Pancreatic Cancer Sequencing Project
towards personalized patient care

We have created this educational material to inform the public about some exciting new developments in pancreatic cancer research, with an emphasis on how this research may one day be applied to patient care.

Sequencing of pancreatic cancer genomes has the potential to help scientists and doctors to provide better patient care.

In 2011, 44,030 Americans were diagnosed with pancreatic cancer. For every 100 patients diagnosed with pancreatic cancer, only 26 will be alive 1 year after diagnosis; and only 6 after 5 years. Pancreatic cancer has the lowest survival rate among all major cancers.

Like other cancers, pancreatic cancer is fundamentally a genetic disease, a disease caused by damage to DNA. Think of DNA as an instructional manual for making parts of the cell. Genes are segments of DNA that act like instructional sentences in the manual. The accumulation of abnormal changes in genes, known as mutations, leads to mistakes in the instructions. These mistakes can lead to unrestrained cell growth, like a runaway car with no brakes.

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We sincerely hope this information will be educational and helpful for you and your families.

-Ralph Hruban, M.D.
The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins University School of Medicine
Sequencing of DNA is like reading the letters in the instruction manual. It is how scientists look for DNA mutations. The instructions in a cell include a full complement of DNA, which is 3.2 billion letters long. Previous DNA sequencing technologies was very slow and expensive. The Human Genome Project cost $3.8 billion and 13 years to complete. Today with the 2nd generation DNA sequencing technologies, the entire human genome of an individual can be sequenced in a few weeks for less than $10,000.

Sequencing of pancreatic cancer genomes has the potential to help scientists and doctors to provide better patient care, such as early cancer detection and targeted agents for cancer treatment. Now let’s learn more about breathtaking technological advances that can make personalized medical care a reality.

What is DNA sequencing?

The information in our genomes is coded with chemical bases in DNA molecules. The entire human genome contains 3.2 billion bases – each base is one of four types: A, T, G, or C.

The order of these As, Ts, Gs, and Cs determines numerous aspects of the ways our cells and bodies function. DNA sequencing is the way we determine the order of the bases. It is the method we use to study the human genome and discover errors in the genetic code, called mutations. These mutations lead to many human diseases and play a pivotal role in the development of cancer.

In pancreatic cancer genome research, our goal is to find mutations, errors in the DNA code, that are specific to the tumor and not present in normal DNA. To do this, we use DNA samples from a patient’s tumor tissue, and the matching individual’s normal tissue.

Both genomes are sequenced and compared to find the mutations that are only in the tumor. Using this technique, we can locate cancer-specific mutations that might have contributed to the patient’s pancreatic cancer. These cancer-specific mutations represent key targets for the development of new approaches to cancer screening and treatment.

We hope to use these techniques to develop new strategies to diagnose and treat pancreatic cancer, so that we can make a real difference for patients suffering from this devastating disease.
How is pancreatic cancer sequencing research being done at Hopkins?

Our overall goal is to translate knowledge of DNA changes to clinical tools for better management of pancreatic cancer patients. With this in mind, our pancreatic cancer genomic research includes three major components:

First, for patients with resectable tumors, we can sequence their cancers. After their tumors have been resected and examined for diagnosis, excess tissue from the resected tumors will be purified for cancer DNA sequencing. At the same time, we collect peripheral blood samples from the same patient to provide normal DNAs.

Next, we sequence the cancer genome and the normal genome separately. Then we compare the two results to identify base sequence changes that are specific to the cancer. Because genes are the instructions for the proteins made in cells, the changes in genes will lead to changes in cell signaling pathways and processes.

Our goal is two-fold: One goal is to identify therapies that target the specific mutations in a patient’s tumor. A second goal is to develop early detection tests. Pancreatic cancers are usually detected when they are advanced and the survival rate is very low. These cancers have been growing for some time undetected. Our goal is to develop a blood test that detects mutations derived from pancreatic cancer cells before the development of symptoms. Early detection has the chance to significantly reduce cancer deaths.

Secondly, we can sequence cysts. For patients with pancreatic cysts, minimally invasive procedures like endoscopic ultrasound with fine needle aspiration biopsy can be used to sample cyst fluid. This cyst fluid will contain cells and DNA shed from the cyst wall. The DNA molecules in the cystic fluid will then be purified and sequenced to help us categorize the cyst type and therefore design the best treatment for that patient.

Third, we can sequence the DNA from family members of patients with pancreatic cancer. By doing this we can determine if they inherited genes that predispose them to cancer. Just as we inherit our eye and hair colors from our parents, so too do some people inherit a mutation that increases their risk of developing cancer. We can find these mutations by sequencing. Once a mutation is identified in a family, all family members can be checked for the same mutation. Most family members will not have the mutation, which would be a relief. Family members with the mutation will then be managed appropriately before the manifestations of the disease.

-Nickolas Papadopoulos, Ph. D.
Director of Translational Genetics, Ludwig Center for Cancer Genetics
The Johns Hopkins University School of Medicine
What are the implications of pancreatic cancer sequencing project?

First of all, this project provides a lot of evidence supporting the hypothesis that cancer is, in essence, a genetic disease.

Second, the project should help patients and their families to understand why cancer runs in their family and if they themselves are at increased risk.

Third, the project provides a scientific basis of the development of new therapies. Through the mutations we find in these cancers, we can identify the biochemical pathways that are altered in the tumors. We hope that we will be able to design personalized therapies for different patients according to the mutations that are found in their tumors.

For example, when we sequenced pancreatic neuroendocrine tumors, we discovered mutations in the genes controlling a pathway called mTOR. These tumors should be particularly sensitive to drugs that inhibit the mTOR pathway. And we should be able to use these drugs to treat patients with this specific type of cancer.

Last and perhaps the most important implication, relates to the early detection of disease. Pancreatic cancer is often called “silent killer” because symptoms generally don’t occur until the cancer is too advanced to treat. With the information we learn from sequencing early lesions in the pancreas, we hope to be able to develop an early detection test. If we can catch these cancers early, before they spread to other parts of the body, patients may be able to be cured just with surgery alone.

-Bert Vogelstein, M.D.  
Director, Ludwig Center for Cancer Genetics & Therapeutics,  
The Johns Hopkins University School of Medicine