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Gene-specific risk of syndrome-associated cancers in first-degree relatives of pancreatic cancer patients with pathogenic/likely pathogenic variants

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This abstract is based on unpublished data. OBJECTIVES/GOALS: The estimates of unbiased first-degree relatives (FDRs) risk of cancers would enhance genetic counseling of at-risk FDRs in families where the pancreatic cancer (PC) proband carrying a germline variant. This study aims at quantifying gene-specific risks of six cancers among FDRs of PC patients with germline variants in cancer-associated genes. METHODS/STUDY POPULATION: In the prospective, clinic-based Mayo Clinic Biospecimen Resource for Pancreas Research registry, 4,562 PC patients had previously undergone germline genetic testing for pancreatic cancer-associated genes through either research studies or clinical testing. Of these, 234 PC probands were found to carry germline pathogenic/likely pathogenic variants (PLPV) among 9 genes of interest and had provided detailed demographic and cancer data on their FDRs by questionnaire. We focused on six cancer types (ovary, breast, uterus, pancreas, colon, and malignant melanoma) in FDRs as reported by the probands. Standardized incidence ratios were calculated to estimate risk of six cancers among FDRs of PC patients carrying PLPV by gene. RESULTS/ANTICIPATED RESULTS: 1,670 FDRs (mean age 58.1+17.8SD; 48.9% female) were included in the study. We found significantly increased risk of ovarian cancer in female FDRs of PC probands who carry PLPV in BRCA1 (SIR 9.49, 95% CI:3.06-22.14) or BRCA2 (3.72, 95%CI:1.36-8.11), and breast cancer risks were higher with BRCA2 (2.62, 95%CI:1.89-3.54). Uterine cancer risk was increased in FDRs of PC probands who carry PLPV for Lynch Syndrome mismatch repair (MMR) (6.53, 95% CI:2.81-12.86). PC risk was also increased (ATM 4.53, 95% CI:2.69-7.16; BRCA2 3.45, 95%CI:1.72-6.17; CDKN2A 7.38, 95% CI:3.18-14.54; PALB2 5.39, 95%CI:1.45-13.79). Increased colon cancer risk was observed in FDRs of probands who carried MMR PLPV (5.83, 95%CI:3.70-8.75), while melanoma risk was elevated for FDRs of probands with CDKN2A PLPV (7.47, 95%CI:3.97-12.77). DISCUSSION/SIGNIFICANCE: PLPV in nine syndrome-associated genes in PC probands are associated with increased risk of six cancers in FDRs. The findings underscore the importance of risk estimation of various other cancers in PC families for screening, early detection, intervention, and cascade genetic testing.

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Lipid metabolism and synthesis pathway analysis of Sigma-2 Receptor/TMEM97 in breast cancer cells

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OBJECTIVES/GOALS: Breast cancer has an increased requirement for lipids. The sigma-2 receptor plays a critical role in the effective uptake of lipoproteins by forming a complex with the LDL Receptor. We investigate the role of the sigma02 receptor in modulating lipid uptake pathways in breast cancers, and how this can be leveraged as a viable therapeutic strategy. METHODS/STUDY POPULATION: CRISPR/Cas9 will be used to ablate TMEM97 in the MDAMB231 and MCF7 cell lines. This study seeks to identify pathways that are dysregulated upon TMEM97 knockout (KO) by characterizing RNASeq data to identify differentially expressed genes and perform pathway analysis. RESULTS/ANTICIPATED RESULTS: Knockout of TMEM97 in breast cancer cells is is expected to decrease lipid uptake. Treatment with statins in these knockout cells is expected to result in decreased cell viability and result in a quiescent cell population. DISCUSSION/SIGNIFICANCE: This is an important mechanistic study to understand the importance of lipid homeostasis in cancer cell proliferation and how it can be targeted to improve therapeutic anti-tumor strategies. Understanding the pathways that TMEM97 modulates is vital for therapeutic strategies to curb the proliferation of breast cancer cells.

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Metformin prevents the diagnosis of Long Covid in phase 3 trial of early treatment.

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OBJECTIVES/GOALS: Chronic or new symptoms after infection with severe-acute-respiratory-coronavirus-2 (SARS-CoV-2) has been termed post-acute sequelae of Covid-19 (PASC) or Long Covid. Our objective is to present results from COVID-OUT, a phase 3 double-blind, randomized controlled trial of early outpatient treatment of Covid-19 with repurposed medications. METHODS/STUDY POPULATION: COVID-OUT enrolled adults age 30 to 85 with overweight or obesity who had proof of SARS-CoV-2 infection and fewer than 7 days of symptoms. In this 2 by 3 factorial design trial of metformin, ivermectin, fluvoxamine, or exact-matching placebo of each medication, participants were randomized 1:1:1:1:1:1 to the 6 treatment allocations. This abstract focuses on whether early treatment with metformin prevented Long Covid. Immediate release metformin was titrated to 1500mg daily over the first 6 days. We assessed the incidence of clinician-diagnosed Long Covid with follow up through 10 months after enrollment. We also assessed where

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participants were diagnosed with Long Covid, and where they received Long Covid treatment. RESULTS/ANTICIPATED RESULTS: Of 1124 participants, 98 (8.7%) report having a healthcare provider make a diagnosis of long covid. By arm, 6.9% (39/564) of metformin participants report having a diagnosis for long covid as compared with 10.5% (59/560) of matched placebo controls. The absolute reduction attributable to metformin was 3.6% (95%CI, 0.3% to 7.0%; P=0.031) with a relative risk reduction of 34% (95% CI, 3% to 55%). The metformin cost per long covid case averted was $28 (95%CI, $15 to $306). 10-month follow-up data will be available at the time of presentation as well as an analysis of baseline factors associated with the development of Long-Covid, independent of treatment allocation in the trial. DISCUSSION/SIGNIFICANCE: Metformin reduced the incidence of clinician-diagnosed long covid by 34% in a double-blind randomized placebo-controlled trial, and previous research published in-vitro activity by metformin against SARS-CoV-2 and other RNA viruses. Further investigation of metformin as early treatment for SARS-CoV-2 is warranted.

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Preliminary Results: Prevalence and Pathophysiologic Mechanisms of Amenorrhea Among Women Survivors of the 2014–2016 Ebola Outbreak in Sierra Leone

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OBJECTIVES/GOALS: 1. Establish the prevalence of amenorrhea among women Ebola survivors of reproductive age. 2. Determine whether amenorrhea in Ebola survivors is associated with hyperthyroidism, primary ovarian failure, and/or low weight METHODS/STUDY POPULATION: This study will enroll a cohort of 150 women Ebola survivors and 150 uninfected controls from Kenema, Sierra Leone. Participants will complete women's health questionnaires with detailed menstruation history and provide blood samples. Serum levels of thyroid stimulating hormone, follicle stimulating hormone, and albumin will be measured in order to explore the role of thyroid dysregulation, ovarian failure, and low weight in amenorrhea associated with prior Ebola infection. RESULTS/ANTICIPATED RESULTS: Enrollment for the study is still in progress. As of November 14, 2022, 68 female Ebola survivors of reproductive age and 124 uninfected controls have been enrolled. Among this preliminary group, there is a high baseline level of menstrual irregularities in both survivors and controls. Prior to the Ebola outbreak, 97% of all participants reported less than 6 periods per year and 59% reported periods lasting 3 days or less. The prevalence of missed periods increased after the Ebola outbreak in both groups. Four Ebola survivors (5.9%) reported missing periods before infection, compared to 16 (23.5%) survivors after infection. Two uninfected controls (1.6%) reported missing periods before the Ebola outbreak, compared to 12 (9.7%) after the outbreak. DISCUSSION/SIGNIFICANCE: The next steps of this project are to complete enrollment, conduct data analysis, and perform laboratory studies. An enhanced understanding of amenorrhea is needed to develop novel medical interventions, to inform healthcare guidelines and policies, and to develop personalized treatment strategies to better care for women who have survived Ebola.

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Social Anhedonia in the Daily Lives of People with Schizophrenia: Examination of Anticipated and Consummatory Pleasure*

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OBJECTIVES/GOALS: Social anhedonia is considered a key feature of schizophrenia that leads to social withdrawal. Research in general anhedonia suggests those with schizophrenia exhibit deficits in anticipated (predicted), but intact consummatory (in-the-moment), pleasure. This study will determine if these temporal differences apply to daily social anhedonia. METHODS/STUDY POPULATION: This project will use experience sampling methods (ESM) to measure real-world social pleasure in people with schizophrenia and healthy controls. Using electronic surveys, participants will predict social activities they plan to do throughout their day and report anticipated pleasure for each. Then, in subsequent surveys, participants will report their consummatory social pleasure shortly after engaging in each of these activities. We will use a time-lagged approach to match anticipated/consummatory pleasure ratings for specific social events and compute a difference score to determine discrepancy. Multi-level modeling will be used to determine if clinical status (schizophrenia/control) predicts anticipated pleasure, consummatory pleasure, and/or their discrepancy. RESULTS/ANTICIPATED RESULTS: Data collection for this project was recently completed. The schizophrenia and control groups (n = 30 per group) were demographically matched for age, sex, race, and ethnicity. Data processing and analyses are currently underway. We hypothesize that, in line with laboratory research in general anhedonia, those with schizophrenia will exhibit deficits in anticipated, but not consummatory, social pleasure throughout their daily lives. Moreover, when anticipated and consummatory pleasure ratings for the same social activities are matched, we expect those with schizophrenia to exhibit larger discrepancies between predicted and in-the-moment pleasure. DISCUSSION/SIGNIFICANCE: This project serves as a critical intermediate step to bridge the gap between laboratory research and patient treatment. ESM bypasses limitations of laboratory studies and increases ecological validity. Results will provide a nuanced understanding of social anhedonia and help identify precise targets to treat social withdrawal in schizophrenia.

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Establishing a histologically defined NAFLD cohort in the Million Veteran Program for further genetic analyses

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OBJECTIVES/GOALS: Research in Non Alcoholic Fatty Liver Disease Genetics is ongoing. In this project, we aim to: 1.Identify and describe a histological NAFLD Cohort in the MVP Biobank by extracting liver biopsy proven NAFLD patients using natural language processing (NLP) 2.Confirm previously defined NALFD

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