NFPTR
national familial pancreas tumor registry
NEWS
Volume 19

GREETINGS FROM THE NFPTR TEAM!

Each year, we work hard to make strides against pancreatic cancer, and this year was no exception. We are excited to share with you (in our largest newsletter yet!) all the progress we have made this past year in fighting this disease.

While we still have much to learn in order to one day prevent pancreatic cancer, every step we make counts—steps we would not be able to make without the diligent help of families like yours. We are grateful to all of our families for their continued support and participation!

Inside this newsletter, you will read about the progress we have made with our DREAM Team, including the GENERATE study, which is a new project we are very eager to share with you. On page 3, we talk about the potential value of surveillance for high-risk individuals in catching pancreatic cancer early, giving better outcomes and survival rates. We continue with our progress in identifying certain genetic changes that may be related to pancreatic cancer through the Genome -Wide Association Studies (GWAS), and we talk about an important update to the guidelines for genetic testing. On page 6 we discuss the exciting projects we are able to conduct on pancreatic cancer risk assessment and intervention through the Specialized Program of Research Excellence (SPORE) program here at Johns Hopkins.

NFPTR: David McKean (researcher), Dr. Alison Klein (Director), Nancy Porter (coordinator), Sharon Varghese (coordinator)

We want to take this space to also recognize Mary Hodgin, who diligently served as our Pancreatic Multidisciplinary Clinic (PMDC) coordinator for the last 10 years. (Check out last year's newsletter for our *In the Spotlight* article featuring Mary Hodgin). Mary spent countless hours each day ensuring patients had a top-notch experience at our clinic. This year, Mary has decided to step down from her role and retire, making more time for her family and exciting hobbies. We will truly miss Mary at our multidisciplinary clinic, but we wish her the best! (picture on page 5)

As we look back on the past year, we are incredibly grateful for the support and participation from our families. Our research and progress in finding a cure for this disease is only made possible because of you. Please complete and return your update card when you have the chance, and be in contact with us if you have any questions at all. Thank you!

INSIDE THIS ISSUE

WE'RE GOING ELECTRONIC!

Starting this year, we will also be offering an electronic update card! Be sure to **check your email for our new e-update card!**

Please add **pancreas@jhmi.edu** to your e-mail contacts to ensure that you receive our annual newsletters and update cards. This will allow us to follow up with you more quickly and to have the most up-to-date information in our database. If you have any questions, please give us a call!

If you would like to only receive electronic newsletters from us in the future, **check ☑ "Yes, I would like to only receive electronic newsletters in the future"** at the bottom of the enclosed update card.

Did you not receive our E-Newsletter? Email us at **pancreas@jhmi.edu** to make sure we have your most current email on file.

Pancreatic Cancer Interception Dream Team Update

In late 2017, our Stand Up to Cancer (SU2C) Pancreatic Cancer Interception Dream Team began. The goal of this team is to collaborate on projects aimed at "intercepting" cancer, or catching cancer at its earliest stages with effective screening, and halting progression with drugs and vaccines. Since current screening tests remain unsuitable for use in the general population, the Dream team has made this goal a main priority. We have begun to research new approaches that have promising potential to help catch cancer earlier and give patients better outcomes.

Our Dream Team effort spans the six institutions below, working together to transform the outcomes of those at high risk for pancreatic cancer:

- Johns Hopkins University
- Dana Farber Cancer Institute
- MD Anderson Cancer Center
- Moores Cancer Center UC San Diego
- Massachusetts Institute of Technology
- Mayo Clinic

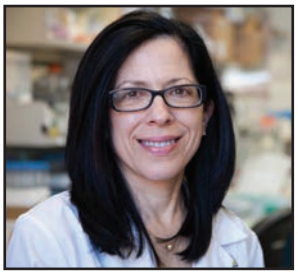
GENETIC RISK EDUCATION One aim of this study is to help family members of patients develop a better understanding of genetic testing and their inherited cancer risk. In the next few weeks, the **GENetic Education Risk Assessment Testing (GENERATE)** study will launch. By informing families about inherited risk, we hope to help those relatives protect themselves from pancreatic and other cancers.

Eligibility includes:

- Having a blood relative who has pancreatic cancer that was caused by an inherited change (mutation) in a gene
- No personal history of pancreatic cancer
- No prior genetic testing or counseling for cancer risk
- Age 18 or older with a U.S. mailing address

As part of this study, relatives will receive online education about genetic testing and will need to complete a series of questionnaires. For more information about eligibility and enrolling, please contact pancreas@jhmi.edu

VACCINE PREVENTION In addition, Dr. Elizabeth Jaffee's laboratory at Johns Hopkins will be leading work to develop a vaccine to help prevent the progression of pancreatic cancer. The KRAS oncogene is one of the most commonly mutated genes in pancreatic ductal adenocarcinoma (PDAC) cases and is involved in the first steps of developing pancreatic cancer.



Dr. Elizabeth Jaffee

About 30 KRAS-positive individuals who have precancerous lesions in their pancreas will be enrolled in the first vaccine trial aimed at preventing pancreatic cancer. The trial will focus on developing the body's immune system against disease-causing changes in the KRAS gene as a means of preventing pancreatic cancer growth. It is important to note that as individuals age, many develop KRAS changes in their pancreas but only a small fraction of individuals with KRAS changes go on to develop pancreatic cancer. As such, a vaccine that targets KRAS but has minimal side effects could be beneficial.

BLOOD TEST DETECTION One continuing goal of the Dream team is to eventually identify a blood test in order to diagnose PDAC in its early stages and thereby give patients more options for treatment and a longer survival. The Dream team has access to blood samples from pre-diagnostic individuals who subsequently developed PDAC within 1-5 years. The team will compare proteins, autoantibodies, and metabolites from blood in a "biomarker bakeoff" in order to create the best panel and test for determining who should receive additional pancreatic screening, such as screening with endoscopic ultrasound, which has been shown to detect some pancreatic cancer early in individuals at high-risk of pancreatic cancer (see CAPS story on next page).

THE FELIX PROJECT

Dr. Elliot Fishman

As part of SU2C and through the support of the Lustgarten Foundation, Dr. Elliot Fishman and collaborators are working to spot pancreatic tumors with the development of a novel artificial intelligence (AI) program. In 2018, the U.S. Food and Drug Administration approved a computer AI program that helps doctors diagnose strokes, along with another AI program that can diagnose broken wrists. Dr. Fishman hopes to further this line of research and extend AI to the diagnosis of pancreatic tumors. With nearly 40 million Americans receiving CT scans of the abdomen every year (for car accidents, back pain, etc.), implementing this AI program into CT software has the potential to catch cancer at its earliest stages, before symptoms appear, and in ways that the human eye could not recognize. The Felix Project is working hard to train computers to detect the difference between a healthy pancreas and one with a tumor. If successful, the information could be used to detect tumors throughout the body, all through one CT scan.

It's our hope that our team will identify interception points and stop pancreatic cancer in its tracks, opening up more possibilities for treatment and saving many lives.

Cancer of the Pancreas Screening Study Shows Surveillance Improves Survival

Marcia (Mimi) Canto, MD

In our 1st newsletter in 2000, we talked about Dr. Mimi Canto's work on screening for pancreatic cancer using endoscopic ultrasonography (EUS) in her pilot research program called 'Cancer of the Pancreas Screening Study' (CAPS). Over the years our newsletters have highlighted some of the great work being done through the CAPS studies. In fact, the work conducted in the CAPS study provided some of the foundation on which the current SU2C Interception studies are based (See page 2).

Most recently, Dr. Canto and the CAPS team published results from the CAPS 1 -4 studies, evaluating the surveillance of individuals at high risk of pancreatic cancer. Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer, and is currently the 3rd leading cause of cancer deaths in the U.S.; the 5-year survival rates remain below 10%. Pancreatic cancer screening is not recommended for the general population, but is currently being evaluated for high-risk individuals with a lifetime risk greater than 5%.

The current study evaluated 354 high-risk individuals (based on family history and genetic factors) who were enrolled in any of the CAPS 1-4 studies from 1998 to 2014. All study participants underwent a baseline EUS, or EUS and CT based on which CAPS study they enrolled in. Routine surveillance utilized annual imaging using EUS, MRI, or CT (more frequent imaging surveillance was done for individuals with pancreatic cysts or lesions).

Overall, pancreatic cancer and its high-grade precursor neoplasms developed in 7% of high-risk study participants; 93% of those individuals had detectable lesions with worrisome features before diagnosis. Of note, 90% of the pancreatic cancers detected during routine surveillance were able to be removed surgically with 85% survival at 3 years. This study also led to the discovery that certain detectable radiologic abnormalities could predict progression of disease, which in turn increases survival, as nearly all screening-detected tumors are able to be treated surgically.

The results of this study support the growing body of literature showing a potential benefit in the screening and surveillance of individuals at high risk of developing pancreatic cancer. However, more research needs to be done to determine the best age to begin pancreatic cancer screening, and to improve biomarkers for early detection.

The CAPS study is currently recruiting individuals for its 5th phase at locations in CT, MD, MA, MI, NY, OH, and PA.

For more information on how to participate, please contact Hilary Cosby at: hcosby1@jhmi.edu

Team at Annual CAPS Consortium Meeting

New Common Low Risk Genetic Variants for Pancreatic Cancer Identified

While much of the research by the NFPTR team focuses on inherited genetic changes that cause a high lifetime risk of pancreatic cancer (>5%), there are also many inherited genetic changes that individually cause a small increase in the risk of pancreatic cancer (i.e. increase lifetime risk from about 1.0-1.2%). These changes are typically found through large Genome-Wide Association Studies (GWAS) where the frequency of what are often common genetic variants (occur in >10%) of the population are compared between individuals who developed pancreatic cancer and those who did not.

For the past decade, Dr. Alison Klein, along with teams from the Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4) have been working to find these common changes, some of which we have discussed in our past newsletters. This year we reported the results of the largest pancreatic cancer GWAS to date. This study identified five new susceptibility regions on genes that are thought to play a role in pancreatic cancer development. Dr. Klein and her collaborators analyzed more than 11.3 million variants in 21,536 people.

The newly identified genetic variants – located on human chromosomes 1 (position 1p36.33), 7 (position 7p12), 8 (position 8q21.11), 17 (position 17q12) and 18 (position 18q21.32) – may increase the risk of pancreatic cancer by 15-25% for each copy present in the genome. Dr. Klein says, "On an individual level, having one of these variants isn't very predictive of cancer, in that they're only associated with a modest change in risk, but when taken together, they help to create the fuller picture of how pancreatic cancer develops".

A pancreatic cancer associated variant was found in the *NOC2L* gene. This gene makes a protein that binds directly to the tumor protein p53, a major driver gene in pancreatic cancer. It also binds with another tumor protein gene called p63. Dr. Klein and colleagues had previously shown that there were pancreatic cancer associated variants in the p63 gene. Additional pancreatic cancer genetic variants were identified in the *HNF4G* and *HNF1B* genes. These are genes called hepatocyte growth factors, which are involved in the regulation of cell growth and have been shown to play a role in the regulation of the pancreas and in the development of cancer.

Dr. Klein is working on continuing studies to delve deeper into the genetics of pancreatic cancer, and Klein says, "There is still a lot more that we don't know about hereditary factors in pancreatic cancer risk".

Did You Know? Genetic Testing Now Recommended For All Pancreatic Cancer Patients

In our newsletter last year, we reported that about 4% of all pancreatic cancer patients were found to have an inherited change in a high-risk cancer predisposition gene. In the past year, several other studies have confirmed this finding and found the rate of disease-causing changes may be even higher – 6% or greater. Based upon these studies, Clinical Practice Guidelines in Oncology were updated by the National Comprehensive Cancer Network (NCCN) to expand testing criteria. Testing for inherited disease-causing changes in hereditary cancer genes including *BRCA1/2*, *ATM*, *PALB2*, *CDKN2A*, and DNA mismatch repair genes, is now recommended for all patients with pancreatic cancer.

Identifying these disease-causing changes can help provide information about the patient's cancer as well as the best treatment plans for the patient. For example, studies out of Johns Hopkins have shown that cancers with defects in *BRCA2* or *PALB2* mutations may respond better to platinum-based therapies. Clinical trails led by Dr. Dung Le, a medical oncologist at the Sidney Kimmel Comprehensive Cancer Center, and others led to the FDA approval of checkpoint inhibitors for cancers with defects in DNA mismatch repair, or so-called "micro-satellite unstable cancers". As we continue to study patients with disease-causing changes in specific genes, we hope to continue to find improved treatments for the cancers that develop in these patients by targeting the specific disease-causing changes.

Finding an inherited disease-causing variant also has implications for family members. The children and siblings of pancreatic cancer patients found to have an inherited disease-causing variant have about a 50% chance of also having the same disease-causing change. As we discussed previously on page 2, the GENERATE study is looking at how best to educate family members about their personal cancer risk. We encourage all family members of pancreatic cancer patients found to have a disease-causing change in a hereditary cancer gene to consider genetic testing and education, either through the GENERATE study or a local genetic counselor (www.nsgc.org).

However, we still don't know all of the causes responsible for the clustering of pancreatic cancer in some families. The NFPTR continues to look for these causes as well and study families where a disease-causing change has been identified.

PLEASE REMEMBER TO RETURN YOUR UPDATE CARD ENCLOSED WITH THIS NEWSLETTER OR CHECK YOUR EMAIL FOR YOUR E-UPDATE CARD

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

Specialized Program of Research Excellence (SPORE) RENEWAL

The Specialized Program of Research Excellence (SPORE) is a multidisciplinary program here at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center. The aim of the SPORE is to facilitate comprehensive, translational research of gastrointestinal cancers. We are happy to announce that our SPORE program has been renewed this year, allowing us to continue our work in improving risk assessment, therapeutic interventions, and early detection for pancreatic and colorectal cancers. The Johns Hopkins SPORE is lead by our director, Dr. Alison Klein. The SPORE program includes 4 main projects:

Project 1: Improving Pancreatic Cancer Risk Assessment Risk assessment of pancreatic cancer can improve through evaluation of genetic variants and their association with pancreatic cancer risk, and examination of a person/family's history of other cancers in relation to pancreatic cancer risk. We hope that this project will provide the scientific basis to inform risk assessment and genetic counseling for high-risk individuals who would benefit most from early screening. This project is co-lead by Drs. Alison Klein and Michael Goggins.

Project 2: Neo-Antigen Vaccines for Pancreatic and Colorectal Cancer Genetic mutations in the tumor can produce tumor-specific mutant proteins that are not expressed in normal cells, which are called neo-antigens. This project will evaluate the possibility of developing approaches that will combine a neo-antigen targeted vaccine with immunotherapy that will elicit a clinical response in pancreatic cancer patients. This project is co-lead by Drs. Elizabeth Jaffee, Daniel Laheru, and Nilo Azad.

Project 3: Diagnosis and Management of Pancreatic Cysts The aim of project 3 is to develop an appropriate test tool that can be used to improve the management of pancreatic cysts. The test will incorporate imaging, molecular, clinical, and protein data. The goal is for this test to be utilized in a clinical setting to help patients with pancreatic cysts avoid unproductive surgery or surveillance, and improve their options and outcomes. This Project is co-lead by Drs. Anne Marie Lennon, Ken Kinzler, and Bert Vogelstein.

Project 4: Tumor Microenviroment Genetics and Immunobiology to Drive Combination Therapies This project addresses questions about cancer responsiveness to immunotherapy and looks into why some tumors are responsive and others are resistant to immunotherapy. We intend to create immunotherapies that combat resistance, changing resistant tumors into tumors that respond to immunotherapy. This study builds upon the pioneering work conducted in our GI SPORE program demonstrating that tumors with micro-satellite instability respond to immunotherapy with checkpoint inhibitors. As part of this work, patients' samples from recently completed and ongoing clinical trials of immunotherapy agents, including combinations of treatment vaccines and checkpoint agents, will be studied. This study is lead by Drs. Dung Le, Lei Zheng, and Elizabeth Jaffee.

Congratulations On Your Retirement Mary Hodgin!

CROSSWORD ANSWERS

ACROSS: 2 GENOME | 4 KLEIN | 7 PDAC | 8 VACCINE | 9 SPOUSE | 11 SURVEILLANCE | 12 SCREENING

DOWN: 1 INTERCEPTION | 3 TWOTHOUSAND | 5 UPDATECARD | 6 GENERATE | 10 SPORE

WAYS YOU CAN HELP

If you are interested in learning more about any of the studies discussed here, please send us an email at pancreas@jhmi.edu

Control Participation Spouses are eligible to serve as a "control" for us by donating a blood or saliva sample and completing a family history questionnaire. A control group is crucial for our research as it allows us to validate the significance of pancreatic cancer genes that we discover. If you are interested in enrolling as a spouse control, please send us an email.

Donations Those of you wishing to support the NFPTR pancreas cancer research at Johns Hopkins may do so by sending your tax-deductible contribution payable to NFPTR to our mailing address listed below. Or by visiting: pathology.jhu.edu/pancreas/support.php

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LEARN MORE ABOUT OUR RESEARCH

Below is a short list of citations of key discoveries made by the NFPTR over the past twenty years. Due to space limitations, we can only show a few of our publications, but we hope that this conveys some of the progress we have made. To view abstracts and full versions of these publications, please visit the NCBI PubMed website (ncbi.nlm.nih.gov/pubmed) and search by the **PMID #**

1. Klein et al. Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. *Nat Commun*. 2018 Feb 8. **PMID: 29422604**
2. Canto et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. *Gastroenterology*. 2018 Sep. **PMID: 29803839**
3. Goggins et al. Intercepting Pancreatic Cancer: Our Dream Team's Resolve to Stop Pancreatic Cancer. *Pancreas*. 2018 Nov/Dec. **PMID: 30325853**
4. Deng et al. Determinants and prognostic value of quality of life in patients with pancreatic ductal adenocarcinoma. *Eur J Cancer*. 2018 Mar. **PMID: 29413686**
5. Skaro et al. Prevalence of Germline Mutations Associated with Cancer Risk in Patients With Intraductal Papillary Mucinous Neoplasms. *Gastroenterology*. 2019 Feb 1. **PMID: 30716324**
6. Walsh et al. Agnostic Pathway/Gene Set Analysis of Genome-Wide Association Data Identifies Associations for Pancreatic Cancer. *J Natl Cancer Inst*. 2018 Dec 12. **PMID: 30541042**
7. Grant et al. Exome-Wide Association Study of Pancreatic Cancer Risk. *Gastroenterology*. 2018 Feb. **PMID: 29074453**
8. Cohen et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. 2018 Feb 23. **PMID: 29348365**
9. Tamura et al. Mutations in the pancreatic secretory enzymes CPA1 and CPB1 are associated with pancreatic cancer. *Proc Natl Acad Sci USA*. 2018 May 1. **PMID: 29669919**
10. Schunke et al. Long-term analysis of 2 prospective studies that incorporate mitomycin C into an adjuvant chemoradiation regimen for pancreatic and periampullary cancers. *Adv Radiat Oncol*. 2017 Aug 3. **PMID: 29556579**
11. Felsenstein et al. New Developments in the Molecular Mechanisms of Pancreatic Tumorigenesis. *Adv Anat Pathol*. 2018 Mar. **PMID: 2891462**
12. Antwi et al. Pancreatic Cancer Risk is Modulated by Inflammatory Potential of Diet and ABO Genotype: A Consortia-based Evaluation and Replication Study. *Carcinogenesis*. 2018 May 25. **PMID: 29800239**
13. Kuboki et al. Single-cell sequencing defines genetic heterogeneity in pancreatic cancer precursor lesions. *J Pathol*. 2019 Mar. **PMID: 30430578**

NFPTR NEWSLETTER CROSSWORD

ACROSS
2 Subject of large association studies
4 NFPTR director
7 Most common form of pancreatic cancer
8 Focus of a SPORE project
9 Control participant
11 Goal of CAPS study
12 Not only for showing movies

DOWN
1 SU2C goal
3 NFPTR newsletter premiere year
5 'Important to our research'
6 Genetic testing education study
10 Seed of sorts