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

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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†

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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

https://doi.org/10.1017/cts.2021.668 Published online by Cambridge University Press

status at 353 CpG sites. DNAm AA is the residual of DNA methylation age regressed on chronological age in a linear model. Spearman's correlations and linear regression examine the relationship between DNAm AA and depressive symptoms (Beck Depression Inventory) and cardiometabolic status. The potential association and impact of SES, trauma, substance use, and stress were also considered. RESULTS/ANTICIPATED RESULTS: Contrary to our hypothesis, DNAm AA did not associate with the severity of depressive symptoms. Correlation between DNAm AA and affective symptom subscore (BDI) approached significance ($p = 0.06$). We observed significant correlations between DNAm AA and specific depressive symptoms including participants' reported disappointment, disgust, or hatred toward themselves ($p < 0.05$), difficulty with making decisions ($p < 0.05$), and worry about their physical health ($p < 0.05$). DNAm AA was also significantly correlated with BMI ($p > 0.001$). Significant relationships were not evident in the subsequent regression analysis examining potential relationships between DNAm AA and depression. To our knowledge, this is the first study to examine associations between DNAm AA and depressive symptoms in AAW. DISCUSSION/SIGNIFICANCE OF FINDINGS: Depression limits life quality and quantity and is highly comorbid in CMCs. AAW have a high risk of comorbidity. This study deepens knowledge with respect to the associations between depression, CMCs, and aging with a clinically accessible marker in a population with disproportionate risk.

Mechanistic Basic to Clinical

66942

Metabolomic endotype of bioenergetic dysfunction predicts mortality in critically ill patients with acute respiratory failure

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ABSTRACT IMPACT: The pathophysiologic features of a metabolomic endotype that predicts patient outcomes due to sepsis have the potential to direct new therapies that target immune dysregulation and bioenergetic insufficiency. OBJECTIVES/GOALS: Acute respiratory failure (ARF) requiring mechanical ventilation is a frequent complication of sepsis and other disorders. It is associated with high morbidity and mortality. Despite its severity and prevalence, little is known about metabolic and bioenergetic changes that accompanying ARF. METHODS/STUDY POPULATION: In this study, semi-quantitative and quantitative ultrahigh performance liquid chromatography mass spectrometry (UHPLC MS) analysis was performed on patient serum collected from the Trial with Acute Respiratory failure patients: evaluation of Global Exercise Therapies (TARGET). Serum from survivors (n=15) and nonsurvivors (n=15) was collected at day 1 and day 3 after admission to the medical intensive care unit as well as at discharge in survivors. Pathway analysis of the biochemical changes was performed to determine whether the disruption in specific metabolic pathways can identify the bioenergetic and metabolomic profile of these patients. RESULTS/ANTICIPATED RESULTS: Significant metabolomic differences were related to biosynthetic intermediates of redox cofactors nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP), increased acyl-carnitines, and decreased acyl-glycerophosphocholines in nonsurvivors compared to survivors. The metabolites associated with poor outcomes are substrates of enzymatic processes dependent on NAD(P), while the abundance of NAD cofactors rely on the bioavailability of dietary vitamins B1, B2 and B6. Changes in the efficiency of the nicotinamide-derived cofactors' biosynthetic pathways also associate with an alteration of the glutathione-dependent drug metabolism as characterized by the substantial differences observed in the acetaminophen metabolome. DISCUSSION/SIGNIFICANCE OF FINDINGS: This metabolomic endotype represents a previously unappreciated association between severity of outcomes and micronutrient deficiency, thus pointing to new pharmacologic targets and highlighting the need for nutritional remediation upon hospitalization to improve patient outcomes due to ARF.

Team Science

24234

Development of a computerized neurocognitive test of interhemispheric transfer for use in pediatric settings

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ABSTRACT IMPACT: As newborn screening is now available for X-linked adrenoleukodystrophy, there is a need to establish meaningful disease markers to detect the onset of the severe demyelinating cerebral form of this disease at the earliest possible stage, and to quantify early disease progression to evaluate the relative efficacy of therapies. OBJECTIVES/GOALS: Longitudinal testing of neurocognitive and motor function using smartphone and tablet-based applications holds promise for early detection and quantification of brain white matter changes in patients with adrenoleukodystrophy (ALD) and other rare demyelinating diseases, but this methodology requires validation in pediatric populations. METHODS/STUDY POPULATION: We developed an iPad application with a game-like interface to assess interhemispheric transfer across the corpus callosum, the brain structure where cerebral demyelinating disease typically begins in patients with ALD. Feasibility data from remote test administrations with healthy children were collected to analyze and speed and timing of finger tapping movements requiring bimanual coordination on a touchscreen. RESULTS/ANTICIPATED RESULTS: Among our pilot sample of healthy school-aged children, age-related improvements in finger tapping speed were observed in both single-hand and alternating-hand conditions. Results indicate that remote testing using iPad applications is a viable way to collect psychometric testing data rapidly in pediatric populations and is feasible during a pandemic. Next steps in this research project will be: (1) evaluating the stability of repeated test administrations (test-retest reliability), (2) assessing agreement between performance on our iPad application and validated measures of interhemispheric transfer and fine motor function, and (3) comparing performance of children with known corpus callosum white matter abnormality to performance of healthy children. DISCUSSION/SIGNIFICANCE OF FINDINGS: Brief neurocognitive tests that can be frequently administered may have the ability to capture subtle brain changes in developing children. Approaches enabling remote

https://doi.org/10.1017/cts.2021.668 Published online by Cambridge University Press