prediction. Validation on our proprietary cohort revealed a drop in performance with overall mixed results by AUC (POLE 0.50, MSI-H 0.69, CNV-H 0.78, and CNV-L 0.61). Overall precision 0.57, recall 0.45. Again, CNV-H with the most accurate prediction but F1 score dropped from 0.77 in the CPTAC to 0.47 on validation. POLE was the least accurate prediction subtype. DISCUSSION/SIGNIFICANCE OF IMPACT: The CNV-H subtype demonstrated robust performance, suggesting the model effectively captures the features associated with this subtype. CNV-L had moderate performance. MSI-H and POLE were notably lower. WSI-based AI models show translational potential for subtype prediction in the management of endometrial cancer but more work is necessary.

Other

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A Pilot Study of DataDay: Daily support for people with dementia

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OBJECTIVES/GOALS: This pilot study aims to assess the implementation of the DataDay app in memory clinics for patients with MCI or dementia, focusing on usability, user satisfaction, and impact on health outcomes. We seek to identify barriers and facilitators to implementation and evaluate its effect on reducing unnecessary hospital stays. METHODS/STUDY POPULATION: This mixed-methods study will involve 50 participants, 25 diads of patients with MCI or mild-to-moderate dementia and their caregivers from the community. Participants will use DataDay for 12 weeks, receiving reminders to log daily activities such as nutrition, mood, cognition, and physical activity. Baseline demographic data will be collected from self-reported surveys. Participants will receive training on app use, with follow-up interviews at 4, 8, and 12 weeks to gather feedback. Quantitative data analysis will include repeated measures analysis of variance to compare pre- and post-intervention outcomes, such as medication use and ER visits. Thematic analysis will be conducted on interview transcripts to understand user experiences. RESULTS/ANTICIPATED RESULTS: We anticipate the study will demonstrate the feasibility of the DataDay app for self-management in individuals with MCI or dementia. Expected outcomes include improved medication adherence, reduced emergency room visits, and increased user engagement with daily health monitoring. Qualitative feedback is expected to highlight user satisfaction with the app's reminders and ease of integration into daily routine. We also expect potential challenges to be identified such as initial learning difficulties and technology-related frustration. The data will help refine the app for better usability and inform strategies for widespread implementation in memory assessment clinics. DISCUSSION/SIGNIFICANCE OF IMPACT: The study will provide insights into the practicality of implementing DataDay in memory clinics. The results will highlight necessary adjustments and provide key factors for successful adoption in other clinics. DataDay aims to allow individuals with MCI or dementia to manage their condition at home and enhance their quality of life.

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Extracellular vesicle metabolic protein changes during ischemic stroke†

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OBJECTIVES/GOALS: Ischemic stroke treatments assist in restoring blood flow, but do not guarantee good outcomes. Since extracellular vesicles (EVs) able to cross the blood brain barrier, total (nonspecific) and astrocyte enriched EVs (TEVs, AEVs, respectively) from plasma may emerge as plasma biomarkers for prognostication and targeted therapeutics. METHODS/STUDY POPULATION: "Blood and Clot Thrombectomy Registry and Collaboration" (BACTRAC; NCT03153683) is a human stroke biobank at the University of Kentucky that collects samples at the time of mechanical thrombectomy during emergent large vessel occlusions (ELVO; ischemic stroke). EVs were isolated, via size exclusion chromatography, from unbanked plasma and concentrated resulting in TEVs. AEVs were immunoprecipitated with anti-EAAT1 (GLAST), an astrocyte-specific transmembrane glycoprotein. Isolated protein was sent to Olink and ran on their metabolic panel. Demographics and medical histories of the subjects were exported from REDcap and investigators were blinded during EV analysis. RESULTS/ANTICIPATED RESULTS: ELVO subjects (8 females/5 males) were an average age of 71.1 ± 11.7 years. Lower TEV enolase 2, a neuronal glycolysis enzyme, associated with increased stroke severity (NIHSS; rs = -0.7819, p = 0.0476). Higher systemically TEV quinoid dihydropteridine reductase (QDPR), essential co-factor enzyme, was associated with more severe strokes (NIHSS; rs = 0.8486, p = 0.0123) and lower cognition (MoCA; r2 = 0.7515, p = 0.0254). Interestingly, higher intracranial AEVs QDPR was associated with lower infarct volumes (rs = -0.7333, p = 0.0202), less severe strokes (NIHSS; rs = -0.6095, p = 0.0388), and better cognition (MoCA; r2 = 0.6095, p = 0.0388). Increased AEV nicotinamide adenine dinucleotide kinase another essential co-factor enzyme, intracranially also correlated to higher cognition (MoCA; rs = 0.8356, p = 0.0298). DISCUSSION/SIGNIFICANCE OF IMPACT: Plasma TEV and AEV metabolic proteins correlate with the progression of stroke outcomes and should be investigated as target therapies during MT to improve outcomes.

Precision Medicine/Health

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Enhancing the clinical utility of whole-genome sequencing for pharmacogenomic clinical decision support

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OBJECTIVES/GOALS: Pharmacogenomic (PGx) testing identifies genetic variations affecting medication response but is not yet in routine clinical whole-genome sequencing (WGS) workflows. We aimed

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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

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