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†

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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†

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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

https://doi.org/10.1017/cts.2024.724 Published online by Cambridge University Press

progression, showing remarkable early biomarker potential. These findings lay the groundwork for early detection and innovative therapies to halt DKD and improve patient outcomes.

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Biomarkers and neurocognitive impairment in traumatic brain injury patients

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OBJECTIVES/GOALS: This study aims to explore the relationship between plasma biomarkers (GFAP, NF-L, and IL-1β) and cognitive impairment in moderate to severe TBI patients. We will assess biomarker levels and their link to neurocognitive outcomes at acute and chronic stages of injury. METHODS/STUDY POPULATION: We will recruit 100 patients aged 21 years and older with moderate to severe TBI (Glasgow Coma Score 3–12) from a trauma hospital. Blood samples will be collected at 24–72 hours post-injury and again at 3 and 6 months. Plasma levels of GFAP, NF-L, and IL-1β will be measured using multiplex ELISA. Neurocognitive tests will be administered at 3 and 6 months to assess cognitive function. Correlations will be made between biomarker levels, neurocognitive performance, and disability scores (Disability Rating Scale and Glasgow Outcome Scale). Exosome isolation from plasma will allow for detailed analysis of astrocyte-derived biomarkers and their association with long-term cognitive impairment and recovery. RESULTS/ANTICIPATED RESULTS: We anticipate that plasma levels of GFAP, NF-L, and IL-1β will be elevated in the acute phase of moderate to severe TBI and will correlate with injury severity. At 3 and 6 months, higher levels of IL-1β, in particular, are expected to be strongly associated with cognitive deficits. We also anticipate that biomarkers in astrocyte-derived exosomes will provide more specific insights into long-term neuroinflammation and its impact on cognitive function. These findings could pave the way for targeted, personalized interventions to improve recovery in TBI patients. DISCUSSION/SIGNIFICANCE OF IMPACT: This research focuses on inflammation's role in cognitive impairment and disability in TBI patients. We propose using multiple biomarkers – GFAP, IL-1β, NF-L – paired with advanced techniques like exosomes and multiplex analyses to identify novel therapeutic targets, aiming for personalized treatment strategies, as well as prognosis.

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Nanoscale imaging of pT217-tau in aged rhesus macaque entorhinal and dorsolateral prefrontal cortex: Evidence of interneuronal trafficking and early-stage† neurodegeneration

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OBJECTIVES/GOALS: pT217-tau is a novel fluid biomarker that predicts onset of Alzheimer's disease (AD) symptoms, but little is known about how pT217-tau arises in brain, as soluble pT217-tau is dephosphorylated postmortem in the humans. Aging macaques naturally develop tau pathology with the same qualitative pattern and sequence as humans, including cortical pathology. METHODS/STUDY POPULATION: The etiology of pT217-tau in aging brains can be probed in rhesus macaques, where perfusion fixation allows capture of phosphorylated proteins in their native state. We utilized multi-label immunofluorescence and immunoperoxidase and immunogold immunoelectron microscopy to examine the subcellular localization of early-stage pT217-tau in entorhinal cortex (ERC) and dorsolateral prefrontal cortex (dlPFC) of aged rhesus macaques with naturally occurring tau pathology and assayed pT217-tau levels in blood plasma using an ultrasensitive nanoneedle approach. RESULTS/ANTICIPATED RESULTS: pT217-tau labeling is primarily observed in postsynaptic compartments, accumulating in: 1) dendritic spines on the calcium-storing smooth endoplasmic reticulum spine apparatus near asymmetric glutamatergic-like synapses and 2) in dendritic shafts, where it aggregated on microtubules, often "trapping" endosomes associated with Aβ42. The dendrites expressing pT217-tau were associated with autophagic vacuoles and dysmorphic mitochondria, indicative of early neurite degeneration. We observed trans-synaptic pT217-tau trafficking between neurons within omega-shaped bodies and endosomes, specifically near excitatory, but not inhibitory synapses. We also examined pT217-tau in blood plasma in macaques across age-span and observed a statistically significant age-related increase in pT217-tau. DISCUSSION/SIGNIFICANCE OF IMPACT: We provide direct evidence of pT217-tau trafficking between neurons near synapses to "seed" tau pathology in higher brain circuits, interfacing with the extracellular space to become accessible to CSF and blood. The expression of pT217-tau in dendrites with early signs of degeneration may help to explain why this tau species can herald future diseases.

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Impact of feminizing hormone therapy on rectal mucosal HIV target cells in Thai TGWSM†

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OBJECTIVES/GOALS: Transgender women who have sex with men (TGWSM) have higher HIV risk. The rectal mucosal (RM) immune environment of TGWSM who choose feminizing hormone therapy (FHT) has been shown to be distinct from the RM of cisgender men who have sex with men (MSM). We studied the impact of FHT on the adaptive immune cellular composition of the RM. METHODS/STUDY POPULATION: We sampled cross-sectional and longitudinal cohorts of TGWSM and cisgender MSM from The Silom Clinic in Bangkok, Thailand from December 2020 to December 2023. We included participants aged >18 years, all cisgender MSM and TGWSM with FHT levels in the therapeutic range for cisgender women. We performed RM biopsies and analyzed the adaptive immune cell characteristics via flow cytometry. We will perform binary linear regression to assess the association between systemic FHT levels and the percentage of CD4+ T cells expressing key biomarkers. Primary outcomes include the percentage of CD4+ T cells that express CCR5, with a secondary outcome of the percentage of CD4+ T cells that express Ki67. RESULTS/ANTICIPATED RESULTS: The cross-sectional cohort included 100 TGWSM on FHT and 50 cisgender MSM. The longitudinal cohort included 25

https://doi.org/10.1017/cts.2024.724 Published online by Cambridge University Press