SIGNIFICANCE OF FINDINGS: The lack of knowledge of pharmacogenomic variation in African populations contributes to ethnic disparities in patient outcomes. This study addresses this gap by adding to our comprehension of variants in clinically relevant genes, giving insight into underlying mechanisms of ethnicity-based drug responses.

74325

Vast sex-specific differences in transcriptional landscapes of pancreatic neuroendocrine tumors*

Nikolay A. Ivanov, Thomas J. Fahey III, Christopher E. Mason and Irene M. Min
Weill Cornell Medicine

ABSTRACT IMPACT: Here, we describe extensive sex-specific differences in the transcriptomes of pancreatic neuroendocrine tumors (PNETs). Given that the clinical course of PNETs differs by sex (female sex is associated with better survival), achieving a greater understanding of the specific molecular sexual dimorphisms is invaluable for advancing personalized treatment. OBJECTIVES/GOALS: Epidemiologic studies demonstrate that pancreatic neuroendocrine tumors (PNETs) exhibit sexual dimorphisms with regards to prognosis, disease recurrence, and complication rates. We sought to compare the transcription and DNA methylation landscapes of PNETs by sex, to elucidate molecular differences that may underlie this sex disparity. METHODS/STUDY POPULATION: RNAseq data was generated from PNETs surgically resected at our institution (9 Female; 12 Male patients). RNA was extracted with the RNeasy Mini Kit, stranded sequencing libraries were prepared with TruSeq, and paired end sequencing was done on the HiSeq 2500/4000 systems. Transcript-level quantification was performed with salmon, and DESeq2 was used for differential expression analysis. To account for significant variation due to covariates other than sex, surrogate variables were computed with the SVA package and adjusted for. The goseq package was used for gene set over representation analysis. Matched DNA methylation (DNAm) and RNAseq data was downloaded from GEO (16 F; 16 M). Raw DNAm data was processed with minfi. Differential methylation analysis was done with limma and bumphunter. Analysis was done in R. RESULTS/ANTICIPATED RESULTS: We found that 826 autosomal genes were differentially expressed (DE) by sex in PNETs (at FDR $\leq$0.1). Gene set over representation analysis performed on the DE genes revealed significant enrichment for several processes, including 'ascorbate & aldarate metabolism' and 'positive regulation of ERK1 & ERK2 cascade' (all FDR $\leq$0.1). When we compared DNAm profiles between sexes, we found 8 CpGs which were differentially methylated by sex (at FDR $\leq$0.1), 7 of which were proximal to genes. Methylation of one of the sex-associated CpGs, overlapping the gene TIMM8B, was found to be negatively correlated with gene expression (rho=-0.41; p-value=0.02). Interestingly, TIMM8B deletion has been previously reported in other non-pancreatic neuroendocrine tumors. There were no differentially methylated regions between sexes. DISCUSSION/SIGNIFICANCE OF FINDINGS: Our findings demonstrate that PNETs exhibit extensive sexual dimorphisms with regards to gene expression profiles but have largely congruent methylomes by sex. These molecular differences may contribute to the variability in clinical course between men and women, and their characterization is vital for the advancement of personalized medicine.

Dissemination and Implementation

82786

Quantification of the Accuracy of Stereotactic Radiosurgery using Surface Guided Imaging with 3D Printed Head Phantoms

Victoria Bry[1], Daniel Saenz[1], Evangelos Pappas[2],Niko Papanikolaou[1] and Karl Rasmussen[1]
[1]The University of Texas Health at San Antonio; [2]University of West Attica

ABSTRACT IMPACT: This work assesses clinical implementation of a surface guided imaging system to improve the accuracy radiation delivery for treatment of brain lesions using a patient CT derived head phantom. OBJECTIVES/GOALS: Advancements in radiotherapy design have made clinical demand for efficient and accurate methods to deliver stereotactic radiosurgery (SRS) for treatment of intracranial lesions. This study assesses the potential of using surface guided imaging for setup using a 3D patient specific head phantom. METHODS/STUDY POPULATION: A single isocenter, multiple metastases SRS plan was generated on a CT derived RTsafe Prime phantom made of tissue equivalent materials and a polymer gel insert. Five targets of varying diameters were treated with 8Gy of radiation using two different positioning techniques. The first gel insert was irradiated within the phantom according to internal alignment with standard orthogonal x-ray imaging while the second setup used surface guided imaging, based on external anatomy. 42 hours after irradiation, the phantom was scanned in a head coil using a 1.5T MRI. MR images were fused with the patient CT data and structure set to further evaluate calculated and measured dose distributions. RESULTS/ANTICIPATED RESULTS: Discrepancies in phantom setup according to standard orthogonal x-ray imaging compared to surface guided imaging demonstrated to be <1mm in each translational (vertical, longitudinal, and lateral) and angular (rot, roll, pitch) directions. The 3D gel inserts permitted spatial analysis to compare dose distributions of measured values to those calculated in a treatment planning system (TPS). 3D GI (Gamma Index) analysis showed good alignment in high dose regions and resulted in passing rates >94% (5%/2mm) and >87% (3%/2mm). Finally, 3 of 5 targets showed better 3D GI passing rates and less geometric offset for positioning with the surface guided imaging. DISCUSSION/SIGNIFICANCE OF FINDINGS: 3D spatial analysis of human like phantoms demonstrated that patient positioning according to external anatomy performed comparable to standard methods aligning to the internal anatomy, for a multiple met SRS treatment.

97856

Implementation of DPYD and UGT1A1 pharmacogenetic testing to guide chemotherapy dosing

Lisa A. Varughese[1], Kelsey S. Lau-Min[1], Ursina Teitelbaum[1], AnnaClaire Osei-Akoto[1], Nandi Reddy[2], Nevena Damjanov[1], Ryan Massa[1] and Sony Tuteja[1]
[1]University of Pennsylvania; [2]Penn Medicine at Lancaster General Health

ABSTRACT IMPACT: The implementation of DPYD and UGT1A1 pharmacogenetic testing, a promising tool of precision medicine,

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translates evidence-based research into clinical oncology practice with personalized dosing to better predict interpatient variability in chemotherapy tolerability. OBJECTIVES/GOALS: Patients with DPYD and UGT1A1 genetic variants are at risk for severe toxicity from fluoropyrimidines and irinotecan, respectively. We propose that providing clinicians with the option to order a pharmacogenetic (PGx) test with relevant dose recommendations will increase test uptake to guide pharmacotherapy decisions and improve safety outcomes. METHODS/STUDY POPULATION: We plan to conduct a non-randomized, pragmatic, open-label study in 600 adult patients with gastrointestinal (GI) cancers initiating a fluoropyrimidine- and/or irinotecan-based regimen at three cancer centers within a health system. Implementation metrics of a new, in-house laboratory developed PGx test will be measured, including feasibility of returning results within one week, fidelity of providers following dose recommendations, and penetrance via test ordering rates. Clinical aims will include assessing severe toxicity during the first six months of chemotherapy. Outcomes will be compared to a historical control of GI cancer patients enrolled in a biobank and treated with standard dose chemotherapy. RESULTS/ANTICIPATED RESULTS: We anticipate that there will be an increase in PGx test uptake given its shorter turnaround time to facilitate clinical decision-making prior to the first dose of chemotherapy. Through integration of test results in the electronic health record (EHR) and clinical decision support tools for patients with actionable genotypes, we also expect that providers will have a high level of agreement to the recommended dose adjustments. We anticipate a decreased incidence of severe (Grade >3) toxicity among prospectively genotyped patients in the first six months of chemotherapy compared to DPYD and UGT1A1 variant carriers in the historical control group. Exploratory clinical utility data on costs of hospitalizations, chemotherapy treatment, PGx test, and medical services will also be reported. DISCUSSION/SIGNIFICANCE OF FINDINGS: This study aims to address barriers identified by key stakeholders to implementing PGx testing to better tailor chemotherapy dosing to the genetic profiles to patients. This may prevent adverse event-related hospitalizations, improve quality of life for patients, and reduce health system resource utilization costs.

Evaluation

77680

Nasal Nitric Oxide Levels as a Diagnostic Tool for Primary Ciliary Dyskinesia in Puerto Rico

Wilfredo De Jesus Rojas MD, FAAP[1], Evangelia Morou-Bermudez, DDS, PhD[2], Valerie Wojna, MD[3], Simon Carlo, MD[4], Ricardo Mosquera, MD[5]

[1]University of Puerto Rico, Medical Sciences Campus, School of Medicine, Department of Pediatrics; [2]University of Puerto Rico, Medical Sciences Campus, School of Dental Medicine; [3]University of Puerto Rico, Medical Sciences Campus Department of Internal Medicine; [4]Ponce Health Science University School of Medicine; [5]Department of Pediatrics, University of Texas Health Science Center, Houston Medical School, Houston, Texas

ABSTRACT IMPACT: The implementation of nasal nitric oxide (nNO) as a diagnostic tool to understand the phenotypic/genotypic profiles of Primary Ciliary Dyskinesia (PCD) in Puerto Rico (PR) will be translated in early disease diagnosis, avoidance of comorbidities, and increase survival in our population. OBJECTIVES/GOALS: This study aims to evaluate the role of nNO levels in PCD diagnosis in the Puerto Rican population. Also, we aim to describe the clinical, genetic, and physiological characteristics of PCD in Puerto Ricans to develop a better understanding of the disease. METHODS/STUDY POPULATION: We plan to conduct a cross-sectional study on participants recruited from patients of the Pediatric Rare Lung and Asthma Institute in PR. We will compare nNO levels among genetically confirmed PCD patients, suspected PCD patients with variant of unknown significance (VUS) mutations, suspected PCD patients without genetic mutations, and age-matched healthy subjects. We plan to analyze clinical data and genetic variants to understand the natural history of the disease. The nNO measurements will be completed following previous published protocols. We will also assess the accuracy of the nNO measurements by repeating the measurements two weeks after the initial measurement. RESULTS/ANTICIPATED RESULTS: We hypothesize that many of the VUS present in our population may represent potential new founder mutations not previously reported in the literature. Our expectation is to identify new atypical PCD phenotypes contemplating the heterogenous genetic Puerto Rican pool. We anticipate that nNO levels will help to screen, identify, and confirm diagnosis of patients with clinical PCD in PR. Our findings will be translated in avoidance of further comorbidities and mortality due to earlier disease PCD diagnosis and will expand our genetic understanding about PCD in PR and other diverse populations with heterogenous genetic admixture. DISCUSSION/SIGNIFICANCE OF FINDINGS: We present a significant and novel research proposal that plan to impact the quality of life of patients living with PCD in PR. The implementation of state-of-the-art diagnostic tools like nNO measurement will positively impact and expand our current capabilities to diagnose rare lung diseases like PCD on the island.

Health Equity & Community Engagement

27416

DNA Methylation Age Acceleration and Depressive Symptoms in African American Women with Cardiometabolic Conditions†

Nicole Perez[1], Allison Vorderstrasse[2], Gary Yu[1] and Jacquelyn Taylor[3]

[1]New York University; [2]University of Massachusetts at Amherst; [3]Columbia University

ABSTRACT IMPACT: This study deepens knowledge with respect to the associations between depression, cardiometabolic conditions, and accelerated aging with a clinically accessible marker in a population with disproportionate risk for comorbidity. OBJECTIVES/GOALS: The aim of this secondary analysis is to examine associations between DNA methylation age acceleration (DNAm AA) and depressive symptoms in African American women (AAW) considering the presence of cardiometabolic conditions (CMCs) including hypertension, diabetes, obesity. METHODS/STUDY POPULATION: Genomic and longitudinal clinical data (collected 2015-2020) from the Intergenerational Impact of Genetic and Psychosocial Factors on Blood Pressure Study (InterGEN) cohort (n=227) were utilized for this analysis. DNA methylation age (estimated by the Horvath method) incorporates DNA methylation

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