



NFPTR (left to right): Diane Echavarria (Coordinator), Dr. Alison Klein (NFPTR Director), Chelsea Michael (Coordinator)

FROM THE DIRECTOR

Each year as we put together this newsletter, I am amazed at what has been accomplished and am proud to be a part of such a productive and interdisciplinary pancreatic cancer research team. Despite this progress, I am humbled by the fact that we still have a long way to go before we conquer pancreatic cancer. Our biggest thanks go to each of the families enrolled in the registry. Your participation, willingness to help our research studies and ongoing support of pancreatic cancer research is the cornerstone of all our work.

The primary goals of the NFPTR are to understand the causes of pancreatic cancer so that we can find ways to detect pancreatic cancer early as well as to develop more effective treatments for pancreatic cancer. We have made progress on each of these fronts this year.

This year, as detailed on page 2, we discovered that 3% of families with familial pancreatic cancer have a mutation in the *ATM*. We are continuing to hunt for pancreatic cancer susceptibility genes using the same approaches we used to find the *ATM* gene, in addition to using other genetic approaches. This year the results of the 3rd Cancer of the Pancreas Screening (CAPS) study were also published (see page 3). The screening studies described in this newsletter represent just a fraction of the exciting pancreatic cancer research at Johns Hopkins and the NFPTR.

For updates throughout the year please visit the main Johns Hopkins Pancreatic Cancer website, [//pathology.jhu.edu/pancreas/news.php](http://pathology.jhu.edu/pancreas/news.php)

Thank you again for your ongoing support and best wishes for the New Year!

-Dr. Alison Klein

FROM THE COORDINATORS

It is hard to believe that as recently as the 1970s familial clustering was a phenomenon that was only observed and not yet explained by science as cellular, molecular and genetics research was only beginning. Inherited factors can play a role in both the familial and sporadic forms of pancreatic cancer. With the discovery of the first *inherited* genetic mutations in oncogenes and tumor suppressor genes (*BRCA1* and *BRCA2* genes) in the 1990s, this registry and other Hopkins researchers began their search for inheritable genetic mutations that could lead to an increased risk for pancreatic and other cancers. Since that point onwards, family history information and patient, family member and control samples have the key to our survey of inheritable factors.

Sequencing technologies keep improving allowing us to more effectively study genomes and exomes so we may continue to discover new pancreatic cancer susceptibility genes. Through collaborations within our institution and with other prestigious groups from around the world, the registry has continued to be at the forefront of this research studying the risk factors surrounding pancreatic cancer, collaborating in the development of a screening test for pancreatic cancer and the pursuit of better, targeted treatment options.

Please contact us with any questions, suggestions or updates as we're always happy to hear from you! On behalf of our NFPTR team we thank you for your continued participation in the registry and wish you and yours a very happy and healthy holiday season.

-Chelsea and Diane

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Under a licensing agreement between Myriad Genetics Inc. and the Johns Hopkins University, Drs. Klein, Eshleman, Hruban and Goggins, are entitled to a share of royalty received by the University on sales of products described in this newsletter. The terms of this arrangement are being managed by The Johns Hopkins University in accordance with its conflict of interest policies.

A PARP INHIBITOR TO TREAT PANCREATIC CANCER

Dr. Michael Goggins is leading a phase 1 and 2 clinical trial for patients with locally advanced and metastatic adenocarcinoma of the pancreas that have had no more than a year of treatment prior to enrollment. This trial is available at The Johns Hopkins Hospital and at Columbia University Medical Center. As detailed below, this research study is offering a new combination treatment in the hopes it will provide a good alternative for treatment of this disease. According to Dr. Goggins, the treatment has been "reasonably well tolerated" thus far and, as of the publication date of this newsletter, the trial is still recruiting patients at both sites.

Laboratory studies indicate that some pancreatic cancers, particularly cancers that have defects in the *BRCA2/PALB2* pathway, may be sensitive to a new class of drugs called PARP inhibitors. Phase 1 research trial patients receive the PARP inhibitor olaparib with a low-dose combination of irinotecan, and cisplatin (IC). Both irinotecan and cisplatin have some activity against pancreatic cancer as found in previous clinical trials. If this combination is well tolerated, the trial will also add



Dr. Micheal Goggins

Mitomycin C to the combination (ICM). For the phase 2 trial the plan is to use IC or ICM, with or without the PARP inhibitor olaparib. This trial will determine if there is an added benefit to using IC/ICM with the PARP inhibitor, the rationale being that the combination will prevent the development of resistance to olaparib in patients. Although PARP inhibitors have been extensively studied in previous clinical trials as a single agent and in combination with other chemotherapeutics, this is the first clinical trial evaluating a PARP inhibitor for pancreatic cancer in combination with IC or ICM.

If you are interested in learning more about this clinical trial visit:

[//clinicaltrials.gov/ct2/show/NCT01296763](http://clinicaltrials.gov/ct2/show/NCT01296763)

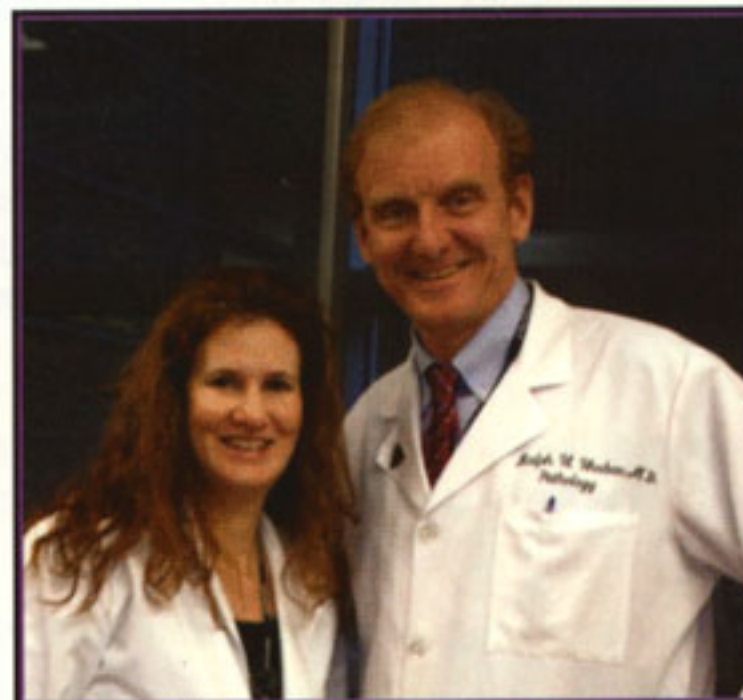
CONTINUED SUCCESS IN THE SEARCH FOR PC GENES

One of the goals of the NFPT is to find the genes that cause some families to have an increased risk of pancreatic cancer. As part of this ongoing work Drs. Alison Klein, Ralph Hruban and Bert Vogelstein led a study funded by the Lustgarten Foundation that discovered a gene that may impact an individual's risk for developing pancreas cancer. NFPT scientists collaborated with colleagues involved in other familial pancreatic cancer registries to sequence all the genes of patients within two families that had a high occurrence of pancreas cancer. In both families all pancreatic cancer patients shared the same mutation in the *ATM* (ataxia telangiectasia mutated) gene. One of the *ATM* gene's normal functions is to coordinate DNA repair by recognizing broken DNA strands, which is consistent with the findings that *ATM* may play a role in pancreatic cancer.

To understand the significance of these mutations researchers then examined the *ATM* gene in samples from 166 patients with familial pancreas cancer, as well as from 190 healthy non-blood relatives of pancreatic cancer patients who had enrolled in the registry. Significant mutations were present in four of the patients with cancer, but no mutations were found in the control group. These results suggest that mutations in the *ATM* gene may account for about 2.4% of families with a familial clustering of pancreatic cancer. While additional studies are needed to verify this finding and to better understand the specific role of *ATM* mutations in familial pancreatic cancer risk, this study helps us to further understand why pancreatic cancer aggregates in some families.

The approach used in the study- sequencing the complete genome of a patient with pancreatic cancer- was not possible a few years ago. Rapid improvements in DNA sequencing technology now allow scientists to sequence an individual's genome quickly and at a reasonable cost, on the order of thousands of dollars per patient. The NFPT team used a similar approach in 2009 to determine that 1-3% of familial pancreatic cancer kindreds carry harmful mutations in the *PALB2* gene. While this approach is very powerful and has led to the discovery of two familial pancreatic cancer genes to date, it is not without its challenges. Each individual genome sequence contains over 6 million changes in their DNA sequence, these changes, in part, are what make each individual unique. Identification of the single genetic change that causes familial pancreatic cancer amidst the millions of changes is very challenging, and

in many cases may take years of subsequent research. We are optimistic that in the coming years this approach will continue to lead to the discovery of additional familial pancreatic cancer genes.



Drs. Alison Klein and Ralph Hruban

CANCER OF THE PANCREAS SCREENING STUDY-3 (CAPS) RESULTS ARE IN!

Currently there are no established clinical guidelines for early detection screening for pancreatic cancer. However, Johns Hopkins gastroenterologist Dr. Marcia (Mimi) Canto has been leading a series of Cancer of the Pancreas Screening (CAPS) clinical trials to examine potential screening practices for high-risk individuals. The results of the third installment of this study were published this year.

"We've confirmed that EUS and MRI [MRCP] are best for detecting small precancerous lesions within ducts." -Dr. Mimi Canto, M.D.

As part of CAPS3, 216 patients underwent MRCP (a special MRI procedure), CT and EUS (endoscopic ultrasound) at one of five participating institutions including Johns Hopkins, Mayo Clinic, UCLA, Dana Farber and MD Andersen. Specialists independently evaluated each type of imaging result for a variety of abnormalities, not sharing the results with one another to reduce bias. One key finding was that that MRCP and EUS detect more lesions than CT; further studies are needed to compare MRCP and EUS.

What types of lesions did the screenings reveal?

Most of the participants (57.4%) had no lesion. In those diagnosed with lesions, the vast majority of the lesions were small changes that can appear in healthy individuals such as tiny cysts that do not require surgery. This subset is being followed periodically with further imaging tests. Five participants with changes that were suspicious for larger pre-cancerous lesions underwent surgery. Screening also led to fine-needle aspiration biopsies in twelve patients, two of which were part of the aforementioned surgical group. During the scope of the CAPS3 protocol, none of the participants were found to have invasive pancreatic adenocarcinoma.

The next phase of the screening study, CAPS4, is currently open to enrollment though only at The Johns Hopkins Hospital. Unaffected family members that may be eligible for CAPS4 include:

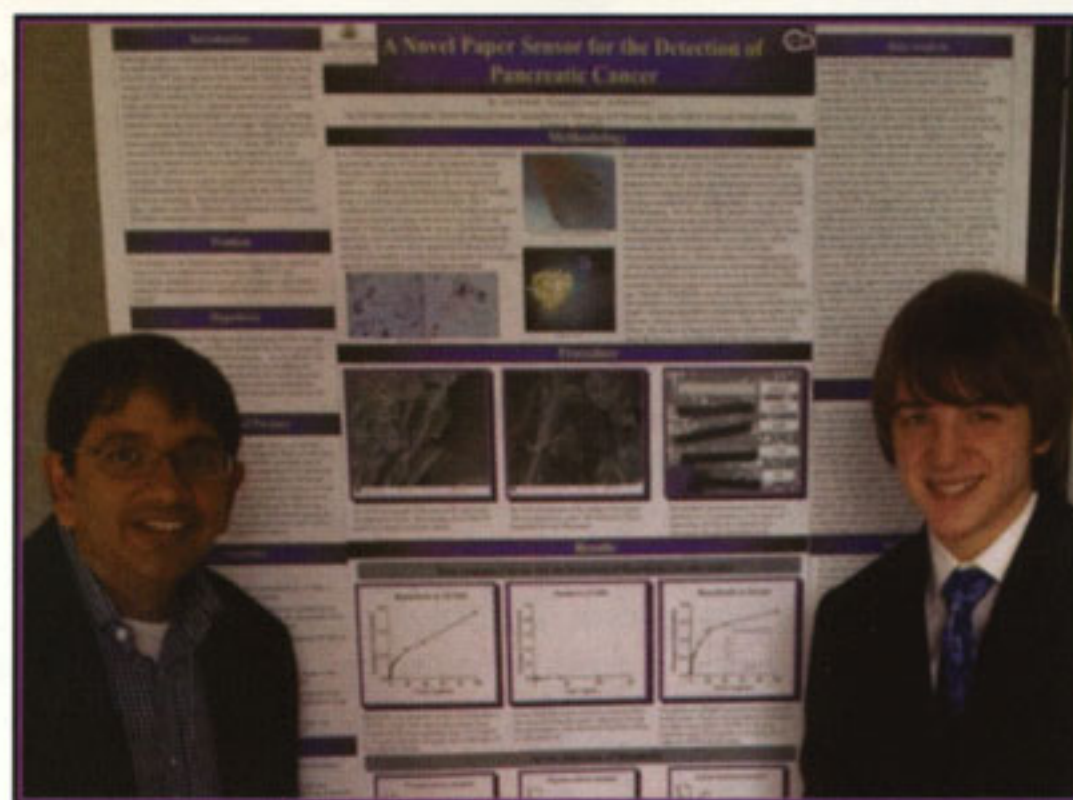
1. Those diagnosed with Peutz-Jeghers syndrome.
2. Those with two close relatives with pancreatic cancer on the same side of the family, one being a parent, sibling or a child.
3. Those with a known BRCA1, BRCA2 or CDKN2A/p16 mutations with a family history of pancreatic cancer.

If you are interested in learning about enrollment email Hilary Cosby at caps4@jhmi.edu.

STUDENT STUDYING PANCREATIC CANCER WINS 2012 INTEL PRIZE

In the spring of 2012, fifteen year-old Jack Andraka was awarded the top prize of \$75,000 in the 2012 Intel International Science and Engineering Fair for pancreatic cancer research conducted in Dr. Anirban Maitra's lab at Johns Hopkins under the direct supervision of Dr. Venugopal Chenna. Andraka had an idea for a screening test to detect the presence of high levels of mesothelin protein in the blood and urine of patients with pancreatic adenocarcinoma by way of a quick and cheap dipstick test based on the current test for diabetes.

Through a pilot study, using a carbon-nanotube-coated paper dipstick, Andraka found mesothelin could be detected in their blood of mice with pancreatic adenocarcinoma, as well as a small sampling of patients with highly advanced pancreatic adenocarcinoma. While the pilot study results are encouraging, larger, more extensive studies are required to determine if the test is both **sensitive enough** to detect lower levels of the protein as would be observed in patients with smaller or earlier cancers, and **specific enough** to differentiate between patients with pancreatic cancer and those with other conditions. Most useful would be a test able to



Dr. Anirban Maitra and 15-year-old Jack Andraka

identify patients with very early pancreatic cancers or pre-cancers that could be offered surgery. This project requires much refining at the laboratory level before it can be applied to patients. We congratulate Jack Andraka and forward-thinking young scientists like him who turn their focus on unanswered questions surrounding this dreaded disease.

HOW YOU CAN HELP:

Spouses are eligible to donate a blood or saliva sample as a "control" (a person without pancreatic cancer to serve as a comparison). Email us at pancreas@jhmi.edu with "Control" in the subject line to receive further information.

PLEASE REMEMBER TO RETURN YOUR UPDATE CARD ENCLOSED WITH THIS NEWSLETTER.

Even if there have been no changes in your family, this information is very important to our research.

Family members with at least one first-degree relative with pancreatic cancer (sibling, parent, or child) as well as another family member with pancreatic cancer on the same side of the family may be eligible to donate a blood sample. Email us at pancreas@jhmi.edu with "Blood

CERTIFICATE OF CONFIDENTIALITY

We want to remind the participants that the NFPtr continues to be protected by a Certificate of Confidentiality (NCI-01-062) from the National Institutes of Health, Department of Health and Human Services.

This certificate further helps us protect the confidential information that you have provided by giving us legal protection from having to involuntarily release any information about you. With this certificate, we cannot be forced by court order to disclose any information for criminal, administrative, legislative, or other proceedings.

If you have any questions regarding this or would like a copy, please contact Diane Echavarria: (410) 955-3502

MEDICAL DONATION RESEARCH PROGRAM

Dr. Iacobuzio-Donahue's Gastrointestinal Cancer Rapid Medical Donation Program (GICRMDP) continues to gather crucial information about metastatic gastrointestinal cancer by participants who volunteer prior to their death to undergo a rapid, research autopsy. If this research study is something you or a family member would like to learn more about, feel free to contact Dr. Iacobuzio-Donahue at ciacubu@jhmi.edu or call her at (410) 955-3511.

CONTACT INFO

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LEARN MORE ABOUT OUR RESEARCH!

Below is a short bibliography of our most recently published research conducted by investigators working with the NFPtr. You can view abstracts of these articles by visiting www.pubmed.com and searching by **PMID**. If you have any questions about any of the studies, please call or email the NFPtr directly at pancreas@jhmi.edu or 410-955-3502.

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