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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This abstract is based on unpublished data.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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