SD=0.7). DISCUSSION/SIGNIFICANCE OF IMPACT: Baseline HbA1c, DDFF, and DSGMH were important predictors of subgroups of patients defined by 12m HbA1c. Psychosocial variables were important predictors beyond demographic and clinical variables. Clinicians and researchers may wish to target interpersonal aspects of diabetes distress and strengths in work with young adults with T1D.

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Normatively modeled cortical thickness deviation profiles in antipsychotic-naïve first-episode psychosis patients

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OBJECTIVES/GOALS: Biological heterogeneity within psychosis spectrum disorders has proven to be a major obstacle in identifying reproducible pathophysiologic markers of disease. Here, we used normative modeling to assess cortical thickness deviations at the individual level. We then grouped patients into subgroups based on number of deviations. METHODS/STUDY POPULATION: T1 MPRAGE scans from 113 antipsychotic-naive first-episode psychosis patients were normatively modeled as well as 397 unrelated individuals from HCP Young Adult. The patients were subdivided by whether they had a greater than expected number of large deviations in cortical thickness across all regions by comparing norms established in the HCP dataset. RESULTS/ANTICIPATED RESULTS: We identified four distinct subgroups of patients who more commonly share spatial deviation patterns compared to the overall group. The positive deviation subgroup, negative deviations subgroup, and both positive and negative deviations subgroups were larger in the first-episode psychosis sample than would be predicted from the healthy control data. DISCUSSION/SIGNIFICANCE OF IMPACT: Our data provide further evidence for the existence of subtypes of psychosis spectrum disorder that differ in patterns of cortical thickness, specifically a subtype with increased cortical thickness. Normative modeling approaches might constitute an important step toward precision psychiatry.

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Evaluating the microbiome–immune crosstalk as a driver of inflammation in primary ciliary dyskinesia

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OBJECTIVES/GOALS: To examine gut microbiome–immune interactions that may contribute to respiratory dysfunction in Puerto Rican patients with primary ciliary dyskinesia (PCD), aiming to identify novel biomarkers that inform targeted interventions and address health disparities in rare diseases. METHODS/STUDY POPULATION: This cross-disciplinary pilot study integrates clinical, genomic, and microbiome data from patients with PCD carrying the Puerto Rican RSPH4A founder variant (c.921+3_6delAAGT; n = 8) and healthy controls (n = 8). Fecal samples will undergo 16S rRNA V4 sequencing and bioinformatic profiling using QIIME2, ANCOM, and PICRUSt2. Plasma cytokines (IL-6, IL-8, TNF-α, and IL-10), CRP, and ESR quantify systemic inflammation, while pulmonary tests (FEV_1 and FVC) will assess lung function. Correlation analyses will define microbial taxa linked to inflammatory and respiratory outcomes, elucidating the role of the gut–lung axis in disease progression. RESULTS/ANTICIPATED RESULTS: We anticipate reduced microbial diversity and enrichment of pro-inflammatory taxa (e.g., Bacteroides and Prevotella) in PCD participants. Microbial shifts are expected to correlate with elevated inflammatory cytokines and decreased lung performance. These findings will highlight gut dysbiosis as a modifiable driver of inflammation, offering a foundation for future translational interventions such as diet or probiotic therapies. DISCUSSION/SIGNIFICANCE OF IMPACT: This study advances precision medicine for rare lung diseases by elucidating gut–lung axis mechanisms in a genetically defined Puerto Rican PCD cohort, generating foundational data for future microbiome-targeted therapies and strengthening Puerto Rico's translational research capacity.

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Exposure therapy for anorexia nervosa: Targeting weight gain anxiety as a treatment mechanism

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OBJECTIVES/GOALS: Treatments for adults with anorexia nervosa (AN) are inadequate, with no FDA-approved medications and only 30% achieving remission in psychotherapy trials. This ongoing KL2-funded pilot study evaluates Exposure Therapy for AN (Exp-AN), which targets anxiety about weight gain – a key mechanism maintaining AN. METHODS/STUDY POPULATION: Preliminary results (target N=16) include six adults (100% female, 83% White, 17% Black, ages 18–24, mean=20.5 years) with AN or atypical AN who have completed Exp-AN, a standardized 20-session outpatient therapy delivered in both in-person and virtual formats over 20 weeks. Exp-AN combines *in vivo* (e.g., stepping on a scale) and imaginal (e.g., listening to scripts about catastrophic weight gain) exposures to challenge anxious beliefs and enhance tolerance related to weight gain. Measures assessing treatment acceptability, AN symptomatology, and anxiety about weight gain were administered at baseline and end-of-treatment. Mean scores and effect sizes were calculated and compared to predetermined benchmarks to evaluate preliminary signals of acceptability, efficacy, and target engagement. RESULTS/ANTICIPATED RESULTS: On two acceptability items (scale: 1="not at all" to 7="extremely"), participants rated Exp-AN as 5.8/7 on helpfulness and 6.3/7 on logic, meeting our 5/7 benchmark. All within-subjects effect sizes (Cohen's d from paired samples t-tests) met our benchmark for large effects (d≥0.8),

https://doi.org/10.1017/cts.2026.10588 Published online by Cambridge University Press

indicating improvements from baseline to end-of-treatment in: AN symptomatology (d=1.37), anxiety ratings about weight gain (d=1.22), anxious beliefs about weight gain (d =1.06), and tolerance of weight gain (d=1.40). Pearson's correlations exploring whether changes in weight gain anxiety were associated with AN symptom improvement met our benchmark (r≥0.5) for anxiety ratings (r=0.55) and anxious beliefs (r=0.65), but not tolerance of weight gain (r=0.18). DISCUSSION/SIGNIFICANCE OF IMPACT: Results support Exp-AN's acceptability and preliminary efficacy. Reductions in weight gain anxiety correlated with symptom improvement, suggesting target engagement. By targeting specific mechanisms, this work advances precision medicine and treatment optimization. Findings warrant a fully powered randomized controlled trial.

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Exploiting global viral immunity to develop a novel viro-immunotherapy using oncolytic viruses and CAR T-cells for hepatocellular carcinoma

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OBJECTIVES/GOALS: Hepatocellular carcinoma (HCC) is a therapeutic challenge due to poor tumor immunogenicity, low endogenous T cell response, and a complex tumor microenvironment (TME). We propose an immunotherapeutic strategy leveraging widespread antiviral immunity – particularly memory T cells against SARS-CoV-2 spike (SPIKE) – to redirect T cells into tumors. METHODS/STUDY POPULATION: By engineering oncolytic viruses (OV) to express SPIKE, the approach aims to recruit virus-specific T cells and re-activate them through viral boosting, enhancing tumor clearance. This has been successfully shown in a B-16 melanoma model, another solid tumor system. We will also develop a dual-specific CAR T cell platform against SPIKE and GPC3, the most common HCC tumor-associated antigen (TAA), enabling antitumor targeting which can also benefit from OV readministration. The experimental plan includes purification and titration of a single-cycle adenovirus expressing SPIKE (SC-Ad-SPIKE), infection of murine and human HCC cell lines to validate SPIKE expression and replication, and *in vivo* treatment of subcutaneous or orthotopic murine tumors in pre-immunized or naïve mice using OV. RESULTS/ANTICIPATED RESULTS: This strategy offers a translatable platform to re-focus existing antiviral memory toward otherwise weakly immunogenic tumors like HCC, potentially enhancing clinical efficacy through oncolytic virotherapy and CAR T cell engineering. We should see better average tumor clearance and survival in the groups treated with the OV and CAR T against SPIKE than controls with only GPC3 given the lack of reliance on tumor-GPC3 expression. DISCUSSION/SIGNIFICANCE OF IMPACT: Our approach could be crucial for patients given how varied current responses are to available therapies. The combination of a generalized OV therapy and a more targeted CAR T provides a promising new solution to the current unmet need of many HCC patients globally.

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Arousability from sleep as a multidimensional construct: Cross-sectional analysis and machine-learning based feature selection*

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OBJECTIVES/GOALS: To develop and assess a multidimensional measure of arousability by integrating respiratory, autonomic, cortical, and movement-related events and to identify sex-specific arousal phenotypes using clustering analyses and LASSO-based machine learning for feature selection and model optimization. METHODS/STUDY POPULATION: We will conduct a retrospective cross-sectional analysis using sleep and clinical data from >10,000 adults in three different cohorts. Arousability will be defined by event-level metrics across respiratory, autonomic, cortical, and movement domains. Variable clustering will be used to construct a multidimensional composite index of arousability based on those domains. Generalized linear models will test sex differences in individual metrics composite indices. LASSO regression will be applied to select arousability features most predictive of sex, mortality, and cardiovascular disease (CVD). RESULTS/ANTICIPATED RESULTS: We anticipate identifying distinct arousability dimensions and sex-specific arousal profiles. Women are expected to show greater non-respiratory arousals, while men will show higher respiratory-related arousals. The resulting multidimensional index will capture arousal burden more comprehensively than traditional metrics like the apnea–hypopnea index. This will aid in understanding sex-based difference of sleep fragmentation, as well as understanding the sleep mechanisms most associated with mortality and CVD. DISCUSSION/SIGNIFICANCE OF IMPACT: This study will advance precision sleep medicine by developing a multidimensional, data-driven arousability index and identifying sex-specific

https://doi.org/10.1017/cts.2026.10588 Published online by Cambridge University Press