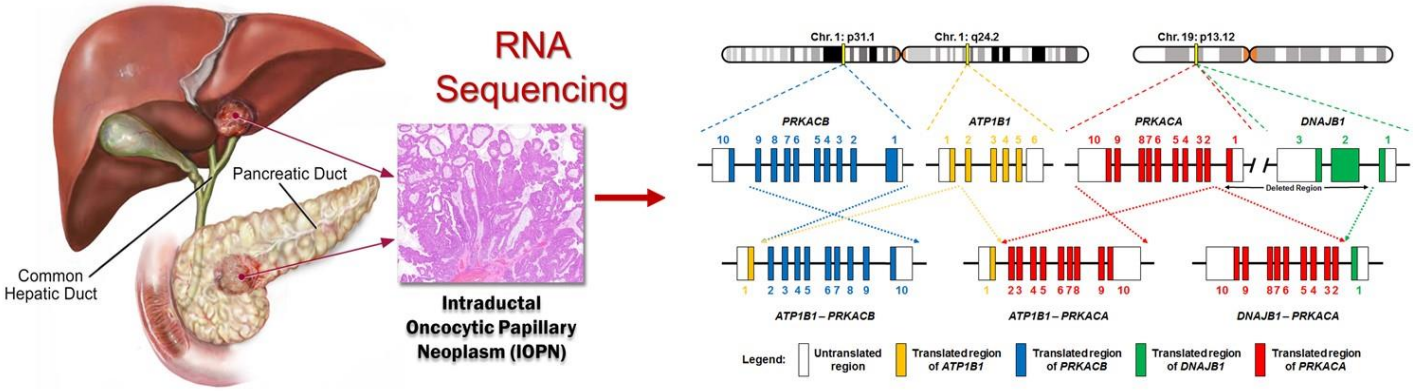
In the United States, with rapid advancements and utilization of radiographic imaging, the detection of pancreatic cysts has become increasingly frequently. In fact, it is estimated that over 6 million Americans each year are found to harbor a pancreatic cyst. Unfortunately, the prevalence of a pancreatic cyst increases with age and up to 24% of Americans above the age of 70 years have a pancreatic cyst. The majority of these cysts are benign and can be monitored clinically. In contrast, a subset of pancreatic cysts, called mucinous cysts, can progress into pancreatic cancer. However, most mucinous cysts are indolent in nature and only a minority will transform into pancreatic cancer.

Currently, a multidisciplinary approach to the evaluation of pancreatic cysts is advocated and involves a team-based approach between the divisions of gastroenterology, radiology, pathology and surgical oncology. Despite a combination of imaging and laboratory technologies for pancreatic cyst assessment, the accurate distinction between mucinous cysts and other pancreatic cysts, and those mucinous cysts harboring pancreatic cancer can be challenging. As a result, pancreatic cysts are often followed by serial imaging and biopsy studies, which can strain US medical resources, is a huge financial burden, and a source of anxiety for both the patient and physician alike over the risk of pancreatic cancer. Further, an overdiagnosis of pancreatic cancer within a pancreatic cyst can result in unnecessary surgical intervention, which is associated with significant mortality and morbidity.

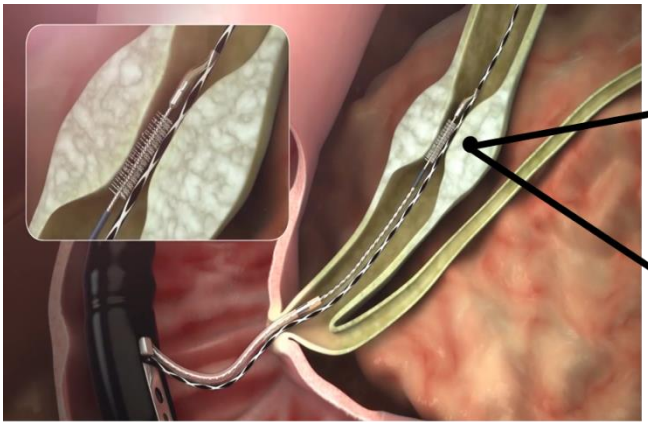
Funding by the Sky Foundation within the laboratory of Dr. Singhi at the University of Pittsburgh Medical Center has led to the development of a clinically available novel precision medicine platform (PancreaSeqV2) for accurate identification of mucinous cysts and early detection of pancreatic cancer. This unique test, termed PancreaSeqV2, uses small amounts of pancreatic cyst fluid to detect molecular alterations present within the pancreatic cyst that are associated with mucinous cysts and pancreatic cancer. The Sky Foundation has enabled PancreaSeqV2 to be used on >1,000 patients in several major medical institutions, such as Johns Hopkins University, Stanford University, Mayo Clinic Florida, Moffitt Cancer Center, Indiana University, University of Texas Southwestern, and others. This has also led to a number of major publications and ongoing research projects as outlined below.

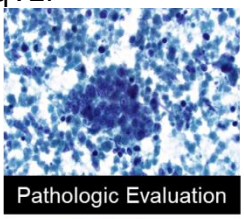
In collaboration with several of the aforementioned major medical institutions and with Sky Foundation funding, we have identified the first gene fusion to characterize a subtype of pancreatic cystic neoplasms called Intraductal Oncocytic Papillary Neoplasms, which are precursors to



pancreatic cancer. This work was reported in the journal of *Gastroenterology* and a parallel report in *Modern*

Pathology from MSKCC recently validated our findings. Moreover, the molecular sequencing backbone for PancreaSeqV2 was used to evaluate an analogous hard to detect and hard to treat area, malignant bile duct strictures. From PancreaSeqV2, we developed BiliSeq to evaluate for malignant bile duct strictures that can be attributed to pancreatic cancer, cholangiocarcinoma and other neoplasms secondarily involving the bile duct. The sensitivity of BiliSeq was superior to standard pathologic evaluation and is currently used by not only UPMC, but other medical institutions – similar to PancreaSeqV2.





Pathologic Evaluation

BiliSeq Testing

Detection of Malignant Bile Duct Strictures

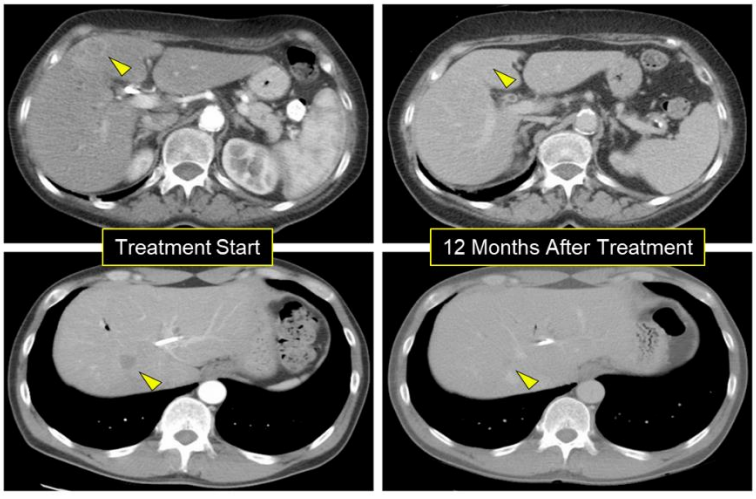
Pathologic Evaluation
- **Sensitivity: 48%**
- **Specificity: 99%**

BiliSeq Testing
- **Sensitivity: 73%**
- **Specificity: 100%**

Of note, BiliSeq also has the ability to identify genomic alterations that can stratify patients for specific anticancer therapy. To date, BiliSeq has identified actionable targets in 18 patients, the most common of which was an *ERBB2* amplification and has led to treatment for a subset of these patients with a trastuzumab-based treatment regimen.

Sudden, Deadly Diagnosis Swiftly Cured with Precision Medicine

- BiliSeq identifies potentially actionable targets among tumors with a 5-year survival of <10%.
- Patrick O'Brien's cholangiocarcinoma was detected by BiliSeq and found to harbor an *ERBB2* amplification.
- Despite evidence of distant metastases, after two years of treatment, Mr. O'Brien is currently disease free.
- Additional patients have had similar treatment success.



Another aspect of Sky Foundation funding has been in the area of neuroendocrine neoplasms of the pancreas to identify prognostic and therapeutic targets. Pancreatic neuroendocrine tumors and carcinomas comprise a heterogenous group of neoplasms with increasing incidence and ill-defined pathobiology. While most pancreatic neuroendocrine neoplasms are indolent and remain stable for years, a subset may behave aggressively and metastasize widely. Thus, the frequent detection of these neoplasms presents a treatment dilemma. Current prognostic parameters and systems, such as size and histologic grade, have had limited success in predicting their clinical behavior, and, despite improvements in surgical intervention and chemotherapeutic regimens, pancreatic neuroendocrine neoplasms can be challenging to manage. Hence, there is a dire need for biomarkers to accurately prognosticate and stratify patients for specific treatment options.

In collaboration with Foundation Medicine, MD Anderson Cancer Center, University of Colorado and George Washington Hospital, we have evaluated 600 pancreatic neuroendocrine neoplasms by both pathology and targeted comprehensive genomic profiling. We have identified several targetable alterations and prognostic markers and will be publishing this data within the new year with obvious acknowledgement of the Sky Foundation for supporting this project. In addition, we have done parallel sequencing of pancreatic neuroendocrine tumors and matched metastases to determine genomic changes that may predict metastatic spread of these neoplasms. We have sequenced 72 PanNETs to date and we are in the process of bioinformatically analyzing this data to validate clinically. This project is a large collaboration between UPMC, MD Anderson Cancer Center, Vanderbilt University and Washington University. Data analysis should be completed by March/April of next year.

To summarize our accomplishments in 2019:

- PancreaSeqV2, a genetic pancreatic cyst test was developed and clinically implemented in over 13 medical institutions in the United States and in 2019 alone used to evaluate >1,000 patients.
- We identified a novel marker of pancreatic cancer and pancreatic cysts that was published a month ago in Gastroenterology and acknowledged the Sky Foundation for their support. As of 2 weeks ago, we have identified another marker and will be discussing this soon.
- BiliSeq was developed as a genetic test to evaluate for bile duct strictures due to pancreatic cancer and other tumors. This is now been released as a clinical test for not only UPMC, but UTSW, WVU and a few other sites.
- In collaboration with 4 other institutions, we have pathologically and molecular evaluation >600 neuroendocrine neoplasms of the pancreas. We are finishing up data analysis, which should out in the next few months.