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Urine Biomarker Predictors of Incident Hospitalization in People Living with HIV

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OBJECTIVES/GOALS: This study aims to determine 1) which urine biomarkers of kidney health measured in the ambulatory setting predict incident hospitalization; 2) to determine whether time-updated measures of ambulatory urine biomarkers and their changes/trajectories have added value over baseline alone. METHODS/STUDY POPULATION: Participants in the Predictors of Acute Renal Injury Study (PARIS), a prospective cohort of 478 HIV+ patients followed at the Johns Hopkins HIV Clinic, had sociodemographic, clinical data, and biosamples taken until hospitalization or up to 3 years annually. Among those hospitalized, clinical data and biosamples were collected serially during hospitalization and at 3 and 12 months post-discharge. For each of the 10 biomarkers measured, we will evaluate the association of the biomarker and risk of incident hospitalization using Cox hazards regression, adjusting for sociodemographics, comorbidities, HIV history, and medications. Biomarkers will be evaluated at baseline and as time-updated and change over time. RESULTS/ANTICIPATED RESULTS: We anticipate that higher baseline levels and increasing levels of urine albumin, Î±1M, Î²2M, NGAL, IL-18, KIM-1, MCP-1, YKL-40 will be independently associated with increased risk of incident hospitalization whereas higher and increasing levels of uromodulin and EGF will be associated with lower risk of incident hospitalization. These biomarkers collectively capture the following dimensions of kidney health: endothelial injury, tubular injury and function, inflammation, and fibrosis. We anticipate increased risk of incident hospitalization in HIV+ persons in the highest tertile of baseline, time-updated, and change over time biomarkers, relative to those within the lowest tertile. DISCUSSION/SIGNIFICANCE: This study will improve our understanding of the evolution of biomarkers of kidney health from the ambulatory to the hospitalized setting and will quantify the clinical implications of subclinical kidney damage among people living with HIV, a high-risk patient population with unique kidney pathophysiology.

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Longitudinal immune profiling reveals unique myeloid and T cell phenotypes associated with spontaneous immunoediting in a novel prostate tumor model

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OBJECTIVES/GOALS: Few preclinical models exist to study how tumors transition from prolonged stable disease ('equilibrium') to progressive disease ('escape'). We characterized a new murine tumor model the exhibits such behavior, and sought to identify and validate the role of unique tumor-infiltrating immune cell subsets in this process. METHODS/STUDY POPULATION: We evaluated growth of NPK-C1 (originally LM7304; received from Dr. Cory Abate-Shen at Columbia University), a cell line developed from spontaneous prostate cancer lung metastases in NPK mice (Nkx3.1CreERT2/+Ptenflox/floxKrasLSL-G12D/+R26R-LSL-YFP/+), in immune competent (C57BL/6) and immune deficient mice (J/Nu). We determined the role of CD4 and CD8 T cells in regulating the 'equilibrium to escape' growth dynamics of NPK-C1 via in vivo cell depletions at key inflection points of tumor growth. To deeply profile the immune contexture of NPK-C1 at these inflection points, we developed a 28-color immunophenotyping panel for use on a Cytek Aurora spectral flow cytometer. We performed dimensionality reduction and clustering analyses on these data using tSNE and FlowSOM algorithms within FlowJo (v10.6). RESULTS/ANTICIPATED RESULTS: We found that activated CD4 effector T cells are enriched in regressing NPK-C1 tumors, highlighting a role for CD4 T cells in antitumor immunity. CD8 T cells are also important for NPK-C1 control; specifically central memory-like cytotoxic CD8 T cells. Depletion of either CD4 or CD8 T cells during the equilibrium phase of NPK-C1 growth confirmed the role of these cells in antagonizing NPK-C1 escape. Tregs as a whole were counterintuitively enriched in regressing tumors, however high dimensional analysis reveals their significant phenotypic diversity, with a number of Treg subpopulations enriched in progressing tumors. In the myeloid compartment, we found that iNOS+ DC-like cells are enriched in regressing tumors, while CD103+ DCs are associated with late stage tumor progression. DISCUSSION/SIGNIFICANCE: In total, these analyses of the NPK-C1 model provide novel insights into the roles of lymphoid and myeloid populations throughout key phases of tumor/immune co-evolution, and highlight a role for multi-dimensional flow cytometry-based analyses to more deeply understand immune cell dynamics in the tumor microenvironment.

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A Machine Learning-based Pharmacogenomic Association Study of Major Adverse Cardiovascular Events (MACEs) in Caribbean Hispanic Patients on Clopidogrel.

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OBJECTIVES/GOALS: To summarize baseline characteristics and risk factors for major adverse cardiovascular events (MACEs) and develop a prediction model by testing the association between genetic variants and MACEs in Caribbean Hispanic patients on clopidogrel using machine-learning (ML) techniques. METHODS/STUDY POPULATION: This is a secondary analysis of available clinical and genomic data from an existing database of 600 Caribbean Hispanic cardiovascular (CV) patients on clopidogrel. MACEs is defined as the composite of all-cause death, myocardial

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infarction, stroke and stent thrombosis over 6 months. Dataset is divided into training (60%) and testing (40%) sets, respectively. Two different supervised ML approaches (i.e. multiclass classification and regression algorithms) are applied to the study dataset using Python v3.5 and WEKA, and tested by receiver operating curve (ROC) analysis. A case-control association analysis between MACEs at 6 months and genotypes is performed by using chi-squared test. RESULTS/ANTICIPATED RESULTS: Average age of participants was 68 years-old, 55% males, with high prevalence of risk factors (i.e., overweight: 28.4 kg/m2; hypertension: 83.8%; hypercholesterolemia: 71.9% and diabetes: 54.8%). MACEs rate is 13.8%, with 33.5% resistant to clopidogrel. Logistic regression, KNN and gradient boosting showed the best performance, as suggested by ROC analysis and AUC CV scores of 0.6-0.7. A significant association between MACE occurrence and â‰¥3 risk alleles was found (OR=8.17; p=0.041). We anticipate that these genetic variants (CYP2C19*2, rs12777823, PON1-rs662, ABCB1-rs2032582, PEAR1-rs12041331) will uniquely contribute to clopidogrel resistance and MACEs in Caribbean Hispanics. DISCUSSION/SIGNIFICANCE: Our findings help address in part the long-standing problem of excluding minorities from research, which entails a gap of knowledge about clopidogrel pharmacogenomics in Puerto Ricans. This study provides a possible ML model that integrates clinical and pharmacogenomics for MACE risk estimation.

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Association of sphingolipid de novo synthesis with airway response to magnesium

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OBJECTIVES/GOALS: MgSO4 is a frequently used to treat asthma exacerbations. Its role in the management of pediatric asthma remains controversial. Our objective is to demonstrate that the response of the small (peripheral) airways depends on airway de novo sphingolipid synthesis, clinically and experimentally. The small airways are the main site of asthma pathology. METHODS/STUDY POPULATION: We investigated airway reactivity in response to MgSO4 in murine small airways and children 1. Precision-cut lung slices (PCLS): Using heterozygous knockouts mice of one of the Sptlc2 subunit of the serine palmitoyl-CoA transferase (SPT) which results in reduced tissue sphingolipid levels compared to wild-type control littermates (Sptlc2+/+). We compared small airway dilation to MgSO4 in Sptlc2+/- and Sptlc2+/+ mice. This was assessed by directly visualization of small airway contractility in PCLS from Sptlc2+/- mice using video phase-contrast microscopy 2. Clinical response to MgSO4 in children by using a respiratory score before and after the treatment. The response to MgSO4 was the correlated to asthma-associated 17q21 specific single nucleotide polymorphisms (SNPs) from DNA isolated from buccal swabs RESULTS/ANTICIPATED RESULTS: Sphingolipid-mediated activity alters magnesium response in small airways. We assessed whether down-regulation of SPT could lead to alterations in MgSO4-induced small airway dilation and in MgSO4 responsiveness in mouse tracheal rings and found that the magnesium-induced relaxation of airways pre-contracted with methacholine was impaired in Sptlc+/- mice compared to the control group (p=<0.05) Clinical response to MgSO4 in children with status asthmaticus. A respiratory score was assessed in a cohort of 5 to 21-year-old who received IV MgSO4. An increase of 3 or more points was considered positive. Only 32% of the patients showed a favorable improvement to the medication, showing variability of response between individuals. The correlation of sphingolipid-deficient SNPs and MgSO4 responsiveness is ongoing DISCUSSION/SIGNIFICANCE: This suggest that decreased SPT activity in the respiratory track alters the response of the airways to magnesium. Connecting decreased de novo SL synthesis to alterations in cellular magnesium homeostasis provides a mechanistic link to differential airway reactivity to MgSO4 in pediatric asthma management.

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Web-based Methods for Family Health History Collection

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OBJECTIVES/GOALS: Family health history is widely recognized as an important step of genetic counseling; however, <50% of adults collect family health history due to implementation gaps such as suboptimal collection tools. Our objective is to create KIT, an interactive chatbot to administer a family history survey in comparison to a form-based data collection tool. METHODS/STUDY POPULATION: Both family health history collection tools were designed by adapting the NIH All of Us Research Family History Survey. The study population consists of 1000 individuals recruited from the crowdsourcing platforms, subreddits r/Health, r/SampleSize, and r/GeneticCounseling and Amazon Mechanical Turk. Eligible participants must be U.S. adults who know at least two first-degree relatives with at least one condition. Study participants are randomized to interact with either tool and complete a survey that measures the usability, engagement, accuracy, and impact of the two data collection strategies. We will use an independent t-test to compare differences in our outcome variables between the two family health history collection tools with demographic variables as covariates. RESULTS/ANTICIPATED RESULTS: The hypothesis of this study is that KIT will be more usable, more engaging, with similar accuracy in comparison to form-based tools, which are currently being used for family healthy history collection at low rates. The primary outcome of this study is usability, which will be measured based on standardized surveys. Secondary metrics of this study include engagement, accuracy, and impact. Engagement metrics include time to completion and number of resource link clicks. To assess accuracy and impact, we have included survey questions about the quality of the final summary report provided by both tools. Additionally, we ask users to rank areas for design feature improvement and feature importance; these features were determined by shared-decision-making concepts. DISCUSSION/SIGNIFICANCE: This study provides recommendations for design features important for the usability, engagement, and impact of future family health history collection tools. With a more usable and engaging tool, we can maximize rates of collection and support both patients and genetic counselors by ensuring features align with shared-decision-making frameworks.

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