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The Role of TCF7L2 in Hepatic Metabolic Zonation

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OBJECTIVES/GOALS: Single nucleotide polymorphisms in the transcription factor 7-like 2 (TCF7L2) gene are associated with Type 2 Diabetes (T2D) and nonalcoholic fatty liver disease (NAFLD). The metabolic function of TCF7L2 in the liver remains to be fully elucidated, but we hypothesized that TCF7L2 contributes to NAFLD through regulation of zonal metabolic pathways. METHODS/STUDY POPULATION: Using single nuclei RNA sequencing, we examined Tcf7l2 expression in periportal (PP) hepatocytes around the portal triad and pericentral (PC) hepatocytes surrounding the central vein of the liver. To visualize TCF7L2 transcriptional activity we used a TCF reporter mice, which expresses an H2B-eGFP fusion protein downstream of the conserved TCF DNA binding site. We disrupted Tcf7l2 transcriptional activity in mouse liver by breeding mice with a floxed Tcf7l2 exon 11, which encodes part of the DNA binding domain (DBD), to albumin-Cre mice (Hep-TCF7L2Î"DBD). Eight-week-old mice were fed a choline-deficient amino acid-defined high fat (CDAHFD) diet for 8 weeks. In liver samples harvested from these mice, we examined disruption to several key zonated metabolic pathways, and quantified the development of fibrosis. RESULTS/ANTICIPATED RESULTS: Single nuclei analysis revealed that Tcf7l2 mRNA was expressed primarily in parenchymal cells of the liver but was ubiquitous across the liver lobule. However, in immuno-fluorescence analysis of TCF reporter mice, the transcriptional activity of TCF7L2 was highly restricted to PC hepatocytes. Classic PC hepatocyte markers, including glutamine synthetase (Glul), were absent in Hep-TCF7L2Î"DBD mice. Following the CDAHFD, Hep-TCF7L2Î"DBD mice developed more severe fibrosis in histological analysis, and expressed elevated levels of genes involved in fibrogenesis, collagen synthesis and TGFβsignaling. Hep-TCF7L2Î"DBD mice also displayed hepatic cholesterol accumulation following the CDAHFD, which was likely the result of impaired pericentral bile acid synthesis. DISCUSSION/SIGNIFICANCE: Our results suggest that TCF7L2 plays an important role in the regulation of zonated metabolic pathways, which may contribute to the development of fibrosis. Ongoing analyses are exploring the mechanisms regulating the zonal transcriptional activity of TCF7L2.

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The tradeoff between kinematic and muscular control of reaching as a potential biomarker of motor performance in stroke

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OBJECTIVES/GOALS: Nearly 3 million Americans live with arm impairment following stroke. While as many as 20% of patients fully recover, individual differences in recovery make one-size-fits-all rehabilitation approaches suboptimal. The goal of this study was to use our custom rehabilitation platform to identify neuromuscular biomarkers of arm control in stroke. METHODS/STUDY POPULATION: Chronic stroke survivors (N = 10) reached for targets in a virtual reality environment using both hands. They completed 162 reaches divided into 3 blocks. Following baseline, we used our custom exoskeletons to provide 50% arm weight assistance to the impaired limb and 50% arm weight resistance to the non-impaired limb. We removed the exoskeletons during the retention block. We used electromyography to approximate muscle activity in the anterior deltoids. Relative contribution (RC) was calculated as the displacement of the impaired arm divided by the sum of displacements for both arms. Muscle contribution (MC) was calculated as the root mean square of impaired arm muscle activity divided by the sum of activity for both deltoids, normalized to maximum voluntary contraction. RESULTS/ANTICIPATED RESULTS: During baseline, RC of the impaired limb was 43%; patients reached significantly less with their impaired arm compared to their non-impaired arm (p = 0.02). MC of the impaired deltoid was 56% and was similar between arms (p = 0.5). During loading, RC did not change relative to baseline (p = 0.87), but MC tended to decrease by 11% (p = 0.12). These results suggest a tradeoff between kinematic and muscular control of reaching. This new finding closely matches our previous work in 12 healthy controls, where we found a 2% increase in RC and a 11% decrease in MC. Importantly, 4/10 patients exhibited an inverse tradeoff (i.e., decrease in RC and/or increase in MC). We will analyze neuroimaging data to determine the role lesion size and location play in predicting an individual's response to gravity compensation. DISCUSSION/SIGNIFICANCE: Our tradeoff analysis serves as a potential neuromuscular biomarker of stroke survivors' responsiveness to gravity compensation. This forms the basis for personalized technologies for stroke rehabilitation. With further development, clinicians can use our platform to fine-tune compensation levels based on the individual needs of the patient.

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Translating a precision dosing approach for opioid use disorder in Puerto Rico: Pilot testing of the clinical utility and patient/provider acceptability

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OBJECTIVES/GOALS: The purpose of this pilot study is to evaluate the clinical utility and patient/provider acceptability of a buprenorphine (bup) precision dosing approach for opioid use disorder (OUD) in Puerto Rico (PR) to in estimate the most adequate bup dosing regimen based on the unique pharmacological and clinical characteristics of these patients. METHODS/STUDY POPULATION: The goal of this pilot study is to evaluate the extent to which people delivering (providers) or receiving (patients) opioid use disorder care in PR consider our 'bup precision dosing approach' to be appropriate, based on anticipated or experienced cognitive and emotional responses. We will use the Theoretical Framework of Acceptability (TFA) to conduct this evaluation. We expect to generate a baseline understanding of the acceptability

of our bup precision dosing approach in terms of clinical utility and attitudes by OUD patients and providers in clinics in PR, We will conduct focus groups and surveys to document patients and providers perceptions, beliefs, attitudes and reception of our bup evidence-based dosing approach. RESULTS/ANTICIPATED RESULTS: We seek to answer the following questions: How do OUD providers and patients in PR view, and how will they engage with our buprenorphine precision dosing approach? Will our intervention based in science be accepted be these individuals? What are their attitudes towards this? How they perceive the efficacy of this intervention to be? What are the barriers and facilitators of this evidence based intervention? This knowledge is crucial before clinical implementation is pursued, we expect to comprehend the unique attitudes and perceptions of these population that supports the successful implementation in the nearby future and enhance the innovation uptake of our bup dosing model for OUD in PR. DISCUSSION/SIGNIFICANCE: It is important that adequate assessments that assess acceptability and feasibility prior to implementation and while still in developmental phases are conducted to plan ahead for the implementation of interventions since innovation uptake depends largely on contextual factors, not just innovation effectiveness.

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Translation of novel multidisciplinary health technologies in the Ontario healthcare system: A case study of pharmacogenomic testing

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OBJECTIVES/GOALS: There is a need for high-quality and efficient translation of health technologies in the Ontario healthcare system. The goal of this project is to understand the decision-making processes of government expert groups developing recommendations for the system-level implementation of pharmacogenomic testing. METHODS/STUDY POPULATION: This prospective observational case study includes the Ontario Health Pharmacogenomics (PGx) Working Group focused on developing recommendations for a PGx testing implementation strategy in the province. Ontario Health is the government agency that oversees provincial healthcare planning and service delivery. Using qualitative ethnographic methods, we will observe and document the working group's activities over a 10-month period. Data collection involves meeting recordings, correspondences, researcher field notes, decision-making processes, and group characteristics. Using descriptive statistics and inductive qualitative analyses, the data will be examined to build theory and frameworks for knowledge translation. RESULTS/ANTICIPATED RESULTS: The results will be presented through a case report, process maps, decision milestones, visualizations, and procedural recommendations for future expert groups. This study will contribute to the body of foundational knowledge about translational sciences and support the National Center for Advancing Translational Sciences'guiding principles. To enhance translational processes and train the future translational workforce, this research can be used for educational initiatives. In addition, the observed processes will inform a theory about how expert recommendations are developed in public healthcare systems. DISCUSSION/SIGNIFICANCE: This research addresses a current gap in understanding around translational processes, government decision-making, and the development of recommendations for the adoption, implementation, and dissemination of the novel health technologies transforming public healthcare in Canada.

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Trends Between Periodontitis and Medial Arterial Calcification in Undiagnosed Type II Diabetes Mellitus.

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OBJECTIVES/GOALS: The overall objective of this study is to determine if medial arterial calcification (MAC) is an independent predictor of diabetes and to evaluate the relationship between MAC, periodontitis and Type II diabetes mellitus. METHODS/STUDY POPULATION: A retrospective case-control model analyzing radiographs for periodontitis and MAC to identify potential biomarkers for underlying systemic conditions, such as diabetes. Charts of patients attending UPENN School of Dental Medicine clinics between 2015 and 2022 were reviewed. Demographics, medical and dental history, diabetic status (identified by POC blood glucose level, fasting blood glucose and/or A1C), and medication history were documented amongst other variables. Patients aged 18 years or older with diabetes and having full mouth intraoral radiographs (FMX), panoramic radiographs and CBCTs were included. Patients with radiographs of poor quality were excluded. Multivariate analysis was used to determine possible associations between diabetes and periodontitis among persons with or without MAC. RESULTS/ANTICIPATED RESULTS: In our pilot study involving 28 participants, 53% of the population with moderate or severe periodontitis had MAC. By the Fisher's Exact Test, there was an association, meaning those with more periodontal disease are more likely to have MAC (p=0.014). Sixty-three percent of patients with diabetes had MAC, while 19% of patients without evidence of diabetes also had MAC, (p=0.067). There was not enough evidence of association between diabetes and presence of MAC at this time, due to a small sample size, however there was a high prevalence of MAC among the diabetics. We hypothesized that periodontitis, a condition that shares many risk factors with diabetes would also be associated with incident MAC. Findings from this study will be key for the implementation of preventive screening protocols and referral systems. DISCUSSION/SIGNIFICANCE: Diabetes is on the rise and about half of diabetics are undiagnosed. CBCT imaging frequently used in dentistry can detect incidental findings such as MAC. This study has the potential of detecting statistically significant links between MAC, periodontitis and diabetes, hence serving as a sensitive radiographic biomarker for diabetes.

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Unitary neural correlates of executive control in pediatric transdiagnostic psychopathology

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OBJECTIVES/GOALS: Childhood psychiatric symptoms are highly comorbid. Their co-occurrence and association with negative life