centers that provide CAR-T cell therapy and allow for the harmonization of follow-up protocols. METHODS/STUDY POPULATION: Literature review and semi-structured interviews with patients, clinical coordinators, and other experts in the field will be used to determine what parameters must be included in the mobile application prototype to effectively monitor the side effects of CD19-directed CAR T-cell therapy. The mobile phone application will be designed using process mapping to integrate data from self-reporting and wearable technologies, including the Garmin smart watch. Figma will then be used to develop new screens based on an existing patient monitoring app for Allogeneic Stem Cell Transplant follow-up. Finally, a preliminary feasibility study will be conducted to collect feedback on the app prototype from CAR T-cell therapy patients, providers, and stakeholders. RESULTS/ANTICIPATED RESULTS: The anticipated results of this study include an app prototype that will include the functionalities required to monitor patients for adverse effects of CD19-directed CAR T-cell therapy. This will include the parameters that will be recorded or measured using a combination of self-reporting, a reliable body temperature sensor, and the Garmin watch which monitors basic vitals, activity, and sleep. Additional parameters may be added during the stakeholder co-design process. The app prototype will include a physician interface where doctors can monitor their patients and will be alerted if they require further physician assessment. It is expected that the app will provide standardized monitoring of patients when they are discharged from the hospital after receiving CAR T-cell therapy. DISCUSSION/SIGNIFICANCE: This app will allow physicians to monitor patients for general follow-up and adverse effects, including cytokine release syndrome and neurotoxicity. Future studies may utilize this app to develop best practices for harmonizing CAR-T follow-up protocols across Canada.

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Impaired Coronary Endothelial Response to Exercise among Postpartum Women with Preeclampsia

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OBJECTIVES/GOALS: Preeclampsia increases cardiovascular (CV) risk, likely via persistent endothelial dysfunction and angiotensin II type 1 receptor autoantibodies (AT1R-Ab). We aim to assess coronary endothelial function (CEF) and AT1R-Ab levels in postpartum preeclampsia with a hypothesis this mediates CV risk. METHODS/STUDY POPULATION: We prospectively enrolled age and CV risk factor matched postpartum women. Coronary MRI was performed at rest and with isometric handgrip stress, an endothelial dependent stressor. CEF was quantified as % stress-induced change in coronary cross-sectional area (%CSA) and in coronary blood flow (%CBF). AT1R-Ab was measured using a novel antigen capture enzyme-linked immunosorbent assay. RESULTS/ANTICIPATED RESULTS: Women with and without preeclampsia were similar in age (mean 32.7+5.0 years), BMI (mean 28.0+6.3 kg/m2) and race/ethnicity (58% White, 35% Black and 4% Hispanic). %CSA was lower with (-2.1+13.6) vs without preeclampsia (8.8+17.1), p=0.023. %CBF was also lower with (11.3 [-11.8, 25.2]) vs without preeclampsia (25.7 [-0.7, 62.9]), p=0.039. AT1R-Ab was higher among women with preeclampsia (p=0.029) and was inversely associated with %CBF (beta coefficient -4.6 [-8.9, -0.3], p=0.037) but not with %CSA. DISCUSSION/SIGNIFICANCE: Women with preeclampsia have elevated AT1R-Ab and impaired CEF demonstrated by insufficient coronary reserve with exercise. Coronary endothelial dysfunction and dysregulation of the renin-angiotensin pathway likely contribute to long-term CV risk and should be considered for targeted risk reduction.

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Value estimation of the Diabetes Prevention Program: How well does clinical trial-based cost-effectiveness apply to the real world?

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OBJECTIVES/GOALS: Many economic evaluations rely on clinical trial data that may not represent real world populations and intervention effectiveness. We compare risk and cost-effectiveness for the Diabetes Prevention Program (DPP) clinical trial cohort and a real world population eligible for the national DPP to assess the impact of using real world data. METHODS/STUDY POPULATION: To produce real world (US population) representative results, we identified National Health and Nutrition Examination Survey (NHANES) subjects eligible for the national DPP and adjusted projections using survey weights. We used clinical predictive models to estimate individual diabetes risk, and microsimulation to estimate lifetime costs, benefits, and net monetary benefits (NMB) for lifestyle intervention and metformin. We compared results across the DPP clinical trial and NHANES populations. RESULTS/ANTICIPATED RESULTS: Three-year risk of diabetes onset for the DPP trial population (mean of 19.7%, median of 10.3%) exceeded corresponding risk for the NHANES population (mean of 14.6%, median of 4.8%). The proportion of individuals with a three-year diabetes risk < 10% for the DPP trial population (49%) was less than the corresponding proportion for NHANES (67%). Mean NMB for metformin for the DPP trial population ($9,749) exceeded the corresponding value for NHANES ($5,391). The proportion of subjects with negative NMB was 49% for the DPP trial population and 67% for NHANES. Lifestyle intervention had a mean NMB of $34,889 for the DPP trial population and $28,652 for NHANES. Only 20% of the NHANES population eligible for national DPP met inclusion/exclusion criteria for the DPP trial. DISCUSSION/SIGNIFICANCE: Real world populations eligible for the national DPP include a greater proportion of low-risk individuals, and for these people, prevention programs may confer smaller benefits. Technology assessments based on clinical trial data should be revised using real world population and treatment effect data.

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Targeting One-Carbon Metabolism in Brain Cancer†

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OBJECTIVES/GOALS: Glioblastoma (GBM) is the most malignant brain tumor in adults and remains incurable with an average survival of 15 months after diagnosis. There is great need for treatment options without side effects that are devastating to the quality of life for patients. GBM tumors can circumvent cellular damage by

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upregulating antioxidant production. METHODS/STUDY POPULATION: Highly aggressive tumors tend to exhibit increased oxidative metabolism, and thus rely on a mechanism to eliminate reactive oxygen species (ROS) in order for cells to evade autophagy and cell death. We propose that recurrent GBM cells achieve this is by promoting methionine metabolism, upregulating glutathione production and preventing ROS accumulation. We investigated the expression of AHCY and MAT2A, two key enzymes in the methionine pathway, at the gene and protein level in both GBM and non-GBM tissues. We probed for markers of cell death following pharmacological inhibition and siRNA knockdown, and performed metabolite-mediated rescue experiments. Finally, we evaluated changes in cellular respiration using the Seahorse XFe96 real-time mitochondrial stress test following inhibitor treatment. RESULTS/ANTICIPATED RESULTS: The selective AHCY inhibitor markedly reduced cell viability in different cancer cell types, but significantly reduced cell viability in recurrent GBM cells compared to newly diagnosed GBM (p=.009; MD: -0.828, 95% CI -1.350 to -0.306) and normal astrocytes (p=.073; MD: -0.609, 95% CI -1.305 to 0.085). AHCY and MAT2a protein expression appeared to be higher in GBM cells compared to normal astrocytes, medulloblastoma cells and other cancer cell lines. Genetic knockdown of AHCY and MAT2A demonstrated reduced cell viability, increased Caspase, SOD2, LC3-II and Transferrin receptor expression. Acute treatment with the AHCY inhibitor induced cell death, markedly reduced oxygen consumption rate and ablated spare respiratory capacity in recurrent GBM cells compared to newly diagnosed GBM cells. DISCUSSION/SIGNIFICANCE: Oxidative damage was induced following interference with key methionine pathway enzymes by pharmacological inhibition, while a similar concentration of drug largely preserved normal astrocyte viability. These results point to a novel targetable mechanism of disease progression and expand the realm of treatment options for recurrent GBM.

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Harnessing the potential of transcriptional adaptation as a mechanism for rare Amyotrophic lateral sclerosis

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OBJECTIVES/GOALS: Transcriptional adaptation is a phenomenon in which a mutation in one gene leads to the genetic compensation of another homogenous gene. Understanding the mechanism of transcriptional adaptation may contribute to an explanation for variation in clinical manifestations of rare Amyotrophic lateral sclerosis patient phenotypes. METHODS/STUDY POPULATION: The presence of a premature termination codon triggers transcriptional activation. Therefore, we utilized CRISPR-Cas9 tool to generate a premature termination codon in CHCHD10 gene in multiple types of cells, including induced pluripotent stem cells derived from patient samples with known CHCHD10 mutations causative for Amyotrophic lateral sclerosis. CRISPR-Cas9 tool was delivered via ribonucleoprotein electroporation and transfect cell's DNA was sequenced to validate gene editing. To confirm transcriptional adaption, changes in levels of protein and gene expression will be measured via immunoblot and quantification of CHCHD10 and CHCHCD2 from whole cells lysates of the edited cells. RESULTS/ANTICIPATED RESULTS: We anticipate that CHCHD2 transcriptional adaptation can functionally compensate for the locus loss of function of CHCHD10. This mechanism of transcriptional adaptation may contribute to an explanation for variation in clinical manifestations of patient phenotypes. DISCUSSION/SIGNIFICANCE: Our approach would advance discovery science towards by exploring transcriptional adaptation mechanism in humans, which can lead to novel therapies for rare Amyotrophic lateral sclerosis, such as CHCHD10.

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A Machine Learning Approach to Predicting High-Risk Irritability Trajectories Across the Transition to Adolescence*

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OBJECTIVES/GOALS: Irritability, a proneness to anger and frustration, is a transdiagnostic symptom associated with poor mental health outcomes. Levels of irritability vary across development and high-risk trajectories have been observed. This study aims to use machine learning to predict irritability trajectories across the transition to adolescence. METHODS/STUDY POPULATION: Data were from the Adolescent Brain Cognitive Development (ABCD) Study, which is a 10-year longitudinal study that tracks the brain development, cognitive skills, physical health, and psychosocial functioning of a large, national sample starting from preadolescence. The baseline sample consisted of 11,861 9-10-year-old preadolescent youth. Irritability was parent-rated at baseline, 1-year, 2-year, 3-year, and 4-year follow-ups on the Child Behavior Checklist (CBCL) irritability index. Latent class growth analysis (LCGA) was used to determine developmental trajectories of irritability. Two machine learning approaches were applied to develop predictive models of youth irritability developmental trajectories. We used baseline (preadolescent) variables that spanned a wide range of domains. RESULTS/ANTICIPATED RESULTS: Preliminary results fromthe LCGA indicated best support for a four-class model that differentiated growth trajectories in irritability across the transition to adolescence: 1) persistent low irritability (n = 8691, 73.27%), 2) moderate irritability and decreasing (n = 1257, 10.60%), 3) low to moderate irritability and increasing (n = 1295, 10.92%), and 4) chronic high irritability (n = 618, 5.21%). We expect the machine learning analyses to generate predictive models with acceptable accuracy. We hypothesize that the most important predictors in the models will originate from the youth mental health domain, including baseline youth irritability, externalizing symptoms, internalizing symptoms, and oppositional behaviors, and the parent psychopathology domain, particularly parent irritability. DISCUSSION/SIGNIFICANCE: The present study elucidates unique developmental trajectories of irritability and generates predictive models to classify high-risk irritability trajectories using machine learning approaches. Clinicians can use these predictive models to identify at-risk youth and provide early intervention to preadolescents at high risk.

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