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End user feedback on the Revised Department of Defense (DoD) Progressive Return to Activity (PRA): Primary Care for Acute Concussion Management Clinical Recommendation (CR)

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OBJECTIVES/GOALS: The objectives of the study were to evaluate end-user feedback regarding usefulness and compliance with the revised DoD PRA-CR. The PRA-CR utilizes symptom-guided management strategies to advance service members with acute concussion through 6 stages of gradually increased activity prior to their Return to Duty (RTD). METHODS/STUDY POPULATION: Clinical providers previously trained on the PRA-CR were invited via email to participate in an online survey-based study to examine their opinions and utilization of the revised PRA-CR. Participants who responded to the initial email invitation were provided an electronic Microsoft Forms based survey. Of the 83 total responders, 36 met inclusion criteria and advanced to the end-user survey. Six items were designed to assess inclusion–exclusion criteria (i.e., credentialed medical provider trained in the PRA-CR with experience treating concussion over the previous 2 years). Four items gauging utilization required yes/no responses; 20 opinion items on a 7-point Likert scale ranged from strongly disagree to strongly agree; 5 explanatory items were multi-select; and 1 item allowed free text responses. RESULTS/ANTICIPATED RESULTS: Overall, 87% of respondents who had used the revised CR indicated that it helped them treat patients with acute concussion and 73% rated, "ease of use" favorably. Of the newly added elements to the CR, utilization of the Patient Leadership Guide (PLG) was the highest at 78%, with the majority of the providers rating the PLG as useful in communicating with patients and command. In contrast, only 35% of participants reported using the Physical RTD screening section and 22% indicated using the Cognitive RTD screening tool. Those not utilizing the Physical screening identified a lack of support staff (67%) or setting barriers (47%) as the primary reasons. Those not utilizing the Cognitive RTD screening tool identified multiple barriers to use including availability (72%), inexperience (39%), and baseline data access (33%). DISCUSSION/SIGNIFICANCE OF IMPACT: This study sought end-user (provider) feedback regarding the revised PRA-CR's usability and utility, in addition to their confidence in the tool itself. Overall results were generally positive, except for the updated Physical RTD and newly introduced Cognitive RTD screenings.

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Allogeneic recellularized lung orthotopic (ARLO) transplant research: A short-term non-survival model

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OBJECTIVES/GOALS: This study assesses the feasibility of a human-to-swine lung transplant model for the evaluation of bioengineered organs. Given the critical organ shortage, this research explores bioengineered organs as a potential solution by evaluating early lung function, immune responses, and technical aspects to develop a model for bioengineered lungs. METHODS/STUDY POPULATION: The study employs a non-survival human-to-swine left lung transplant model in an immunosuppressed Yorkshire swine. A combination of cobra venom factor pretreated with methylprednisolone and Benadryl with scheduled dosing of tacrolimus and mycophenolate over a 24-hour period will be administered. The transplanted human lung is assessed over a 24-hour post-transplant period, with hourly pulmonary vein gas sampling and lung tissue resections. The proposed model will assess the immunological response of swine to human lung tissue as well as the efficacy of the immunosuppression model. Tissue samples are taken at intervals to evaluate for signs of rejection, cellular damage, and the overall function of the transplanted lung. All tissues are preserved in formaldehyde for subsequent immunohistology evaluation. RESULTS/ANTICIPATED RESULTS: We anticipate a successful non-survival swine transplant model with pulmonary function sustained for the full 24-hour study using our proposed immunosuppression regimen. Initial testing with a standard human lung will lay the groundwork to assess the effectiveness of the human-to-swine transplant model. Hourly pulmonary vein gas analyses and tissue biopsies are expected to show minimal immune rejection, supported by the preoperative immunosuppression regimen. Early data indicate that the swine tolerates both the surgical procedure and immunosuppressive therapy well, with manageable hemodynamic stability. This model is expected to yield critical insights into lung viability and will identify areas for optimization for long-term survival studies to test the efficacy of bioengineered organs. DISCUSSION/SIGNIFICANCE OF IMPACT: This non-survival swine model offers valuable insights into the acute-phase immune response and functional viability of human-to-swine lung transplant model. The findings will support the development of long-term survival models that will allow the evaluation of bioengineered organs based solely on their functionality as engineered organs.

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Uncovering an unexpected therapeutic target for motivational deficits following early-life exposure to SSRIs

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OBJECTIVES/GOALS: Motivational deficits are associated with depression and poorly treated by current therapeutics. We sought to identify more effective therapeutics for these deficits using a mouse model of early-life exposure to SSRIs, a developmental risk factor identified for depression in humans. METHODS/STUDY POPULATION: Mice were administered the SSRI, fluoxetine (FLX), or a vehicle control from postnatal day P2-P11, a window that mimics brain development occurring during the third trimester in a human pregnancy. Motivation and hedonic perception were assessed in adulthood using the progressive ratio and lickometer tasks, respectively. Behavioral testing was repeated after chronic adult administration of either an SSRI (fluoxetine), an atypical antidepressant and mu-opioid receptor agonist (tianeptine), or a mu-opioid receptor antagonist (methocinnamox). RESULTS/ANTICIPATED RESULTS: Mice administered FLX in early-life showed motivational deficits in the progressive ratio task, while hedonic perception, as measured by the lickometer task, remained intact. Chronic

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administration of FLX in adulthood did not improve motivational deficits and did not alter hedonic perception. Chronic administration of tianeptine (TIA) slightly improved motivational behavior without altering hedonic perception. In contrast, chronic administration of the mu opioid antagonist methocinnamox (MCAM) markedly improved motivational deficits in mice, even while blunting hedonic perception. The ability of MCAM to enhance motivation was selective to early-FLX exposed mice DISCUSSION/SIGNIFICANCE OF IMPACT: Our results reveal that unexpectedly opioid receptor antagonism is effective at improving motivation in mice exposed to SSRIs in early life. This suggests potential novel treatment approaches in individuals with motivational impairments and a history of in utero exposure to SSRIs.

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Xylazine quantitation in Puerto Rican drug users and cardiotoxic protein markers profile expression analysis

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OBJECTIVES/GOALS: Our research addresses critical gaps by examining the prevalence, blood concentrations, and health implications of xylazine abuse, with a focus on its cardiotoxic effects. We aim to map the geographic distribution of xylazine use across Puerto Rico and characterize its impact on cardiomyocytes at relevant exposure levels. METHODS/STUDY POPULATION: To accurately detect and quantify xylazine in blood samples, we will employ chromatographic techniques coupled with mass spectrometry (UPLC/MS or GC/MS). The xylazine prevalence across the island will be mapped based on health system classifications. Samples will be categorized according to the eight healthcare regions of Puerto Rico, as defined by the "Administración de Seguros de Salud" (ASES), ensuring comprehensive geographic representation. We will investigate the expression profiles of proteins associated with cardiac injury and dysfunction in human cardiomyocytes and in the blood of drug users. Blood samples will be provided by "Iniciativa Comunitaria." We will assess the xylazine effects on human cardiomyocyte viability and identify key biomarkers of cardiotoxicity induced by xylazine exposure. RESULTS/ANTICIPATED RESULTS: In previous research, we demonstrated that xylazine induces cell death in endothelial cells through both extrinsic and intrinsic pathways. We also observed an increase in reactive oxygen species (ROS) levels after drug exposure, indicating oxidative stress as a potential mechanism of toxicity. Additionally, DNA damage was detected. Given the known relationship between endothelial damage and cardiomyocyte dysfunction in drug-induced cardiotoxicity, we hypothesize that xylazine concentrations vary regionally within Puerto Rico and that chronic xylazine abuse will elevate markers of cardiac injury and dysfunction at common user doses. DISCUSSION/SIGNIFICANCE OF IMPACT: The increasing xylazine abuse, particularly in Puerto Rico, represents a critical public health challenge. Our study will fill a knowledge gap by providing crucial data on xylazine's cardiotoxicity and mapping its geographic prevalence, with the potential to advise healthcare approaches and improve care for drug-using Hispanic populations.

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Elucidating the role of the rete ovarii in fertility and progesterone signaling

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OBJECTIVES/GOALS: The goal of this study is to determine the function of the rete ovarii (RO), an uncharacterized secretory epithelial appendage to the ovary. I am testing the hypothesis that the RO is critical for the maintenance of the ovarian reserve and fertility, and progesterone signaling plays a role in the function of the RO. METHODS/STUDY POPULATION: For this project, I am utilizing a mouse model. To visualize the rete ovarii (RO) in vivo, I am using a Pax8rtTA; TRE-H2B-Gfp (PTG) reporter mouse, which expresses green fluorescent protein in the RO. To determine the role of the RO in fertility and maintenance of the ovarian reserve, I will surgically ablate the RO or perform a sham surgery on adult female PTG mice. Then, I will follow-up with quantification of the ovarian reserve and long-term fertility tracking studies. To determine how the RO responds to progesterone, the RO will be cultured ex vivo in the presence and absence of progesterone. I will perform a morphometric analysis of the RO, as well as collect secreted proteins from the media for proteomic analysis. RESULTS/ANTICIPATED RESULTS: If the RO is important for ovarian homeostasis, I expect that in the absence of the RO, ovarian functions such as maintenance of the ovarian reserve and fertility will be impaired. Additionally, because the RO expresses progesterone receptors, I anticipate that the RO will be responsive to progesterone as shown in changes in the morphometric analysis and in changes in secreted proteins in the presence of progesterone. DISCUSSION/SIGNIFICANCE OF IMPACT: A major gap in knowledge regarding female physiology and reproductive health is the role of the RO. We expect this work to reveal that progesterone signaling in the RO is important for regulating ovarian functions and to show that the RO is a critical modulator of female fertility and reproductive function.

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Biomarkers for HIV neutralization breadth development in early life

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OBJECTIVES/GOALS: A key strategy in generating a protective HIV vaccine is the elicitation of broadly neutralizing antibodies (bnAbs), capable of neutralizing a large diversity of HIV-1 isolates. The goal of this study is to identify molecular signatures of HIV bnAb development early in life, to guide the development of a successful pediatric HIV vaccine strategy. METHODS/STUDY POPULATION: We previously defined HIV neutralization breadth in 40 ART-naive children living with HIV. Single-cell RNAseq was performed utilizing peripheral blood mononuclear cells (PBMCs) from the top 5 children with highest neutralization breadth scores and compared their transcriptome to that of PBMCs from 5 children that did not develop neutralization breadth within the first three years of life. Additionally, we incorporated analysis of PBMCs from 5 healthy uninfected children, matched to our experimental groups by race,

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