evidence on which to base their decisions for safe and effective rehabilitative strategies. Resistance training protocols prescribed for knee OA patients are often identical to those performed by healthy adult populations, despite differences in levels of impairment and functional ability. A major reason for this has been the lack of comprehensive outcome measures of rehabilitation to evaluate both the patient’s post-treatment functional status and disease progression. Biomarkers in OA research have been used to confirm the disease process and elucidate possible disease mechanisms. However, to our knowledge no previous study has evaluated a panel of biomarkers as a means of following the functional outcome of OA patients undergoing rehabilitation. Therefore the objective of this research is to firstly demonstrate the efficacy of a defined rehabilitation regimen for the treatment of knee OA. The goal is to provide the clinician with a sound theoretical rationale for choosing an effective, and safe, rehabilitation prescription and maximize improvements in quality of life for these patients. Secondly, we aim to identify a urinary biomarker panel in these patients that would aid in following the disease process by providing a non-invasive means of correlating the functional outcome of rehabilitation to the biology within the joint. Ultimately this could allow the tailoring of rehabilitation protocols to the patient’s particular pathology.

METHODS
Institutional IRB was obtained for this study. Following informed consent, 12 patients and 2 healthy controls were enrolled.

Study Criteria: The inclusion criteria for patients in this study were age greater than 55 (average age, 62.1), clinical and radiographic knee OA, without symptoms of hip OA. Patients who had undergone a previous rehab regimen, had known cardiac disease (which would preclude rehabilitation), and urinary tract infection were excluded from the study.

Radiographs: Baseline radiographs of the patient’s knees were taken and scored for evidence of OA using the Kellgren-Lawrence criteria.

Rehabilitation regimen: Baseline measures of muscle strength, contraction velocity, power in watts (W) functional performance, and disability were collected prior to randomization. Patients were randomized into a rehabilitation group (n=8), or control group (n=4). The rehabilitation group underwent a specific supervised treatment 3 times per week for 12 weeks. The training sessions consisted of either a velocity or strength rehab regimen consisting of 3 sets of 8 to 10 repetitions of a leg press exercise (LP) or knee extension exercise (KE) at 40% and 80% maximal strength respectively. Patients randomized into the control group, had a placebo exercise regimen with only lower extremity

Muscle Testing: Muscle strength, velocity and power of the lower extremities were measured using Keiser pneumatic resistance training equipment (Keiser Sports Health Equipment Inc., Fresno, CA).

2) Functional measures: The amount of time it takes for the patient to raise from a seated position (chair time), to walk 10 meters (walk time), and to ascend a set of seven stairs (stairs time).

3) Disability assessment: The Stanford Health questionnaire was used to assess the degree of disability secondary to their symptoms.

4) Biomarker testing: A Urine sample was collected at day 0 and after 12 weeks of rehab, and tested using a Luminex assay for MMP-2,-3,-9,-13, TNF-α, MIP-1α, MCP-1, IL-6, IL-8, KC and RANTES. The biomarker data were normalized to urine creatinine concentration. The levels of these markers in the urine were compared to patients without symptoms of OA (normal group, n=2).

Statistical Analyses: The Wilcoxon Signed Rank test was used to compare the outcome of rehabilitation versus control group treatments. Pearson’s correlation coefficient was used to investigate the correlations between different outcome parameters. Moderate correlations were considered to be r≥0.4 and p<0.05 respectively.

RESULTS
Patients who underwent rehabilitation had a significantly greater degree of improvement in the strength and power they produced performing a LP and KE (p<0.05, Figure A) compared to the group who underwent the control regimen. In addition, the OA rehab group also had a significant reduction in the amount of time they took to rise from a seated position i.e. the chair time (p<0.05, Figure B) On examining correlations of change in function, there were moderate to strong negative correlations between the change in LP and KE power of a patient and the change in stair time (r=-0.550, p<0.05 and r=-0.569, p<0.05) and walk time (r=-0.513, p<0.05 and -0.485, p<0.05). On biomarker assessment there were 3 biomarkers that had detectable levels in the urine: MMP-9, IL-8 and MCP-1. The levels of MMP-9 and IL-8 correlated together strongly (r=0.819, p<0.001). There were significantly higher levels of MMP-9 and IL-8 in the urine of patients with OA compared to normal subjects without symptoms of OA (p<0.001, Figure C). There was no significant difference in the concentration of MMP-9 and IL-8 between groups, post-intervention. We examined whether the MMP-9 and IL-8 concentrations correlated to function at that particular time point. The LP strength and MMP-9 concentration had a moderate negative correlation (r=-0.444, p<0.05). There was also a moderate positive correlation between the concentration of MMP-9 (r=0.569, p<0.01) and IL-8 (r=0.446, p<0.01) in the urine and the chair rise time.

DISCUSSION
To our knowledge, this is the first study that used potential biomarkers as an indicator of functional outcome in rehabilitation. The study compared a defined rehabilitation regimen to a control placebo-training regimen. It was found that the defined rehabilitation regimen prescribed improved the ability to perform certain mechanical movements which in-turn improved the ability to perform certain functional tasks in patients with knee OA. Interestingly, a number of these findings correlated with 2 markers that have been previously associated with OA, MMP-9 and IL-8. The levels of both of these markers were significantly higher in urine of OA patient’s compared to normal patients without symptoms of OA. There is evidence in our study that their levels do moderately correlate with changes in certain functional abilities of OA patients, and could potentially be used to evaluate a patient’s response to rehab, and therefore guide rehab choices during treatment.

SIGNIFICANCE
These data indicate that urinary biomarkers could provide an objective, non-invasive, method for correlating symptomatology and functional outcome to markers of joint pathology. Potentially, these biomarkers could allow the clinician to assess the biological and clinical benefits of different types of exercise and rehabilitation, allowing the clinician to evaluate the rehabilitation regimen effect on the patient’s specific joint pathology.