causal loop diagrams and simulation models developed using CBSD focused on structural racism as a social determinant of health. METHODS/STUDY POPULATION: Community Based System Dynamics (group model building and computer simulation development). Cuyahoga County, Ohio, a previously redlined community of more than 1.2 million people. RESULTS/ANTICIPATED RESULTS: Actionable Community identified leverage points for action to mitigate structural racism. Computer simulation models built on causal loop diagrams built by Community members with loved experience. DISCUSSION/SIGNIFICANCE: Structural and social determinants of health, such as racism, have profound impacts on the health of individuals and populations, however they remain challenging to address in pragmatic ways. CBSD is a novel method to engage community members not proximal to the impact of structural racism in generating maps of the complex, dynamic system they live in.

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A Living Library for Uveal Melanoma

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OBJECTIVES/GOALS: Overall response rates for metastatic uveal melanoma (UM), regardless of treatment modality, are less than 20%, highlighting an urgent need for novel therapies. Herein, we present a UM patient-derived organoid (PDO) biobank as a novel platform for translational research. METHODS/STUDY POPULATION: Patients with primary choroidal or ciliochoroidal UM undergoing enucleation from 7/1/2019-9/30/2022 were invited to enroll. Tumor tissue was harvested within 30 minutes of globe removal. Cells were isolated using the human tumor isolation kit and gentleMACS dissociation protocol (Miltenyi Biotech). PDOs were placed on Cultrex-coated multiwell plates and cultured in supplemented RPMI media. DNA and RNA were isolated using kits from Zymo Research. Exon-enriched libraries and RNA were sequenced using an Illumina HiSeq 4000. Immunohistochemistry (IHC) assessed the following histone post-translational modifications: H3K4me1/3, H3K27Ac, and H3K27me. RESULTS/ANTICIPATED RESULTS: PDOs were established in 19 of 20 (95%) attempted cases. BAP1 protein expression was retained (n=7) or lost (n=12) in the primary tumors, with matching phenotype confirmed in PDOs. In 9 sequenced cases, a driving mutation was present in GNAQ (n=4), GNA11 (n=4), or CYSLTR2 (n=1). Morphology ranged from spindle-like to epithelioid clusters, mimicking primary tumor histopathology. Pigmentation increased with time in culture. Growth in culture was slow, and 1-2 months were allotted prior to passaging in most cases. Whole exome and RNA-sequencing confirmed distinct molecular profiles, with differential staining of active chromatin marks by IHC. DISCUSSION/SIGNIFICANCE: A biobank of primary UM PDOs with unique morphological and molecular characteristics has been established. These will serve as a model of human disease to facilitate translational research and investigate personalized treatments for patients with UM.

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A Mixed Methods Study of Patient and Clinician Views and Experiences of Pharmacogenomic Testing for Major Depressive Disorder

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OBJECTIVES/GOALS: Pharmacogenomic testing for major depressive disorder is an expanding area of precision medicine with multiple direct-to-provider tests available. While clinical evidence supporting testing is expanding, there has been little research on the views and experiences of patients and clinicians utilizing this novel intervention. METHODS/STUDY POPULATION: This ongoing study is conducting semi-structured interviews with clinicians and patients exploring their views of the benefits and limitations of pharmacogenomic testing. Qualitative interviews have been conducted with 10 patients and 10 clinicians who have experience with ordering or receiving results within the past 12 months. Interviews are being thematically coded following a modified grounded theory approach using the Dedoose software. Following the principles of exploratory sequential mixed methods design, findings will be used to develop a survey to be administered to prescribing clinicians in both primary care and psychiatry. The survey will examine clinician's knowledge, interest, and concerns about utilizing testing. RESULTS/ANTICIPATED RESULTS: Preliminary analysis of qualitative interviews indicates that both patients and clinicians find that the broader testing process has benefits beyond the test results themselves. Benefits identified by patients include an increased trust in the process of selecting medications, validation of their negative experiences with medications, and improved communication with their provider. Limitations identified by patients include difficulty in accessing test results, and gatekeeping for testing by providers. Benefits identified by clinicians include increased empathy with patients, medication adherence, and improved communication with patients about medication. Limitations identified by clinicians include difficulty with ordering and interpreting test results. DISCUSSION/SIGNIFICANCE: Medication selection is a difficult process for both patients and clinicians. Improvements to clinician-patient communication and medication adherence are important benefits to consider in the adoption of testing. Future research should include these dimensions in assessment of the benefits and limitations of testing.

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A systems genomics approach to identify novel drug targets of Ewing sarcoma through ancestry-informed human iPSC modeling*

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OBJECTIVES/GOALS: We leverage the disparate incidence of Ewing sarcoma (ES) between European (EUR) and African (AFR) ancestry to study ES tumorigenesis in iPSC-derived cells from donors with a range of AFR ancestry via functional / molecular profiling. Integrated multi-

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omics analysis furthers explore local regulatory networks in pursuit of novel drug targets of ES. METHODS/STUDY POPULATION: In our pilot, eight induced pluripotent stem cell lines were obtained, differentiated into neural crest cells, and then transduced with a lentivirus expressing GFP-2A-EWS/FLI1. We compared wild type (WT) to EWS-FLI1-induced cells and then compared cell survival, gene expression, and EWS-FLI1 binding differences at varying levels of EUR / AFR ancestry admixture. We will build on this pilot data by expanding the number of cell lines and measuring chromatin state. Subsequently we will refine our understanding of the relationships between local ancestry, epigenetic and gene expression changes, and phenotype in tumor progression via integration of multi-omics datasets. Our systems genomics approach will utilize directed local regulatory networks in a Bayesian structure learning framework. RESULTS/ANTICIPATED RESULTS: Induction by EWS-FLI1 resulted in gene expression changes enriched in known ES gene sets. Higher %EUR ancestry correlated with prolonged maintenance of EWS-FLI1. We identified thousands of ancestry-linked changes to gene expression and EWS-FLI1 binding. Eighty of these genes are both differentially expressed and differentially bound based on AFR ancestry admixture level and may be some of the early critical targets that initiate the cascade of molecular changes in ES. We will identify novel drug targets, with potential cross functional use of known drugs. Once we have developed directed local regulatory networks, we will use them to test in silico potential perturbations due to small molecules or novel drugs and predict expression changes. DISCUSSION/SIGNIFICANCE: With a limited number of cell lines, we identify 80 ancestry-linked candidate loci for functional validation through genome engineering. As EWS-FLI1 itself has proven elusive to direct targeting, studying its immediate downstream effects has the potential for establishing new druggable biologic pathways for treatment of ES.

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Addressing the Underdiagnosis of Familial Hypercholesterolemia

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OBJECTIVES/GOALS: Familial Hypercholesterolemia (FH) is a common disorder that is vastly underdiagnosed and causes an increased risk for sudden cardiac death. Cardiology providers (CHCPs) are in an ideal position to care for patients with FH. This research aimed to understand the practice behaviors of CHCPs in the screening, diagnosis, and management of FH. METHODS/STUDY POPULATION: An explanatory mixed methods design was utilized for this study. Adaptation of an existing FH knowledge tool guided survey development. The results of the quantitative survey, along with the Knowledge to Action framework and Theory of Planned Behavior, guided development of the interview protocol. Convenience and snowball sampling recruited CHCPs in the Division of Cardiology at Columbia University Irving Medical Center (CUIMC). Descriptive statistical analysis was performed on survey data. Qualitative interviews were conducted with survey respondents who volunteered to participate. Interviews were audio recorded, transcribed, and analyzed thematically. A descriptive review of the educational materials offered by the Division of Cardiology was conducted to identify FH knowledge domains presented. RESULTS/ANTICIPATED RESULTS: CHCPs with MDs, at CUIMC for 6-10 years, in clinical practice for 1-5 years, and in Inpatient Services had the highest average total FH knowledge scores. CHCPs with RNs, at CUIMC for less than 1 year, in clinical practice for 6-10 years, and in Cath Lab had the lowest average FH knowledge scores. Twenty interviews were completed, and four themes emerged- variability in FH care; issues related to addressing FH at institutional, practice setting and individual levels; importance of identifying FH early; and intervention approaches to overcome barriers to caring for FH patients in cardiology. CHCPs with MDs or with experiential FH knowledge were the only CHCPs to describe FH care beyond the point of screening. The document review revealed that only MDs were provided four lectures over the course of 4 years pertaining to FH. DISCUSSION/SIGNIFICANCE: CHCPs with didactic or experiential FH knowledge provided care beyond screening. Future interventions should increase didactic and experiential FH knowledge by incorporating institutional, local, and national FH resources. Improving the FH care CHCPs provide, can reduce FH-related morbidity and mortality as well as improve FH health outcomes.

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Analysis of the Hepatic Microenvironment Before and After Direct-Acting Antiviral (DAA) Therapy for Viral Hepatitis C

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OBJECTIVES/GOALS: The effect of the Direct-Acting Antiviral (DAA) on hepatic histopathological features from patients treated for HCV has not been thoroughly evaluated. The goals of this retrospective study were to determines differences between the liver biopsies collected before and after DAA treatment and correlated the histopathology with clinical outcome. METHODS/STUDY POPULATION: Spectral imaging was used to evaluate differences in intrahepatic macrophage (CD68, CD14, CD16, MAC 387, and CD163) and T cell (CD3, CD4, CD8, CD45, and FoxP3) phenotypes in paired liver biopsies collected from the same patient before (n=10) and after (n=10) achieving SVR (Figure 1). Imaging analysis and machine learning algorithms were used to evaluate changes in these key immune cells. We also compared differential gene expression of over 700 genes using RNA isolated from liver biopsies with NanoString. RESULTS/ANTICIPATED RESULTS: Multispectral imaging analysis showed a significant increase of proinflammatory/M1-like (e.g., CD14+) and anti-inflammatory/M2-like macrophage (e.g., CD163+) phenotypes in pre-treatment versus post-treatment biopsies, respectively. Gene expression analysis revealed enrichment of inflammatory (HLA-B, STAT1, CXCL10) and interferon induced-antiviral (ISG15, OAS3, MX1 and IFIT1) genes in the pre-treatment vs the post-treatment group. Cell deconvolution analysis also showed a significant increase of M1-like macrophages in the pre-treatment group when compared to the post-treatment group or controls. Upregulation of genes associated with cell proliferation and differentiation (c-KIT and Fos) was observed in the post-treatment biopsies of patients with persistent inflammatory infiltrates. DISCUSSION/SIGNIFICANCE: Protein and gene expression

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