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Diverse Role of blaCTX-M and Porins in Mediating Ertapenem Resistance Among Carbapenem Resistant Enterobacterales

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OBJECTIVES/GOALS: In this study, we aim to report the role of porins and bla_{CTX-M} β-lactamases among Escherichia coli and Klebsiella pneumoniae, focusing on emerging carbapenem resistant Enterobacterales (CRE) subtypes, including non-carbapenemase producing Enterobacterales (NCPE) and ertapenem-resistant but meropenem-susceptible (ErMs) strains. METHODS/STUDY POPULATION: Whole genome sequencing was conducted on 76 carbapenem-resistant isolates across 5 hospitals in San Antonio, U.S. Among these, NCP isolates accounted for the majority of CRE (41/76). Identification and antimicrobial susceptibility testing (AST) results were collected from the clinical charts. Repeat speciation was determined through whole genome sequencing (WGS) analysis and repeat AST, performed with microdilution or ETEST®. Minimum inhibitory concentrations (MIC) were consistent with Clinical and Laboratory Standards Institute (CLSI M100, ED33). WGS and qPCR were used to characterize the resistome of all clinical CRE subtypes, while western blotting and liquid chromatography with tandem mass spectrometry (LC-MS-MS) were used to determine porin expression and carbapenem hydrolysis, respectively. RESULTS/ANTICIPATED RESULTS: $bla_{CTX-M}$was found to be most prevalent among NCP isolates ($p = 0.02$). LC-MS/MS analysis of carbapenem hydrolysis revealed that bla_{CTX-M}-mediated carbapenem hydrolysis, indicating the need to reappraise the term, "non-carbapenemase (NCP)®" for quantitatively uncharacterized CRE strains harboring bla_{CTX-M}. Susceptibility results showed that 56% of all NCPE isolates had an ErMs phenotype (NCPE vs. CPE, $p < 0.001$), with E. coli driving the phenotype (E. coli vs. K. pneumoniae, $p < 0.001$). ErMs strains carrying bla_{CTX-M}, had 4-fold more copies of bla_{CTX-M} than ceftriaxone-resistant but ertapenem-susceptible isolates (3.7 v. 0.9, $p < 0.001$). Immunoblot analysis demonstrated the absence of OmpC expression in NCP-ErMs E. coli, with 92% of strains lacking full contig coverage ofompC. DISCUSSION/SIGNIFICANCE: Overall, this work provides evidence of a collaborative effort between bla_{CTX-M} and OmpC in NCP strains that confer resistance to ertapenem but not meropenem. Clinically, CRE subtypes are not readily appreciated, potentially leading to mismanagement of CRE infected patients. A greater focus on optimal treatments for CRE subtypes is needed.

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Associations with gene-transcript expressions in cocaine use disorder reveal genetic predispositions with other substance use and cardio-neurovascular disease.

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OBJECTIVES/GOALS: Using biomarkers to identify vulnerabilities from cocaine use disorder (CUD) is a focus of recent investigations. Current clinical efforts focus on psychiatric recovery in CUD, however other body systems are missed. Applying blood-based transcriptomics to investigate how clinical conditions relate to CUD can alter current treatment approaches. METHODS/STUDY POPULATION: We conducted a comprehensive longitudinal study of 12 individuals (mean 53 yrs.; M/F ratio 9: 3) with CUD abstinent from cocaine. 44 blood samples collected repeatedly every 3 months for 9 months were bulk RNA sequenced. We began with phenotype harmonization grouping individuals with the following metrics; cocaine withdrawal, cue craving, generalized craving, perceived stress, and days of abstinence. We ran differential gene and transcript expression with time across grouping of metrics using the dream software and used the multivariate test to examine their associations. We used the association of gene-transcripts to determine genetic predispositions with clinical traits using the Multi-marker Analysis of GenoMic Annotation assessing their overlap to a reference GWAS database. RESULTS/ANTICIPATED RESULTS: Individuals were grouped in 2 clusters based on scores of cue craving, generalized craving, cocaine withdrawal, and 3 clusters based on days of abstinence from cocaine use. Gene-transcript(s) associationsrevealed genetic predisposition towards certain clinical conditions and substance use traits. Cannabis use disorder showed significant enrichment between the greater vs. lesser abstinent days, and lesser vs. least abstinent days at 9 months. The "drinks per week" trait showed significant gene enrichment between greater vs. lesser abstinent days at 9 months. Coronary artery disease was also enriched with greater vs. least abstinent days at 3 months. Lastly, significant baseline differences in predisposition to small vessel ischemic stroke were seen in responders with high vs low perceived stress. DISCUSSION/SIGNIFICANCE: These results from a robust and feasible pipeline suggest genetic predisposition in CUD for other substances and cardio-neurovascular

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diseases. This pilot study may lead to larger studies into whole genome-based blood biomarker approaches for monitoring abstinence and other clinical co-morbidities to be addressed in cocaine addiction recovery.

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Using Computer Vision and Wearable Devices to Improve Care of Parkinson's Disease

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OBJECTIVES/GOALS: Inexpensive, accurate home monitoring is the standard-of-care in many diseases like hypertension or diabetes; however, it has yet to be widely used in neurodegenerative diseases. We used wearable activity monitors and computer-vision evaluated assessments to estimate Parkinson's disease (PD)-related disease burden. METHODS/STUDY POPULATION: We recruited 22 people from the University of Iowa Movement Disorders Clinic. Each person completed a standardized set of 3 fine motor tasks using their hands. We recorded a video of this activity, which was evaluated using MediaPipe - an open-source pose classification program from Alphabet - as well as had an nurse-practitioner evaluate the performance on a validated scale (UPDRS). Participants wore a Fitbit Inspire 3 activity tracker at home for the next two weeks. We quantified disease burden using the Parkinson's Disease Questionnaire 39 - a validated 39-item survey about the intensity of PD-related impairment. Using data from the videos and activity trackers, we estimated 1) the standardized UPDRS assessment of motor impairment and 2) the total PDQ-39 score. RESULTS/ANTICIPATED RESULTS: We found observationally recorded fastest sustained (at least 5 minutes) walking speed was a strong predictor of PDQ-39, explaining over one third of the variability in the measure. Range of motion in the videos was a significant predictor of UPDRS scores; however, was only weakly related to the overall PDQ-39 score. Further processing of the signals from the video, including wavelets and frequency domain analysis, may provide better predictive capabilities. PDQ-39 subscores (e.g., cognition, social support, mobility) will be the subject of further analysis. DISCUSSION/SIGNIFICANCE: Home monitoring has become the standard in other fields because of the better generalizability of home measurements. Improving the detection and evaluation of PD using home monitoring will lead to more timely and accurately changes in medication and less need for clinic visits - especially off levodopa.

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Utility of [89Zr]Trastuzumab-PET/MRI Imaging for Quantitative Assessment of Tumor Heterogeneity In HER2+ Breast Cancer

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OBJECTIVES/GOALS: This study was performed to explore the capabilities of simultaneous [89 Zr]trastuzumab-PET/MRI acquisition in a cohort of metastatic HER2+ breast cancer. The insights derived provide additional noninvasive characterization and precise intratumoral analysis tools for healthcare providers. METHODS/STUDY POPULATION: A total of 13 patients, aged between 40 and 70, diagnosed with HER2-positive breast cancer, were selected to participate in this study. Whole-body [89 Zr]trastuzumab-PET/MR imaging was performed 5 ± 1 days post-injection of the radiopharmaceutical during ongoing HER2-directed therapy. Concurrently acquired T1-weighted MRI facilitated the identification of normal organ and tumor regions of interest, which were further analyzed for mean ADC and mean standardized uptake value. Multiparametric intratumoral habitat analysis was performed. Utilizing the median metric values, tumors were evaluated for heterogeneity, specifically assessing high and low HER2 expression through an image processing framework in conjunction with ADC metrics. Long-term treatment response evaluation is ongoing. RESULTS/ANTICIPATED RESULTS: Initial analysis indicate all tumors exhibited higher overall uptake of [89 Zr]trastuzumab across various sites including the bone (p=0.019), brain (p=0.014), and breast (p=0.069), when compared to corresponding normal organs. Additionally, increased ADCmean values were observed in all regions besides brain tumors (bone: p=0.002, brain: p=0.5, breast: p=0.03, juxtapulmonary: p=0.037), indicating distinct patterns of cellularity. Notably, one of five patients with a breast lesion, who exhibited a complete response to HER2-targeted therapy, exhibited the highest breast lesion SUVmean. Brain and lymph node lesions demonstrated intratumoral heterogeneity of HER2 expression. Qualification of multi parametric maps is anticipated to inform on intratumoral heterogeneity DISCUSSION/SIGNIFICANCE: Despite limitation in clinical applications of quantitative approaches due to lack of standardization of processing, initial investigations, in combining molecular imaging of HER2 and quantitative MRI demonstrate potential in characterizing metastatic HER2+ breast cancer for intratumoral classification and therapeutic stratification.

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Application of human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) for modeling of Ankyrin-2 p.R990Q variant-induced ventricular arrhythmia and personalized medicine

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OBJECTIVES/GOALS: The cytoskeletal protein α^2II spectrin interacts with actin and ankyrin-2 in cardiomyocytes which is essential to orchestrate ion channels and membrane proteins in the cardiac dyad. Our goal is to understand molecular mechanism causing severe ventricular arrhythmias due to spectrin dysfunction and explore novel therapies to treat such conditions. METHODS/STUDY POPULATION: We previously published a case of a 36-year-old woman with an ankyrin-2 p.R990Q (ANK2) variant, presented with severe ventricular arrhythmias and sudden cardiac arrest, caused by a novel mutation in the ankyrin-B gene (c.2969G>A) that disrupts the interaction of ankyrin-B/βII spectrin. To model the condition, we will use human induced pluripotent stem cell (DF 19-9-7T, WiCell)-derived ventricular cardiomyocytes (iPSC-CMs) having ANK2 variant, engineered using CRISPR/Cas9 method (Synthego Corp.). We will validate the differentiation of iPSCs into ventricular lineage and characterize the ANK2 ventricular phenotype. Next, we will express light-gated cation channel Channelrhodopsin (ChR2) in the ANK2 iPSC-CMs and investigate the potential role of

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