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Innovation Opportunities within Lymphedema*

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OBJECTIVES/GOALS: Lymphedema is a chronic, debilitating disease characterized by progressive swelling due to lymphatic dysfunction. Lymphedema affects 5+ million people in the US, commonly as a consequence of cancer treatment. We identified the most relevant needs within lymphedema based on clinical impact, commercial viability, and technological feasibility. METHODS/STUDY POPULATION: A narrative review of lymphedema management was performed through a combination of literature review via English language PubMed, landscape determination for current solutions and primary ethnography. Lymphedema-focused physicians, patients, physical therapists and researchers were interviewed on Needs were identified and clustered based on common themes. These clusters were further refined through an iterative process of systematic scoring and expert evaluation. Clusters were evaluated on their potential for clinical and commercial impact as well as technical feasibility. RESULTS/ANTICIPATED RESULTS: General clusters identified included improved diagnostic modalities, curative treatment, disease knowledge among non-specialized clinicians and increased insurance coverage. 3 primary needs were determined to represent the best opportunities for technological innovation. There is a need for a quantitative method of evaluating lymphedema. This would allow for both improved tracking of progression for patients undergoing conservative management, and for better evaluation of surgical outcomes. Oncologists and surgeons need a method of prophylaxis in order to decrease the rate of lymphedema development following cancer treatment. Physicians need a method for early diagnosis of subclinical lymphedema to enable early intervention through proactive screening rather than reactive management. DISCUSSION/SIGNIFICANCE: Increasingly medical device design has moved towards a "bedside to benchtop" model where technology development is targeted based on critical needs within the clinical environment. Identification of these critical needs will serve as to guide future technological innovation in creating clinically impactful advancements.

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Diffusion Basis Spectrum Imaging (DBSI) Prognosticates Outcomes for Cervical Spondylotic Myelopathy after Surgery

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OBJECTIVES/GOALS: Diffusion basis spectrum imaging (DBSI) allows for detailed evaluation of white matter microstructural changes present in cervical spondylotic myelopathy (CSM). Our goal is to utilize multidimensional clinical and quantitative imaging data to characterize disease severity and predict long-term outcomes in CSM patients undergoing surgery. METHODS/STUDY POPULATION: A single-center prospective cohort study enrolled fifty CSM patients who underwent surgical decompression and twenty healthy controls from 2018-2021. All patients underwent diffusion tensor imaging (DTI), DBSI, and complete clinical evaluations at baseline and 2-years follow-up. Primary outcome measures were the modified Japanese Orthopedic Association score (mild [mJOA 15-17], moderate [mJOA 12-14], severe [mJOA 0-11]) and SF-36 Physical and Mental Component Summaries (PCS and MCS). At 2-years follow-up, improvement was assessed via established MCID thresholds. A supervised machine learning classification model was used to predict treatment outcomes. The highest-performing algorithm was a linear support vector machine. Leave-one-out cross-validation was utilized to test model performance. RESULTS/ANTICIPATED RESULTS: A total of 70 patients – 20 controls, 25 mild, and 25 moderate/severe CSM patients – were enrolled. Baseline clinical and DTI/DBSI measures were significantly different between groups. DBSI Axial and Radial Diffusivity were significantly correlated with baseline mJOA and mJOA recovery, respectively ($r=-0.33$, $p<0.01$; $r=-0.36$, $p=0.02$). When predicting baseline disease severity (mJOA classification), DTI metrics alone performed with 38.7% accuracy (AUC: 72.2), compared to 95.2% accuracy (AUC: 98.9) with DBSI metrics alone. When predicting improvement after surgery (change in mJOA), clinical variables alone performed with 33.3% accuracy (AUC: 0.40). When combining DTI or DBSI parameters with key clinical covariates, model accuracy improved to 66.7% (AUC: 0.65) and 88.1% (AUC: 0.95) accuracy, respectively. DISCUSSION/SIGNIFICANCE: DBSI metrics correlate with baseline disease severity and outcome measures at 2-years follow-up. Our results suggest that DBSI may serve as a valid non-invasive imaging biomarker for CSM disease severity and potential for postoperative improvement.

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A serum exocrine enzyme as a biomarker of response to immunotherapy in type 1 diabetes.

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OBJECTIVES/GOALS: We assessed the relationship between C-peptide preservation and a serum exocrine pancreatic enzyme (trypsin) in a recently concluded clinical trial. We hypothesized that immunomodulatory treatment resulting in improved beta-cell function would be associated with improved trypsin levels in subjects with recent-onset type 1 diabetes (T1D). METHODS/STUDY POPULATION: In a three-arm, randomized, double-masked, placebo-controlled trial 'Antithymocyte Globulin (ATG) and pegylated granulocyte colony stimulating factor (GCSF) in New Onset Type 1 Diabetes' 89 subjects with recent-onset T1D (duration <100 days) were enrolled and randomized to 3 groups: low-dose ATG (2.5 mg/kg IV) followed by pegylated GCSF (6 mg subcutaneously every 2 weeks for 6 doses), low-dose ATG alone, and placebo. We compared longitudinal serum levels of an exocrine enzyme (trypsin) in a subset of responders to therapy (defined as subjects with at least 60% of baseline area under the curve (AUC) C-peptide levels at 96 weeks, n=4) versus placebo 'responders' (n=2) and non-responders (n=25), and treated (n=19) versus placebo (n=12) subjects at baseline, 2 weeks, and 6 months after treatment. RESULTS/

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ANTICIPATED RESULTS: There was no observed difference in treated (n=20) versus placebo (n=12) longitudinal trends in trypsin levels when compared to baseline levels. However, responders to immunotherapy (n=4) had 6 month trypsin levels that were 114% of baseline whereas placebo subject 'responders' (n=2), placebo subjects (n=10), and non-responders to immunotherapy (n=15) had trypsin levels that were 81-93% of baseline (unpaired T test p=0.05). Overall, we found that serum trypsin, a marker of exocrine pancreatic function, had a normal upward trend in new-onset T1D subjects who responded clinically to immunotherapy but declined in subjects who did not respond or who were not treated. These results were bordering on statistical significance but did not reach significance, likely due to the small sample size. DISCUSSION/SIGNIFICANCE: An improvement in trypsin, a marker of exocrine function, after response to immunotherapy in new-onset T1D may be due to a direct impact on exocrine function versus an indirect effect from improved beta cell function. Future studies will be needed to confirm our findings in a larger sample and evaluate the mechanism for improved exocrine function.

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Machine Learning Segmentation of Amyloid Load in Ligamentum Flavum Specimens From Spinal Stenosis Patients†

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OBJECTIVES/GOALS: Wild-type transthyretin amyloid (ATTRwt) deposits have been found to deposit in the ligamentum flavum (LF) of spinal stenosis patients prior to systemic and cardiac amyloidosis, and is implicated in LF hypertrophy. Currently, no precise method of quantifying amyloid deposits exists. Here, we present our machine learning quantification method. METHODS/STUDY POPULATION: Images of ligamentum flavum specimens stained with Congo red are obtained from spinal stenosis patients undergoing laminectomies and confirmed to be positive for ATTRwt. Amyloid deposits in these specimens are classified and quantified by TWS through training the algorithm via user-directed annotations on images of LF. TWS can also be automated through exposure to a set of training images with user- directed annotations, and then application to a set of new images without additional annotations. Additional methods of color thresholding and manual segmentation are also used on these images for comparison to TWS. RESULTS/ANTICIPATED RESULTS: We develop the use of TWS in images of LF and demonstrate its potential for automated quantification. TWS is strongly correlated with manual segmentation in the training set of images with user-directed annotations ($R = 0.98$; $p = 0.0033$) as well as in the application set of images where TWS was automated ($R = 0.94$; $p = 0.016$). Color thresholding was weakly correlated with manual segmentation in the training set of images ($R = 0.78$; $p = 0.12$) and in the application set of images ($R = 0.65$; $p = 0.23$). DISCUSSION/SIGNIFICANCE: Our machine learning method correlates with the gold standard comparator of manual segmentation and outperforms color thresholding. This novel machine learning quantification method is a precise, objective, accessible, high throughput, and powerful tool that will hopefully pave the way towards future research and clinical applications.

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An intracranial EEG map of naturalistic images in the human brain*

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OBJECTIVES/GOALS: Our overall goal is to identify the processes used by the human visual system to encode visual stimuli into perceptual representations. In this project, our objective is (i) to collect a dataset of human neural activity in response to 1000 naturalistic color images and (ii) to determine how image parameters drive different parts of the human brain. METHODS/STUDY POPULATION: We recorded iEEG data in 4 human subjects who had been implanted for epilepsy monitoring. Each subject was presented 10 sets of 100 naturalistic stimuli, taken from the Natural Scenes Dataset (Allen et al., 2021), on a screen for 1 second each with 1 second rest intervals between stimuli. The subjects were instructed to fixate on a red dot at the center of the screen and were prompted to recall whether they had seen 3 additional test stimuli at the end of each set to encourage attentiveness. We calculated significant neural responses at each electrode by comparing evoked potentials and high frequency power changes during each stimulus vs. rest. Electrodes with significant responses were then mapped to anatomic locations in each subjects brain and then collectively to a standard brain. RESULTS/ANTICIPATED RESULTS: The natural image set elicited significant evoked potentials and high frequency responses at electrodes in each subject. Response latencies, from 80 to 300 ms after stimulus onset, portrayed the evolution of visual processing along the visual pathways, through key sites such as the early visual cortex, ventral temporal cortex, intraparietal sulcus, and frontal eye field. These responses differed significantly from those elicited by simple patterns, which drove early visual cortex but less so in later regions. DISCUSSION/SIGNIFICANCE: These data show that the human brain responds differently to more complex images. Determining the human brains response to naturalistic images is essential for encoding models that describe the processing in the human visual system. These models may further future efforts for electrical neurostimulation therapies such as for restoring vision.

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Brain-derived Extracellular Vesicles: A Novel Biomarker of CNS Metals Load with Applications in Identifying Neurodegenerative Diseases

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OBJECTIVES/GOALS: This study aims to develop a method to examine whether blood-borne CNS-EV metal cargoes can serve as reliable biomarkers of CNS metal load and reveal a link between metal load and ALS development (i.e., neurodegenerative disease development). METHODS/STUDY POPULATION: CNS-EVs were

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