NFPTR
national familial pancreas tumor registry
NEWS
Volume 21

GREETINGS FROM THE NFPTR TEAM!

Over the past few years, we have seen such great progress in our understanding of why pancreatic cancer clusters in some families as well as insight into how to detect pancreatic cancers early. When the NFPTR started, the 5 year survival rate for pancreatic cancer was less than 5%, and now in 2024 this has nearly tripled to 13%. While this progress is an achievement, we still have a long road ahead in our work to prevent pancreatic cancer and improve outcomes for those who do develop pancreatic cancer. Without the involvement of those enrolled in our registry, our research into the causes and prevention of pancreas cancer would not be possible. While we still have much to learn about pancreatic cancer, every step counts in preventing this disease. We recognize our progress is only made possible through the diligent help of families like yours. We are incredibly grateful to all of the NFPTR families for their continued support and participation! We are always here and welcome you to reach out with questions or updates.

In this newsletter, we highlight some of our ongoing efforts. On page 2, we highlight a new collaborative project that will leverage advances in DNA sequencing technology to improve our understanding of the genes involved in pancreatic cancer risk. This new study complements our ongoing work in identifying common variants in pancreatic cancer risk and understanding the genetics of pancreatic cancer among individuals of African Ancestry from North America. We presented the launch of these studies in our 2021 newsletter (https://nfptr.org/connect). Large-scale studies such as these take years to complete, but analysis of the data is ongoing and we are anticipating results in the next year. Efforts to improve the detection of pancreatic cancer early among individuals at high-risk of pancreatic cancer have also made tremendous strides in the past few years. This includes updated evidence supporting the potential benefit of screening that has results in updated clinical practice recommendations. We discuss the current recommendations for screening and pancreas cancer surveillance tactics, based on publications from the Cancer of the Pancreas Screening Study Consortium and the International Consortium. Finally, we also discuss an early study that addresses our ultimate goal of preventing pancreatic cancer. Dr Neeha Zaidi is leading a groundbreaking pilot study of a pancreatic cancer prevention vaccine. This is a very early-stage study, but one that will hopefully help us move forward in our understanding of how to prevent pancreatic cancer.

HOW TO SEARCH FOR ARTICLES

To view full versions of publications referenced in this newsletter, please visit the NCBI PubMed website (https://ncbi.nlm.nih.gov/pubmed) and search by the **PMID** number. For NCT links, please search by the **NCT** number on the NCBI Clinical Trials website (https://clinicaltrials.gov).

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

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. Or by visiting: https://pathology.jhu.edu/pancreas/donate

UPDATE CARDS

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!

CONTACT US

NFPTR Director: Alison Klein, PhD, MHS
Research Coordinator: Madelyn Harte
Phone: (410)955-3502
Fax: (410)955-9303
Email: pancreas@jhmi.edu
Website: NFPTR.org
Mailing Address: NFPTR
CRB II Room 341
1550 Orleans St.
Baltimore, MD 21231

UNLEASHING THE POWER OF LONG READ SEQUENCING TO UNDERSTAND PANCREATIC CANCER



Dr. Winston Timp **Dr. Michael Schatz** **Dr. Alison Klein**

Our research team led pioneering studies leveraging genomic sequencing technologies to uncover the genetic basis of pancreatic cancer. These early studies led to the discovery that some variants in the *ATM* and *PALB2* genes increase risk of pancreatic cancer, findings that have changed our understanding of pancreatic cancer risk and are now part of clinical care through hereditary cancer genetic testing. However, these technologies have limitations – and we still don't know the genetic underpinnings of about 80% of families with a clustering of pancreatic cancer. Over the past few years, we have seen the development of long read sequencing technologies. These newer technologies will allow us to examine complex structural variants and other classes of variation missed by earlier technologies.

Dr. Klein, together with Dr. Winston Timp, Associate Professor of Biomedical Engineering and Dr. Michael Schatz, Bloomberg Distinguished Professor, in the Department of Computer Science both at the Johns Hopkins Whiting School of Engineering, are conducting a large-scale study of over 400 patients with familial pancreatic cancer from the Johns Hopkins NFPTR, Mayo Clinic and University of Toronto. This study will be one of the first large scale studies to apply this new long-read technology to understand the genetic basis of a disease. Drs. Timp and Schatz are pioneers in the development of these technologies. Funded by the Lustgarten Foundation, the goal of this award is to identify the causes of pancreatic cancer in many families where we have not yet found the genetic cause.

EXPERT AGREEMENT ON PANCREATIC CANCER SCREENING FOR INDIVIDUALS WITH FAMILY HISTORY OF PANCREATIC CANCER

The NFPTR team has worked closely with teams conducting clinical trials for the early detection of pancreatic cancer, including the Cancer of the Pancreas Screening Study and International Cancer of the Pancreas Screening Consortium. Many NFPTR participants also choose to participate in the CAPS study or other screening studies.

Collectively, the evidence from these screening studies have resulted in several groups of experts agreeing on "best practices" for pancreatic cancer screening in high-risk individuals. These expert panels include the International Cancer of the Pancreas Screening Consortium as well as recommendations from the American Gastroenterological Association and the Practice Committee of the American Society for Gastrointestinal Endoscopy. While these expert panels mostly agree on key issues, there are also some differences.

- One area of expert agreement is that, when possible, referral to a Pancreas Center of Excellence should be pursued for high-risk patients undergoing pancreas cancer screening. The experts at these centers, with an individual's health care team, can personalize these recommendations.
- As to who should undergo screening, agreement was reached that individuals at high-risk of pancreatic cancer should be screened but not average risk individuals. High-risk patients include 1) those with a strong family history of pancreatic cancer (two or more affected family members) 2) patients with Peutz-Jeghers syndrome, hereditary pancreatitis, *CDKN2A* gene pathogenic variants and 3), patients at least 1 close relative with pancreatic cancer and Lynch syndrome or pathogenic variants in *BRCA1*, *BRCA2*, *PALB2*, and *ATM* genes.
- There was also agreement that magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) are the preferred screening modalities.
- Additionally, they also concurred that the age at which to begin screening varies across high-risk groups as well as family history of pancreatic cancer, with screening starting at younger ages in those with a young onset pancreatic cancer patient or with specific genetic syndromes or when a family member developed pancreatic cancer at a young age. For more information on these expert practice guidelines see: AGA Guidelines (PMID 32416142) and ASGE Guidelines (PMID 35183358)

Further supporting the potential benefit of screening in high-risk groups, the Johns Hopkins led, Cancer of the Pancreas Study 5 screening study (NCT02000089) reported that out of 1,461 high-risk individuals enrolled into CAPS5, nine patients were diagnosed with a screen detected pancreatic ductal adenocarcinoma (PDAC). Remarkably, the majority of these patients, 7 of 9 (77.8%), had stage 1 cancer, while one had stage II, and one had stage III. This is a profound contrast to the general population where only 5.4% of pancreatic cancer diagnoses were stage I. For more information, please see: PMID 31672839 and PMID 35704792

INFORMING RISK ASSESSMENT FOR PANCREATIC CANCER

Understanding the risk of pancreatic cancer over the lifetime particularly among individuals with a family history of pancreatic cancer is a key foundation not only to the planning of screening and prevention, but also a question many of the families in our registry want to know the answer to. While we always recommend families talk to their health care team, the studies we conduct help inform those discussions.

We recently published a study in the Journal of the National Cancer Institute, based upon following families in the registry for up to 25 years. The goal of this study was to show what the risk of pancreatic cancer was among individuals with a family history of pancreatic cancer. We also looked to see how that risk changes based upon the number of pancreatic cancers in the family and the ages at which those family members were diagnosed with pancreatic cancer.

In this study, we followed over 20,000 individuals in the NFPTR from over 4,400 families. Unfortunately, 167 people developed pancreatic cancer during this time period. We split families into two groups. The first group consisted of families in which two close family members had pancreatic cancer or families with a known pancreatic cancer risk genetic variant (i.e. families that test positive for a mutation in *BRCA1, BRCA2, ATM, PALB2, CDKN2A* or other pancreatic cancer genes: see our website https://nfptr.org/faq). The second group included families not meeting these criteria. We then made sub-groups based upon whether a family member developed pancreatic cancer before age 50, and in the Familial group the number of close relatives with pancreatic cancer. Risk estimates for each of these groups are shown in the table to the right.

These results show the importance of family history in determining pancreas cancer risk. This project supports the current screening recommendations (see page 3) regarding when to begin screening and the age at which screening starts relative to the youngest age of pancreatic cancer in the family. For more information, please see: PMID 36029239

FAMILY HISTORY OF PANCREATIC CANCER	RISK OF PANCREATIC CANCER BY AGE 85
FAMILIAL	
Relative with Pancreatic Cancer Before Age 50	
≥3 Close Relatives	24%
2 Close Relatives	12%
1 Close Relative	7%
Non-Familial	6%
Relative with Pancreatic Cancer After Age 50	
≥3 Close Relatives	18%
2 Close Relatives	9%
1Close Relatives	5%
Non-Familial	4%

VACCINE PREVENTION TRIAL

Dr. Neeha Zaidi

Vaccines use the body's immune system to recognize and eliminate disease-causing pathogens. Vaccines can also be developed to target mutated proteins such as the mutant *KRAS*, an early change in the transformation of a normal pancreas cell to a cancer cell. At Hopkins, Dr. Elizabeth Jaffee has been developing and testing vaccines to treat cancers, including pancreatic cancer, for over two decades. Dr. Neeha Zaidi, Assistant Professor of Oncology, is leading an effort that uses vaccines targeting pancreatic cancer as powerful tools to prevent pancreatic cancer. A small, early-stage trial is testing a vaccine that uses proteins expressed by mutations in the *KRAS* gene, a gene which is nearly always mutated at the very earliest stages of pancreatic cancer. Dr. Zaidi notes the huge window of opportunity for this intervention, because the *KRAS* mutation takes at least a decade from its first genetic alteration to develop into malignancy. The vaccine is designed to teach the patient's immune system to recognize the mutated *KRAS* gene as an invader and have the immune system eliminate the cancer cells. Although this study is in its early stages, these researchers are optimistic and excited about the progress this vaccine could provide in the fight against pancreatic cancer. If this study is successful, large studies will be undertaken. For more information about this trial please see (NCT05013216).

CANCER MATTERS PODCAST

Check out our recent podcast! NFPTR Director, Dr. Alison Klein, and Dr. Bill Nelson, Director of the Sidney Kimmel Comprehensive Cancer Center, discuss both genetic and non-genetic factors that can impact pancreatic cancer risk. Find this episode of the Cancer Matters Podcast at the following link: https://cancer-matters.blogs.hopkinsmedicine.org/2023/10/26/cancer-matters-bill-nelson-risk-pancreatic-cancer/

LEARN MORE ABOUT OUR PANCREATIC CANCER RESEARCH

Below are publications of key discoveries made by the NFPTR over the past few years. Due to spacing limitations, we can only show a few of our publications, but we hope this conveys some of the progress we have made. To view full versions of these publications, please visit the NCBI PubMed website (https://ncbi.nlm.nih.gov/pubmed) and search by the **PMID** number:

1. Kimura H, et al. Functional CDKN2A assay identifies frequent deleterious alleles misclassified as variants of uncertain significance. Elife. 2022 Jan 10;11:e71137. **PMID**: 35001868 ***Key Findings***: Sometimes clinical genetic testing results are uncertain. Specifically, it can be unclear if the change found is important biologically or not. These results are reported as variants of uncertain significance. In this paper, laboratory studies of some of these variants were conducted in order to determine which may be important in cancer risk and those that are not. While further steps are needed, this work helps inform clinical genetic testing results.

2. Kawamoto M, et al. Endoplasmic stress-inducing variants in CPB1 and CPA1 and risk of pancreatic cancer: A case-control study and meta-analysis. Int J Cancer. 2022 Apr 1;150(7):1123-1133. Epub 2021 Dec 6. **PMID**: 34817877. ***Key Findings***: Analysis of data across several studies demonstrated strong associations between pancreatic cancer and some variants in the *CPA1* and *CPB1* genes. Individuals with these gene variants may be at a increased risk of pancreatic cancer. Additional studies by other groups are needed to confirm these findings.

3. Xie F, et al. RAD51B Harbors Germline Mutations Associated With Pancreatic Ductal Adenocarcinoma. JCO Precis Oncol. 2022 Jun;6:e2100404. **PMID**: 35737913

4. Yuan C, et al. The age-dependent association of risk factors with pancreatic cancer. Ann Oncol. 2022 Jul;33(7):693-701. Epub 2022 Apr 6. **PMID**: 35398288

5. Afghani E, Klein AP. Pancreatic Adenocarcinoma: Trends in Epidemiology, Risk Factors, and Outcomes. Hematol Oncol Clin North Am. 2022 Oct;36(5):879-895. Epub 2022 Sep 23. **PMID**: 36154788

6. Mastracci TL, et al. Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases: Workshop Proceedings. Pancreas. 2022 Oct 1;51(9):1061-1073. **PMID**: 37078927

7. Kawamoto M, et al. Endoplasmic stress-inducing variants in carboxyl ester lipase and pancreatic cancer risk. Pancreatology. 2022 Nov;22 (7):959-964. Epub 2022 Aug 17. **PMID**: **35995657** ***Key Findings***: Genetic variation in the carboxyl ester lipase gene, are known to cause maturity-onset diabetes. We wanted to see if variation in these genes increased risk of pancreatic cancer. We did not see and increase frequency of genetic changes in pancreatic cancer patients, therefore we concluded that these genes are not associated with pancreatic cancer risk.

8. Mazer BL, et al. Screening for pancreatic cancer has the potential to save lives, but is it practical? Expert Rev Gastroenterol Hepatol. 2023 Jan-Jun;17(6):555-574. Epub 2023 Jul 3. **PMID**: 37212770

9. Singh RR, et al. Does acute pancreatitis herald pancreatic ductal adenocarcinoma? A multicenter electronic health research network study. Cancer Med. 2023 Feb;12(3):2505-2513. Epub 2022 Jul 31. **PMID**: 35909243 ***Key Findings***: Individuals with prior history of pancreatitis are at an increased risk of pancreatic cancer. This may be an opportunity for early detection the pancreatic cancers detected in this cohort were diagnosed at an earlier stage.

10. Mastracci T, et al. Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases: Workshop Proceedings. Diabetes. 2023 Apr 1;72(4):433-448. **PMID**: 36940317

11. Lindström S, et al. Genome-wide analyses characterize shared heritability among cancers and identify novel cancer susceptibility regions. J Natl Cancer Inst. 2023 Jun 8;115(6):712-732. **PMID**: 36929942

12. Soley N, et al. Feasibility of the Genetic Information Assistant Chatbot to Provide Genetic Education and Study Genetic Test Adoption Among Pancreatic Cancer Patients at Johns Hopkins Hospital. AMIA Jt Summits Transl Sci Proc. 2023 Jun 16;2023:497-504. eCollection 2023. **PMID**: 37350913 ***Key Findings***: Genetic testing can be powerful in leading clinical care of pancreatic cancer patients, but patients and families may feel uncertain about the benefits. The use of a chatbot is a helpful and convenient tool for providing genetic education prior to a patient's appointment.

13. Paranal RM, et al. Somatic loss of ATM is a late event in pancreatic tumorigenesis. J Pathol. 2023 Aug;260(4):455-464. Epub 2023 Jun 22. **PMID**: 37345735

14. Kim J, et al. Relationship between ABO Blood Group Alleles and Pancreatic Cancer Is Modulated by Secretor (FUT2) Genotype, but Not Lewis Antigen (FUT3) Genotype. Cancer Epidemiol Biomarkers Prev. 2023 Sep 1;32(9):1242-1248. **PMID**: 37342060

15. King SD, et al. Genetic Susceptibility to Nonalcoholic Fatty Liver Disease and Risk for Pancreatic Cancer: Mendelian Randomization. Cancer Epidemiol Biomarkers Prev. 2023 Sep 1;32(9):1265-1269. **PMID**: 37351909

16. Rodriguez NJ, et al. A Randomized Trial of Two Remote Healthcare Delivery Models on the Uptake of Genetic Testing and Impact on Patient-Reported Psychological Outcomes in Families With Pancreatic Cancer: The Genetic Education, Risk Assessment, and Testing (GENERATE) Study. Gastroenterology. 2024 Feb 4:S0016-5085(24)00129-X. **PMID**: 38320723 ***Key Findings***: Remote genetic education and testing offers convenience and improved access to family members of pancreatic cancer patients. Remote genetics care options can lead to better uptake of genetic testing.

17. Hassan MM, et al. Genome-wide association study identifies high-impact susceptibility loci for hepatocellular carcinoma in North America. Hepatology. 2024 Feb 20. **PMID**: 38381705