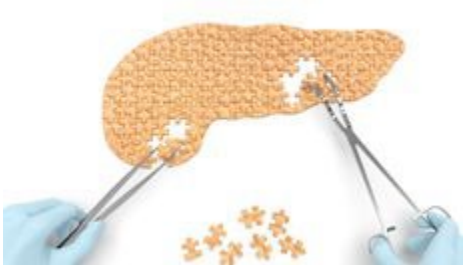
Genomic Test IDs Pancreatic Cysts Likely to Progress to Cancer Better Than Standard Guidelines

Oct 05, 2022 | Catherine Shaffer
Article Publish By Precision Medicine Online



NEW YORK – In a prospective study of more than 1,800 patients at 31 clinical centers in the US, the PancreaSeq test developed at the University of Pittsburgh surpassed currently used guidelines for correctly classifying potentially cancerous pancreatic cysts.

University of Pittsburgh pathologist Aatur Singhi and colleagues reported in a study published today in *Gastroenterology* that after a median follow-up of around two years, the next-generation sequencing-based PancreaSeq panel detected advanced neoplasia in intraductal papillary mucinous neoplasms (IPMNs) and mucinous cyst neoplasms (MCNs) with high sensitivity and specificity. In comparison, when investigators used management criteria from the American Gastroenterological Association and the Fukuoka guidelines established by the International Association of Pancreatology, they diagnosed IPMNs and MCNs with high sensitivity, but low-to-moderate specificity. Those guidelines focus heavily on using features like size and growth rate of the cysts for diagnosis. The researchers said the study results confirmed the utility of PancreaSeq and believe that guideline bodies will update their recommendations to include molecular testing.

Additionally, the researchers looked at 192 of the surgical pathology samples and tested them with PancreaSeq plus Thermo Fisher Scientific's Oncomine test, then compared the findings from these tests against pathology-based assessments. The results further expanded the number of known genomic alterations associated with pancreatic cysts.

Pancreatic cancer develops from either microscopic lesions known as intraepithelial neoplasia or from mucinous cysts, which come in two types, IPMNs and MCNs. Pancreatic mucinous cysts are relatively common, affecting up to 15 percent of people at some point in their lives. Although the majority of these cysts are benign, some progress to pancreatic ductal carcinoma. The standard management protocol is surgical removal of the cyst, but given its risks, especially in elderly patients, doctors often choose to monitor the cysts with serial imaging instead. A more accurate diagnostic

would better inform management decisions as well as help differentiate pancreatic mucinous cysts from other types of cysts.

Based on the latest study, PancreaSeq may be such a test. It determines the cyst type by gauging relevant genomic alterations in the cyst fluid and predicts whether it will progress to pancreatic cancer. PancreaSeq tests for alterations in 22 genes, including BRAF, IDH1/2, KRAS, PIK3CA, PTEN and others. Because only a small quantity of DNA is present in pancreatic cyst fluid, the test is designed to detect very low concentrations of DNA with a very high sensitivity to pick up alterations such as mutations, copy number variations, and fusion genes.

In the published study, PancreaSeq diagnosed mucinous cysts accurately in 90 percent of cases, with a 100 percent specificity, meaning there were no false positives, and it accurately identified mucinous cysts at risk for progressing to cancer in 88 percent of cases, with a 98 percent specificity.

Singhi, who is a co-senior author on the paper, said that pancreatic cancer, when it arises from mucinous cysts, is "fundamentally a genetic disease" with alterations proceeding in a stepwise fashion on that path. "With PancreaSeq, we're able to detect those genomic alterations," Singhi said.

The University of Pittsburgh has been using PancreaSeq routinely in patient care since 2018, and according to Singhi, they screen about 1,000 patients per year. The assay has been offered not only to patients at Pittsburgh, but also to those in other US states and internationally including Canada, England, and Mexico. Singhi said they are able to return a result within seven days of receiving a cyst fluid sample. Data from the latest study showing PancreaSeq's advantages over guidelines-based diagnosis, could drive greater adoption of the test, Singhi and colleagues expect.

So far, other clinical centers are not offering a test quite like PancreaSeq. "There are certainly people doing molecular testing of pancreatic cysts," said Singhi. That includes some university research groups and the diagnostics company Interpace Biosciences, which uses Sanger sequencing, not NGS. Singhi and colleagues demonstrated in 2018 that Sanger sequencing was suboptimal and prone to missing important alterations when used to diagnose pancreatic cysts.

Singhi and his group also discovered a number of novel genomic alterations that had not previously been linked to pancreatic cysts. For example, 5 percent of pancreatic cysts had BRAF alterations. Of those, 8 percent had co-occurring KRAS mutations. BRAF alterations in the study were found to correlate highly with the presence of an IPMN. And RNA sequencing analysis of BRAF-mutated IPMNs showed they had similar gene expression profiles as KRAS-mutated IPMNs. The study authors speculated that BRAF alterations may substitute for KRAS mutations as drivers of the MAPK pathway in the development of IPMNs.

The study also presented an opportunity to look at pancreatic neuroendocrine tumors. "We started encountering pancreatic neuroendocrine tumors that were being tested just

because they were cystic in architecture," Singhi said. "There are certain genomic alterations that can help prognosticate patients with pancreatic neuroendocrine tumors, as well as actually predict if they'll metastasize outside of the pancreas and into the liver."

In clinical practice, most pancreatic cysts are discovered incidentally when a patient seeks treatment for an unrelated condition, such as abdominal pain. Singhi envisions that PancreaSeq could be integrated into the diagnostic workflow when a biopsy is taken from the cyst and help triage the patient for subsequent management via surveillance, surgery, or no treatment. For example, for a cyst that looks concerning, PancreaSeq might predict that it is benign, saving the patient the need for repeat imaging or invasive procedures. On the other hand, PancreaSeq could also identify a seemingly benign cyst that has multiple genomic alterations characteristic of a mucinous cyst.

Singhi's group has used the information gleaned from the study to create an expanded version of the test, PancreaSeq GC, which it released two months ago. It's a DNA- and RNA-based molecular panel testing six types of genomic alterations in 74 genes. PancreaSeq GC is able to test both mucinous and non-mucinous cysts and assign a prognostic score that informs the patient and their physician of the risk of malignancy.

Singhi said PancreaSeq will continue to be marketed as a lab-developed test by the University of Pittsburgh, which already has the lab infrastructure necessary to perform the test and can offer it for minimal cost. The researchers are working with the University of Pittsburgh to establish payor coverage for the test and expect to learn insurers' decisions by year-end.

Going forward, Singhi said that the biggest challenge will be getting the word out about PancreaSeq and that molecularly profiling pancreatic cysts is clinically useful. Although there are currently no biomarker-driven targeted therapies approved to treat these cysts in early stages and prevent progression to pancreatic cancer, Singhi said in the future, a test like PancreaSeq could help identify patients who could benefit from such treatments. "That could certainly be a possibility as we start defining the genomic architecture of different pancreatic cysts. For example, having a G12C inhibitor for KRAS, if we identify an IPMN with a G12C KRAS mutation, that patient could get a targeted therapy for it," said Singhi, adding that clinicians are "still far away from actually doing that in patients."