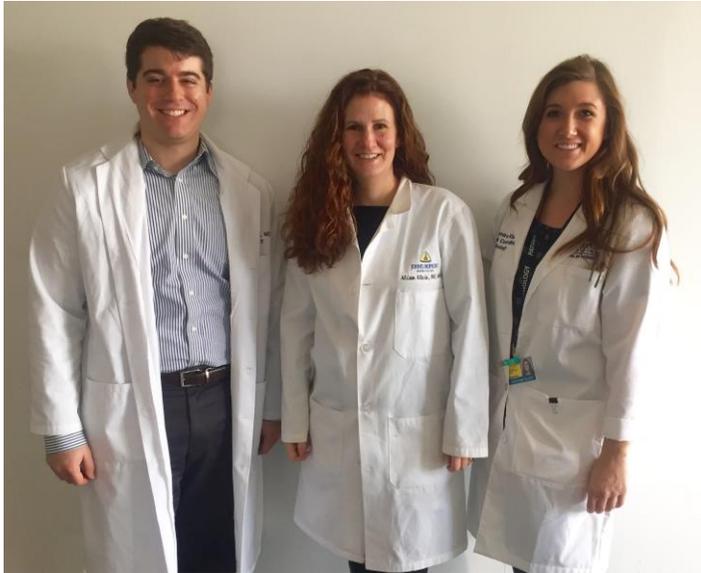


FROM THE NFPTR TEAM



NFPTR (left to right): Eric Miller (Coordinator), Dr. Alison Klein (NFPTR Director), Ally Klann (Coordinator)

The NFPTR team would like to extend our gratitude to all of our families for their support of our registry and research. We have made tremendous progress in understanding the genetic basis of pancreatic cancer; and none of it would be possible without families like yours. Every year we make strides towards understanding what causes pancreatic cancer and 2015 was no exception. There is still a long way to go and we will be counting on your continued support as we seek ways to prevent the consequences of this terrible disease.

Last year we underwent several transitions including welcoming a new staff and launching our electronic version of the questionnaire. Our online questionnaire has been well received by families and is simplifying the enrollment process by allowing us to enroll more families than ever before. We are still working on some aspects of the online questionnaire, so thank you to all families who have enrolled online for your patience. While we are moving towards offering electric communication options, we still offer paper-based options as well.

We are also happy to introduce our new research coordinators, Ally Klann and Eric Miller, to the NFPTR team. Ally graduated from the University of Wisconsin Madison with a B.S. in Biology and a certificate in Global Health in December of 2014. Eric graduated with a B.A. in Biology from Johns Hopkins in 2014 before getting his M.H.S. in Biochemistry and Molecular Biology with a concentration in reproductive and cancer biology from the JH Bloomberg School of Public Health. Ally and Eric both bring a strong background of biology and public health, as well as the desire to work with and educate patients and families. Both work with families seen at the Johns Hopkins Pancreatic Cancer Multidisciplinary Clinic as well as families from around the world. We are happy to have them on the team.

We want to thank both David and Colleen, our previous coordinators for their hard work. Both left their positions with the NFPTR over the summer to continue their education. Colleen is pursuing a master's degree at Georgetown University and David has started medical school at Touro College in New York. We wish them both the best of luck!

Many families have questions regarding genetic testing for pancreatic cancer. The technology for genetic sequencing has changed dramatically over the past 5 years and impacted how clinical genetic testing for hereditary diseases is conducted. In the past, each gene was sequenced individually. However, the changes in technology have led to the development of "panel testing" where several genes are tested simultaneously. While this can reduce the costs of testing, it can often result in inconclusive findings. See page 2 for more information on panel tests from a genetics counselor who works with pancreatic cancer patients at JHU, Elizabeth Wiley.

Individuals with a family history of pancreatic cancer are often concerned about their risk of developing pancreatic cancer. This year Dr. Alison Klein received a Research Investigator award from the Lustgarten foundation to develop a better "risk tool" to provide individuals with a personalized risk estimate. For more on this work see page 2.

On page 3, we profile a new faculty member working with the NFPTR, Dr. Laura Wood. Laura is an exciting new addition to the faculty here at Johns Hopkins. We also highlight a recently completed collaborative study lead by Dr. Klein that has identified some new genetic variants that may be associated with pancreatic cancer risk.

Finally, please see the back page for links to other articles we have contributed to as well as other important sources of information about pancreatic cancer and additional ways you can help.

As 2015 comes to a close, we would like to thank all of those that have participated in the National Familial Pancreas Tumor Registry. Remember, it is because of all of you that we have the resources we need to find a way to prevent this disease. Please complete and return you family's update card (even if there have been no changes) and please feel encouraged to reach out to us with any questions, concerns, or updates!

- *The NFPTR Team*

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GENETIC “PANEL TESTS” FOR PANCREATIC CANCER

When the NFPTR began in 1994, many thought that pancreatic cancer did not run in families. Over the past twenty years we have demonstrated that approximately 5-10% of individuals diagnosed with pancreatic cancer have a first-degree relative (parent, sibling, or child) who also has a diagnosis of pancreatic cancer. While there is still much to learn regarding the causes of this familial presentation of pancreatic cancer, several genes associated with pancreatic cancer risk have been identified. In 10-20% of pancreatic cancer families, genetics can provide an explanation for the cause of the pancreatic cancer and provide information regarding cancer risks for family members.

Sometimes other types of cancer within a family can help guide a healthcare provider's genetic testing recommendations. For example, if an individual with pancreatic cancer has a strong family history of breast or ovarian cancer, testing of the *BRCA1* and *BRCA2* genes associated with Hereditary Breast and Ovarian Cancer Syndrome may be requested. If there is a strong family history of early-onset colon cancer or uterine cancer, testing of the genes associated with a hereditary colon cancer syndrome called Lynch syndrome may be performed. However, it is not uncommon for familial pancreatic cancer to present without the presence of other cancers to guide genetic testing recommendations, and looking at multiple genes associated with pancreatic cancer risk may be beneficial.

Unfortunately, the cost of genetic testing can be quite expensive. Historically, testing has been performed using a method called Sanger sequencing, and the price of testing has been approximately \$1,000 - \$2,000 per gene analyzed. While very accurate, the high cost of Sanger sequencing has prompted researchers to pursue the development of more efficient methods of gene analysis. Within the past several years, a new testing technology called Next Generation

Sequencing (NGS) has been developed. With NGS, multiple genes can be analyzed at the same time at a lower cost than Sanger sequencing. NGS has become invaluable to researchers who are working to identify the genetic cause of diseases, including familial pancreatic cancer (see 2012 and 2013 Newsletter).

Recently, NGS has become available in the clinical setting. This approach to testing is often referred to as “panel testing,” as it involves analysis of a panel of several genes related to pancreatic cancer risk at the same time. While panel testing is still expensive, many genes can be analyzed for the same cost as only one or two genes using Sanger sequencing.

Panel testing has become a useful tool for individuals with familial pancreatic cancer. Because of the ability to test multiple genes at once with a lower financial burden to families and insurance companies, there is an increased chance of identifying the genetic cause for pancreatic cancer in a family.

It is important to note that there are limitations to using a panel approach to genetic testing. For example, when multiple genes are being tested, there is a higher likelihood of finding a variant of uncertain significance. The difficulty in interpreting this inconclusive finding can sometimes cause anxiety or confusion for patients and their families. Additionally, it is possible for testing to reveal a change on a gene for which the precise risks of cancer have yet to be determined, or for which no management recommendations currently exist. As with any genetic testing, it is important to weigh the potential benefits of panel testing against the potential risk that the test results will cause more uncertainty in regards to an individual's cancer risk and management. Your clinical provider or a genetic counselor can help you determine which genetic tests are right for you.

PERSONALIZING PANCREATIC CANCER RISK MODELING

Individuals with a family history of pancreatic cancer often wonder about their risk of developing pancreatic cancer. Many factors that increase risk of pancreatic cancer have been identified. These include medical conditions such as diabetes and pancreatitis, lifestyle factors such as high body-mass index, heavy alcohol intake and cigarette smoking, as well as genetic factors. The risk of pancreatic cancer associated with genetic factors ranges from genetic variants that are associated with a small increase in risk of pancreatic cancer (such as those discovered in the study on page 3) as well as genetic mutations in genes that cause a high-lifetime risk (>10%) of pancreatic cancer.

In order to understand an individual's risk one must consider all of these risk factors (as well as other cancers that may run in the family).

In early 2015 Dr. Alison Klein was awarded a Research Investigator award from The Lustgarten Foundation to develop a “risk-tool” for both patients and clinicians with the

goal of identifying individuals who are at an increased risk of pancreatic cancer – and may ultimately benefit from some of the early detection screening tests now in development. This model builds upon her previous PANCPRO model (see 2005 Newsletter), which estimates the probability an individual carries a genetic mutation associated with a high lifetime risk of pancreatic cancer. This award will support Dr. Klein's development of this model over the next three years.

“The goal of this model, is to develop a personalized risk tool for pancreatic cancer. Individuals who, based on this tool, are the at highest risk of developing pancreatic cancer may not only benefit from lifestyle changes but also some of early detection screening tests that are currently under development. We hope that by careful evaluation of these high-risk populations, we can prevent some pancreatic cancer from developing and ultimately reduce mortality from pancreatic cancer.”

-Dr. Alison Klein, Ph.D, MHS

IN THE NFPTR SPOTLIGHT: DR. LAURA WOOD

We are very excited that Dr. Laura Wood, a talented and promising physician scientist, has recently joined the faculty at Johns Hopkins where she will expand her ongoing research on pancreatic cancer. Laura is a graduate of the MD/PhD program at Johns Hopkins where she excelled both clinically and scientifically. For her groundbreaking PhD work in the laboratory of world-renowned cancer geneticist Dr. Bert Vogelstein, Dr. Wood performed the first whole exome sequencing studies in human cancers. These landmark studies revolutionized the field of cancer genomics. In addition to this work she co-authored several other important studies and led three other cancer genome sequencing studies in pancreatic and bile duct cancers. Dr. Wood was Chief Resident for the Department of Pathology and completed a fellowship in Gastrointestinal and Liver Pathology at Johns Hopkins.

In her new role as an Assistant Professor of Pathology and Oncology, her research will focus on defining the key steps in malignant progression in the pancreas.

Her group is working to define the molecular changes that underlie the “moment of invasion” in pancreatic cancer – this work will help not only to understand a key transition in the biology of pancreatic cancer but also may identify targets for early detection. In addition, her group is developing a novel three-dimensional “organoid” model of pancreatic cancer in order to test the importance of potential biomarkers in living pancreatic cancer cells. Please join us in welcoming Laura to the NFPTR team!



Dr. Laura Wood

GENOME WIDE ASSOCIATION STUDY LINKS NOVEL GENETIC VARIANTS WITH PANCREATIC CANCER RISK

Genetic variation plays an important role in the risk of pancreatic cancer. Some genetic changes confer a very high life-time risk of pancreatic cancer, increasing risk more than 500%. These high-risk variants are often very rare in the population, typically present in less than .1% of the population. On the other end of the spectrum, common genetic changes, present in >5% of the population also play a role in pancreatic cancer risk. However, these common genetic changes often only confer a modest increased risk of pancreatic cancer, less than a 50% increase in risk. Identifying these modest-risk variants can provide insight into the underlying causes of pancreatic cancer.

In order to identify new modest-risk variants, Dr. Klein and her post-doctoral fellows Dr. Erica Childs and Evelina Mocci led a collaborative study funded by the National Institutes of Health, which included genetic information from 9,925 pancreatic cancer patients and 11,569 healthy individuals. Most of the samples were newly genotyped, but about 1/3 were analyzed in so-called meta-analysis of already published data. Sites contributing new data included Johns Hopkins, Mayo Clinic, Memorial Sloan Kettering Cancer Center, MD Andersen Cancer Center, University of California San Francisco, Yale University, Mount Sinai Hospital at the University of Toronto, Queensland Australia and the International Agency for Cancer Research.

As part of this study several new “common” genetic variants associated with pancreatic cancer risk were identified; these variants individually increased risk of pancreatic cancer by 12-38%. Further studies of the function of these genetic regions are already underway. These regions may play important roles in DNA repair, cell growth, and tumor suppression.

However, it often takes a long time to fully understand how these genetic changes are involved in pancreatic cancer risk as sometimes the variation doesn't have an effect on the gene it's in or near, but could have a more distant target.

“These variants are common in the population, and most individuals who have these variants will never develop pancreatic cancer in their lifetime,” cautions Alison Klein, Ph.D. “However, identifying and understanding these changes can lead to a better understanding of why some people develop pancreatic cancer, and if we combine this information with data on other pancreatic cancer risk factors we may be able to identify and one day screen high-risk groups.”



NFPTR (left to right): Dr. Erica Childs, Dr. Alison Klein, Evelina Mocci

HOW YOU CAN HELP:

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 email us at pancreas@jhmi.edu with “Control” in the subject line to receive further information on how to help with this important task!

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!

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 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 Ally or Eric: (410) 955-3502

THANK YOU FOR YOUR SUPPORT!!

We want to thank all of the NFPTR families for their ongoing support. We appreciate everyone's efforts including taking the time to complete our questionnaire, complete the annual response card, providing blood samples for our research studies, as well as their efforts to raise awareness for pancreatic cancer and financial support.

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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 as shown on page two. 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 (<http://www.ncbi.nlm.nih.gov/pubmed>) and search by the PMID number.

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