# **GREETINGS FROM THE NFPTR TEAM!**

The NFPTR team would like to give a sincere and heartfelt thank you to NFPTR families for your continued participation and support!

We would like to welcome our new coordinators, Jason Hochwald and Claudia Xie! Jason received his BA in Public Health Studies from Johns Hopkins University and is scheduled to complete his MHS in Epidemiology in December 2021. He has previously worked on the Cancer of the Pancreas Screening Study (CAPS-5) with Dr. Michael Goggins and is currently conducting research on the effects of cigarette smoking on pancreatic cancer risk.

Claudia received her BS and MS in Biological Sciences from the University of Maryland Baltimore County in 2019 and this past May 2021. She has previously worked as a research fellow at the Center for Food Safety and Applied Nutrition (CFSAN).

In this newsletter, we spotlight Dr. Nicholas Roberts, who is making great strides in advancing our

Meet our new NFPTR coordinators: Claudia Xie and Jason Hochwald

understanding of the genetic and biological basis of inherited pancreatic cancer. We also discuss improvements in early detection, as well as new risk estimates associated with pathogenic variants in the ATM gene. Furthermore, we detail a new international, multicenter study co-lead by Dr. Klein aimed at understanding the genetics of pancreatic cancer in African Americans. As always, we have provided a list of publications if you are interested in learning even more about the work we are doing, which we could not do without the help of families like yours.

As 2021 comes to a close, we would like to thank you again for your continued participation and support. Please complete and return the enclosed update card and short survey on cancer screening. Please also contact us with any questions or updates.

Thank you!

# **WE'RE GOING ELECTRONIC!**

Thank you to the over 2,000 families that submitted their family update electronically last newsletter! Due to its success, we will continue to offer the electronic update card to all families with email addresses in our system.

<u>Please add pancreas@jhmi.edu to your e-mail contacts</u> to ensure that you receive our annual newsletters and update cards. Be sure to **check your email for our new e-update card!** 

If you would like to only receive electronic newsletters from us in the future, check  $\square$  "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.

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national familial pancreas tumor registry

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## IN THE NFPTR SPOTLIGHT: NICHOLAS J. ROBERTS, PH.D., VET.M.B.



**Dr. Nicholas Roberts** 

Dr. Nicholas Roberts is an Assistant Professor of Pathology and Oncology at the Hopkins University Johns School of Medicine, Dr. Roberts an expert in pancreatic is genetics and cancer of experimental models pancreatic cancer the and Roberts laboratory conducts research to understand the genetic and biological basis of inherited pancreatic cancer.

In collaboration with Dr. Alison

Klein and the NFPTR team, Dr. Nicholas Roberts was among the first to conclusively demonstrate an association between pathogenic inherited *ATM* variants and risk of pancreatic cancer as well as risk of IPMNs. Dr. Robert and Dr. Klein also conducted a pivotal study to sequence the germline genomes of 638 patients with familial pancreatic cancer. Their analyses validated the role of previously identified familial pancreatic cancer susceptibility genes such as *ATM, BRCA2, CDKN2A*, and *PALB2*, and found that pathogenic inherited *ATM* variants were one the most frequent causes of inherited pancreatic cancer (see our 2016 newsletter). Furthermore, in a study of 23 patients with a pathogenic inherited *ATM* variant, Dr. Roberts demonstrated an increased incidence of colloid carcinomas, a subtype of pancreatic cancer, and increased survival compared to patients without a pathogenic inherited *ATM* variant.

More recently, Dr. Roberts has applied state-of-the-art 3dimensional tissue culture models called organoids to his research. Dr. Roberts and his lab have studied organoids derived from surgically resected IPMNs and normal pancreas to characterize the early molecular events that lead to the development of this type of precursor lesion. His group has also used the organoid culture system to generate and characterize the first organoid line derived from an intraductal tubulopaillary neoplasm, a rare subtype of pancreatic cancer precursor lesion. The precursor organoid lines developed by the Roberts Laboratory are a valuable resource for pancreatic cancer researchers and continue to be used in research aimed at improving the care patients with pancreatic cancer and patients with precursor lesions.

### **IMPROVING THE EARLY DETECTION OF PANCREATIC CANCER**

Over the past few years, we have seen advances in our ability to detect pancreatic cancer. These advances, while not yet ready for routine clinical use, we hope that clinical trials testing these approaches in high-risk populations will soon make this possible. We are taking a multi-faceted approach exploring different techniques.

**Blood based screening test:** In our 2017 newsletter we highlighted a new blood based cancer screening test developed by Johns Hopkins Researchers, "CancerSEEK". The blood test works by combining ctDNA with protein biomarkers to detect released tumor DNA that are in the bloodstream. Our group recently published a large-scale follow up study to prospectively evaluate the CancerSEEK test; using CancerSEEK in addition to routine cancer screening in 10,000 women age 65-75 without cancer. In this study, there were 96 individuals diagnosed with cancer, including 26 individuals whose cancers were first detected by the CancerSEEK test. Dr. Ann Marie Lennon, lead author in this study stated, "The screening methods that we have are good, but not all cancers have screening tests. For instance, there's no routine screening for ovarian cancer; this study has shown that it's possible to detect cancers, including early cancers, leading to surgery with the intent to cure in individuals with no history of cancer with a blood test — that a blood test can be incorporated into routine clinical care without discouraging patients from engaging in other forms of screening, and that testing can be performed in safe manner." For additional information see: <a href="https://www.hopkinsmedicine.org/news/articles/blood-test-combined-with-pet-ct-technology-shows-promise-in-early-cancer-detection">https://www.hopkinsmedicine.org/news/articles/blood-test-combined-with-pet-ct-technology-shows-promise-in-early-cancer-detection</a>

**Improvements in imaging:** Dr. Elliot Fishman is exploring applying computer algorithms "deep learning" to CT scans to detect underlying cancers. This effort – called "Felix", funded by the Lustgarten Foundation, is being trained to pick up subtle changes that might indicate an early pancreatic cancer. For more about this effort see: <u>https://www.hopkinsmedicine.org/news/</u>publications/hopkins\_medicine\_magazine/features/spring-summer-2019/this-is-our-manhattan-project

**Molecular test for pancreatic cysts:** Our team at Johns Hopkins has developed a comprehensive pancreatic cyst test, "CompCyst" to guide the clinical management of patients with pancreatic cysts. Fluid is removed from the cyst and analyzed at the molecular level. Depending on the results, some individuals may be recommended to have surgery to remove their cysts, others may benefit further monitoring, while others may require no care for their cysts. "Detecting pancreatic cancer is a challenging problem" Klein says. "We've learned so much, and we're beginning to see the bar shift. As we make progress in screening high-risk populations, we will be able to extend what we learn to screen for cancer among the general population."

### WORKING TO IMPROVE RACIAL DISPARITIES IN PANCREATIC CANCER RESEARCH



Dr. Alison Klein

Medicine and the role genetics' plays in it is rapidly changing and growing. This growth has highlighted the scarcity of genetic research in diverse populations. Some studies have reported that African Americans are 20% more likely to develop pancreatic cancer, but research regarding the reasoning behind this increase is lacking. We know that disparities in diagnosis and care are more

prevalent among African Americans and some studies showed better outcomes in African Americans who received quality care. Lifestyle factors such as smoking and obesity also play a role in increasing risk of pancreatic cancer, as well as type II diabetes, all of which are more prevalent among African Americans. There is very little African American representation in genetic research, as most genetic risk profiles are based on European populations. Diverse representation in genetic research is imperative to ensure that genetic-based targeted prevention and treatment studies are equally beneficial to African Americans, and to determine how much of the increased risk is due to social determinates and how much is from genetic causes.

Recently, Dr. Alison Klein was awarded a NIH U01 grant to start to fill this gap in research. Together with investigators from other cancer centers, we will lead a study of 2,000 African Americans (1:1 pancreatic cancer patients to healthy controls) to look for genetic differences that may be pancreatic attributable to an increased risk of cancer. Klein says, "We know genetics play an important role, but we don't know if these genes play the same role across all populations". Whole genome sequencing will allow us to take a better look at the genetic risk profile in African Americans.

Pancreatic cancer doesn't give a lot of early warning signs, making it crucial to identify high risk populations. Type II diabetes is possibly one of those early warning signs, especially among African Americans. We are working to identify when diabetes causes pancreatic cancer and when pancreatic cancer causes diabetes. Differentiating between the two will improve early detection efforts, allowing for better outcomes in high risk populations.

#### PATHOGENIC ATM VARIANTS AND PANCREATIC CANCER RISK

Pathogenic variants in the *ATM* gene have previously been associated with increased pancreatic cancer risk. A pathogenic variant is an alteration in one's genetic code that increases one's risk of an illness. Pathogenic ATM variants have been associated with increased lifetime risk of breast cancer in the past. These variants occur in 1% to 3% of pancreatic cancer patients. However, until recently, the lifetime risk of pancreatic cancer for individuals with pathogenic *ATM* mutations had not been estimated.

A recent publication from our team assessed the age-specific and lifetime cumulative pancreatic cancer risks of ATM mutation carriers. The multicenter cohort study used data from 130 families with a pathogenic ATM variant, participating in the Pancreatic Cancer Genetic Epidemiology Consortium, including families from our registry, the NFPTR. There was a total of 2,227 family members with 155 individuals who tested positive for an ATM pathogenic variant and 16 individuals who tested negative for an ATM pathogenic variant. The rest of the family members did not have a test result.

Our team found that the average age of pancreatic cancer diagnosis among individuals with pancreatic cancer in our

study was 64 years old. Cumulative pancreatic cancer risk among individuals with an *ATM* variant was 1.1% by age 50, 6.3% by age 70 and 9.5% by age 80.

Our team discovered that the lifetime relative risk comparing *ATM* pathogenic variant carriers to non-carriers is 6.5. This means that individuals with an ATM pathogenic variant have a 6.5-fold increased risk of developing pancreatic cancer at some point in their life compared to non-carriers.

The findings from this study will help influence decision-making among individuals with pathogenic *ATM* variants or a family history of these variants by making them more informed of both their lifetime pancreatic cancer risk and their cumulative risk before a certain age. This information will enable more informed decisions on early detection surveillance among high-risk individuals.



Dr. Fang-Chi Hsu

In addition to the update card, please complete & return the enclosed questions regarding cancer screening. You can answer these questions via mail or electronically with the e-update card! Thank you!

#### 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!

## **Certificate of Confidentiality**

We want to remind the participants that the NFPTR continuers 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 being required 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 Claudia or Jason at 410-955-3512 and 410-955-3502

## WAYS YOU CAN HELP

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

**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

## **CONTACT INFORMATION**

NFPTR Director: Alison Klein, PhD, MHS Sr. Research Coordinator: Nancy Porter, MS Research Coordinator: Claudia Xie

Research Coordinator: Jason Hochwald

Phone: (410)955-3512 Fax: (410)955-9303

Email: pancreas@jhmi.edu Website: NFPTR.org

Mailing Address:

National Familial Pancreas Tumor Registry CRB II Room 341 1550 Orleans St. Baltimore, MD 21231

## 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 (<u>ncbi.nlm.nih.gov/pubmed</u>) and search by the **PMID** number:

- 1. Hsu F, et al. Risk of Pancreatic Cancer Among Individuals With Pathogenic Variants in the ATM Gene. JAMA Oncol. Published online September 16, 2021. doi:10.1001/ jamaoncol.2021.3701
- 2. Cristiano, S., et al. Bayesian copy number detection and association in large-scale studies. BMC Cancer 20, 856 (2020). https://doi.org/10.1186/s12885-020-07304-3
- 3. Zhou C, et al. Examination of ATM, BRCA1, and BRCA2 promoter methylation in patients with pancreatic cancer. Pancreatology. 2021 Aug;21(5):938–41.
- Springer S, et al. A multimodality test to guide the management of patients with a pancreatic cyst. Sci Transl Med. 2019 Jul 17;11(501):eaav4772. doi: 10.1126/ scitranslmed.aav4772. PMID: 31316009; PMCID: PMC7859881.
- Blackford AL, et al. Recent Trends in the Incidence and Survival of Stage 1A Pancreatic Cancer: A Surveillance, Epidemiology, and End Results Analysis. J Natl Cancer Inst. 2020 Nov 1;112(11):1162-1169. doi: 10.1093/jnci/djaa004. Erratum in: J Natl Cancer Inst. 2021 Feb 1;113(2):216. PMID: 31958122; PMCID: PMC7669234.
- Klein AP. Pancreatic cancer: a growing burden. Lancet Gastroenterol Hepatol. 2019 Dec;4(12):895-896. doi: 10.1016/S2468-1253(19)30323-1. Epub 2019 Oct 21. PMID: 31648975; PMCID: PMC7376745.
- Lennon AM, et al. Screening for Pancreatic Cancer-Is There Hope? JAMA Intern Med. 2019 Oct 1;179(10):1313-1315. doi: 10.1001/jamainternmed.2019.3323. PMID: 31386154; PMCID: PMC7377200.
- Thompson ED, et al. The genetics of ductal adenocarcinoma of the pancreas in the year 2020: dramatic progress, but far to go. Mod Pathol. 2020 Dec;33(12):2544-2563. doi: 10.1038/s41379-020-0629-6. Epub 2020 Jul 23. PMID: 32704031; PMCID: PMC8375585.
- Zhu J, et al. Associations between Genetically Predicted Blood Protein Biomarkers and Pancreatic Cancer Risk. Cancer Epidemiol Biomarkers Prev. 2020 Jul;29 (7):1501-1508. doi: 10.1158/1055-9965.EPI-20-0091. Epub 2020 May 21. PMID: 32439797; PMCID: PMC7334065.
- Macgregor-Das A, et al. Detection of Circulating Tumor DNA in Patients with Pancreatic Cancer Using Digital Next-Generation Sequencing. J Mol Diagn. 2020 Jun;22(6):748-756. doi: 10.1016/j.jmoldx.2020.02.010. Epub 2020 Mar 20. PMID: 32205290; PMCID: PMC7338889.
- Abe T, et al. Gene Variants That Affect Levels of Circulating Tumor Markers Increase Identification of Patients With Pancreatic Cancer. Clin Gastroenterol Hepatol. 2020 May;18(5):1161-1169.e5. doi: 10.1016/j.cgh.2019.10.036. Epub 2019 Oct 30. PMID: 31676359; PMCID: PMC7166164.
- Yuan F, et al. Genome-Wide Association Study Data Reveal Genetic Susceptibility to Chronic Inflammatory Intestinal Diseases and Pancreatic Ductal Adenocarcinoma Risk. Cancer Res. 2020 Sep 15;80(18):4004-4013. doi: 10.1158/0008-5472.CAN-20 -0447. Epub 2020 Jul 8. PMID: 32641412; PMCID: PMC7861352.
- Tang H, et al. Genome-Wide Gene-Diabetes and Gene-Obesity Interaction Scan in 8,255 Cases and 11,900 Controls from PanScan and PanC4 Consortia. Cancer Epidemiol Biomarkers Prev. 2020;29(9):1784-1791. doi:10.1158/1055-9965.EPI-20-0275
- Chen F, et al. Analysis of Heritability and Genetic Architecture of Pancreatic Cancer: A PanC4 Study. Cancer Epidemiol Biomarkers Prev. 2019;28(7):1238-1245. doi:10.1158/1055-9965.EPI-18-1235
- Mocci E, et al. Smoking Modifies Pancreatic Cancer Risk Loci on 2q21.3. Cancer Res. 2021;81(11):3134-3143. doi:10.1158/0008-5472.CAN-20-3267
- Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol. 2021;18(7):493-502. doi:10.1038/s41575-021-00457-x
- Ding D, et al. Challenges of the current precision medicine approach for pancreatic cancer: A single institution experience between 2013 and 2017. Cancer Lett. 2021;497:221-228. doi:10.1016/j.canlet.2020.10.039