to establish a streamlined bioinformatics pipeline for incorporating PGx reporting into clinical WGS and to determine clinical implications for medication treatment. METHODS/STUDY POPULATION: A PGx profiling pipeline based on existing WGS data was developed, integrating three WGS-based PGx calling tools: Aldy, PyPGx, and Cyrius (CYP2D6 only), to provide genotype calls for 17 key pharmacogenes. The pipeline was validated using WGS data from 70 individuals with diverse backgrounds (36% European, 27% African, 27% Asian, and 10% admixed) from the Genetic Testing Reference Materials Coordination Program (GeT-RM). Results were manually reviewed against published data. The validated pipeline was then applied to 144 clinical patients previously screened for neurodevelopmental disorders or suspected hereditary diseases, followed by diplotype-to-phenotype translation and preemptive PGx-guided medication recommendations based on consensus guidelines and FDA labeling for commonly used medications. RESULTS/ANTICIPATED RESULTS: Congruent phenotype call rates for GeT-RM samples were 100% for 13 genes (CFTR, CYP2B6, CYP2C19, CYP2C9, CYP3A4, CYP4F2, DPYD, G6PD, IFNL3, NAT2, NUDT15, TPMT, and VKORC1), 99% for three genes (CYP3A5, SLCO1B1, UGT1A1), and 97% for CYP2D6, indicating strong pipeline performance. Among 144 clinical patients, 99.3% had at least one clinically actionable PGx results relevant to 36 of top 300 medications in the USA across psychotropic, cardiovascular, musculoskeletal, gastrointestinal, and other therapeutic areas. The most prevalent drug–gene interactions involved sertraline and CYP2B6, affecting 49% patients: 41% were intermediate metabolizers who may require slower titration and lower maintenance doses, while 8% poor metabolizers may benefit from a lower starting dose or alternative antidepressants. DISCUSSION/SIGNIFICANCE OF IMPACT: Our validated WGS-based PGx profiling pipeline successfully extracted actionable PGx data from clinical WGS. By aligning PGx profiles with guideline-recommended clinical actions, we demonstrated the clinical value of integrating PGx reporting in WGS workflows, improving personalized medication management.

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Cognitive models of reading are also models of the brain: Identifying the neural correlates of a computational model of reading†

Ryan Staples[1], Andrew DeMarco[1] and Peter E. Turkeltaub[2]
[1]Georgetown University Medical Center and [2]Georgetown University Medical Center, Medstar National Rehabilitation Hospital

OBJECTIVES/GOALS: Many left hemisphere stroke survivors have a reading disorder (alexia), which is experienced as decreasing well-being. Therapies produce inconsistent results, demonstrating a need for treatment response predictors. We identify neural correlates of a computational model of reading, which may provide biomarkers to improve therapeutic outcomes. METHODS/STUDY POPULATION: Left hemisphere stroke survivors (LHSS) (n = 52) performed an oral reading task and tests of semantic and phonological processing. Artificial neural network (ANN) models, mapping between orthography (visual word form), phonology (auditory word form), and semantics (word meaning), were trained to read single words at an adult reading level. Stroke was simulated by removing percentages (in 10% intervals) of the connections into and out of semantics, phonology, and the combination thereof. The lesioned model producing the smallest average Euclidean distance over word and pseudoword reading accuracy to each LHSS was selected as the matched model. Two voxelwise lesion-symptom mapping (VLSM) analyses identified the neural correlates of the percent of phonological and semantic links removed in the matched models. RESULTS/ANTICIPATED RESULTS: Model reading was correlated with LHSS reading (high-frequency regular words, $r(48) = 0.96$; high-frequency irregular words, $r(48) = 0.94$; low-frequency regular words, $r(48) = 0.97$); low-frequency irregular words, $r(48) = 0.85$; all p's DISCUSSION/SIGNIFICANCE OF IMPACT: Our results show that ANN models of reading, when closely matched to LHSS reading performance, directly connect cognitive processes to the brain. Using matched models as a precision medicine framework to predict therapy response or to identify targets for neurostimulation provides a valuable route toward improving poststroke language outcomes.

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Kidney MiRNA expression in BTBR ob/ob mice at a critical time point in disease development and progression†

Sadaf Ghaderzadeh
Georgetown-Howard Universities Center for Clinical and Translational Science Sadaf Ghaderzadeh, PhD 1,2, Baiyeendang Agbor-Baiyee1, Chidera Obiwuma1, Neal Mohit1, Kanwal K. Gambhir, PhD1, Maurice B. Fluitt, PhD1 1Division o Endocrinology and Metabolism, Deparmtent of Medicine, Howard University College of Medicine, 520 W St, NW, Washington, DC 20059, USA; 2Division of Endocrinology and Metabolism, Department of Medicine, Georgetown University, Washington, DC 20057, USA

OBJECTIVES/GOALS: Diabetic kidney disease (DKD) affects 40% of diabetic patients, leading to renal failure, yet the molecular drivers remain elusive. MicroRNAs, noncoding regulators of gene expression, may hold the key. This study aims to identify key miRNAs in DKD, providing crucial insights for early intervention. METHODS/STUDY POPULATION: miRNA sequencing was conducted on kidneys from 8-week old male BTBR wild type and BTBR ob/ob mice. BTBR ob/ob mice lack the hormone leptin and spontaneously develop type 2 diabetes, with morphological renal lesions characteristic of human DKD. Total RNA was extracted from whole kidney sections and processed using the QIAseq miRNA library kit. Sequencing was performed on an Illumina NextSeq 550 platform. GeneGlobe analysis was used to identify differentially expressed miRNA functional pathways, while ingenuity pathway analysis (IPA) was employed to predict master regulators and causal networks involved in DKD. RESULTS/ANTICIPATED RESULTS: miRNA sequencing identified significantly differentially expressed miRNAs ($p < 0.05$) between 8-week-old BTBR WT and BTBR ob/ob male mice, including miR-34a (-6.86 fold), miR-122 (-5.01 fold), miR-129 (-2.23 fold), miR-142a (+2.78 fold), miR-346 (+4.66 fold), miR-547 (-2.49 fold), miR-592 (+11.81 fold), miR-802 (-6.95 fold), and miR-6539 (-7.93 fold). Qiagen GeneGlobe analysis revealed biological processes potentially targeted by these miRNAs, including endocytosis, phagocytosis, hyperglycemia ($p = 7.59e-3$), and insulin-dependent diabetes ($p = 4.32e-4$). IPA predicted activation of RRAS, a small GTPase regulating cell growth and signaling (Z-score +2), with miR-34a and miR-122 targeting MYC, PI3K, and TGF-β in DKD progression in BTBR ob/ob mice. DISCUSSION/SIGNIFICANCE OF IMPACT: We identified kidney miRNA expression in BTBR ob/ob mice at a pivotal disease stage. miR-34a, miR-122, and RRAS emerged as key drivers in DKD

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