Clinical pathology selected abstracts

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A fecal microbiota signature with high specificity for pancreatic cancer

May 2022—Pancreatic ductal adenocarcinoma is the most common form of pancreatic cancer and a major cause of cancer death, despite its relatively low occurrence rate. Its high mortality levels are attributed to late diagnosis and limited therapeutic options. A sensitive and affordable diagnostic test for pancreatic ductal adenocarcinoma (PDAC) can improve outcomes. Although many PDAC markers have been studied, the only FDA-approved PDAC biomarker is serum carbohydrate antigen (CA) 19-9. However, CA19-9 can be elevated in other disease states, including biliary obstruction, so it is more often used as a marker for PDAC monitoring than screening or diagnosis. Studies are investigating alterations in the oral, fecal, and pancreatic microbiome that have been associated with an increased risk of PDAC and its progression. The authors conducted a study to assess fecal and salivary microbiota as potential diagnostic biomarkers. In the discovery phase of their study, they applied shotgun metagenomics and 16S rRNA amplicon sequencing to samples from a Spanish case-control study (n=136) that included 57 newly diagnosed and treatment-naïve patients, 50 control subjects, and 29 patients with chronic pancreatitis. In the validation phase, they applied the techniques to 76 case-control samples (44 PDAC and 32 controls) from a German study. The results showed that fecal metagenomic classifiers performed much better than saliva-based classifiers for identifying patients with PDAC, with an accuracy of up to 0.84 area under the receiver operating characteristic curve (AUROC) based on 27 microbial species. The AUROC was further improved, reaching 0.94, when microbiome predictions were combined with the less sensitive CA19-9 serum marker. The authors also validated the specificity of the microbiota-based disease classifier in the independent German PDAC cohort (AUROC, 0.83). Using rRNA sequencing and FISH, they showed enriched taxa (*Veillonella, Streptococcus*, and *Akkermansia*) in fecal samples and taxa with differential abundance (*Bacteroides, Lactobacillus*, and *Bifidobacterium*) in healthy and tumorous pancreatic tissues. These microbial signatures can predict PDAC. The authors noted that, in general, they did not observe any salivary PDAC signatures for individual or multispecies models. They concluded that this study suggests that the fecal microbiome may be used to more accurately screen for PDAC when combined with CA19-9. The models showed comparable performance across all PDAC disease stages, with no bias for later stages. The authors also suggested that the panel of PDAC-associated bacterial species may be relevant beyond diagnosis. It shows promise for targeting patients for disease prevention and therapeutic intervention.

Kartal E, Schmidt TSB, Molina-Montes E, et al. A faecal microbiota signature with high specificity for pancreatic cancer. *Gut*. Epub ahead of print March 8, 2022. doi:10.1136/gutjnl-2021-324755

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Effects of CKD testing and disclosing ancestry-specific genetic risk for kidney failure

Chronic kidney disease affects 26 million adults in the United States, and people of African ancestry are shown to have a higher risk of chronic and end-stage kidney disease. High-risk genotypes at the apolipoprotein L1 (APOL1) locus confer a five-fold to 10-fold increased risk of chronic kidney disease (CKD) and end-stage kidney disease from hypertension. These high-risk variants of *APOL1* on chromosome 22 are found in as many as one in seven people of African descent but not in people of European ancestry. This is because the gene variant is associated with resistance to trypanosomal infection and subject to positive selection in West Africa. There is increasing interest in incorporating genetic testing into primary care to identify patients at risk for CKD and then applying these patients' positive findings to their clinical care through such measures as screening for kidney disease and controlling for blood pressure. However, it is not known whether disclosing *APOL1* genetic testing results to patients of African

ancestry and their clinicians will lead to stricter blood pressure control and kidney disease screening or improve patient behaviors. The authors conducted a study to determine the effects of testing and disclosing *APOL1* genetic results to hypertensive patients of African ancestry and their clinicians. They conducted a randomized clinical trial that enrolled 2,050 patients from two health care systems in New York City between Nov. 1, 2014 and Nov. 28, 2016. The patients were hypertensive adults of African ancestry who did not have CKD. The patients were randomly assigned to undergo immediate (intervention) or delayed (waiting list) *APOL1* testing in a 7:1 ratio. The patients assigned to the intervention group received their *APOL1* genetic testing results from staff trained and supervised by genetic counselors, and their clinicians received the results through clinical decision-support functionality in their institutions' electronic health record systems. Patients in the waiting list control group received their results after their 12-month follow-up visits. The main outcomes assessed in the study were changes in three-month systolic blood pressure and 12-month urine kidney disease screening comparing intervention patients with high-risk *APOL1* genotypes to those with low-risk *APOL1* genotypes. Secondary outcomes compared the differences between the intervention group patients with high-risk *APOL1* genotypes and controls. The results showed that the mean systolic blood pressure at baseline and three months was significantly higher in patients with high-risk *APOL1* genotypes than in those with low-risk *APOL1* genotypes and in controls. Furthermore, there was a 12 percent increase in urine kidney disease testing at 12 months among patients with high-risk *APOL1* genotypes versus a six percent increase among those with low-risk *APOL1* genotypes and seven percent among controls. In response to testing, patients with high-risk *APOL1* genotypes reported making more lifestyle changes, including improving their diet and exercise habits and following a blood pressure medication regimen, than those with low-risk *APOL1* genotypes. Overall, 97 percent of the cohort agreed that they would undergo testing again to know their genetic *APOL1* genotype. The authors concluded that disclosing *APOL1* genetic testing results to clinicians and hypertensive patients of African ancestry combined with EHR-based clinical decision support improved blood pressure control and increased kidney disease screening. They suggested that these results support broad implementation of genetic testing in primary care.

Nadkarni GN, Fei K, Ramos MA, et al. Effects of testing and disclosing ancestry-specific genetic risk for kidney failure on patients and health care professionals. A randomized clinical trial. *JAMA Network Open*. 2022. doi:10.1001/jamanetworkopen.2022.1048

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