interview with an Expert:

VIRGINIA CRAVOTTA (VC):
Please define genetics and genetic testing, and explain how testing might be useful to individuals concerned about developing pancreatic cancer.

HAROLD FRUCHT (HF):
Many characteristics are passed down through our genes, including physical traits (such as hair and eye color), as well as mental abilities, talents, and even the likelihood of developing certain diseases. Genetic testing is the process of extracting DNA to look at a specific sequence for abnormalities consistent with a specific disease, such as pancreatic cancer. Genetic testing is part of the larger process of genetic counseling, and in my opinion, testing should not take place without counseling.

VC: Explain more about genetic counseling for pancreatic cancer. What’s involved?

HF: Genetic counseling is an in-depth interaction between an individual and his or her genetic counselor, which is a trained medical professional with a specialty in genetics and inherited diseases (See Box, page 3). At Columbia’s Pancreatic Cancer Prevention & Genetics Program, genetic counseling for pancreatic cancer includes risk stratification**, which is the process of assessing an individual’s likelihood of developing the disease. For pancreas cancer, this involves detailed analysis of an individual’s personal medical history, family history, as well as other information pertinent to the disease. Based on this information, an individual is assigned a level of risk for developing pancreatic cancer. The risk can be average, moderate, or high. The genetics team provides a recommendation based on this risk stratification. For example, at Columbia, we would discuss screening with someone determined to be at high risk for pancreatic cancer.

In addition to developing a pedigree (the individual’s family history in the form of a diagram), the genetic counselor is also responsible for educating the patient on genetic testing, including discussing the potential lifelong implications of knowing specific gene abnormalities. In addition, the genetic counseling includes discussions about what a positive or negative test indicates, and what it does not indicate.

(continued)

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*This discussion covers only the adenocarcinoma form of pancreatic cancer. **Words in bold are defined in the glossary.

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For example, a negative test does not necessarily mean that a person does not have an inherited syndrome, or that they do not have to be screened or remain vigilant about certain cancers. In summary, genetic testing is the blood test, whereas genetic counseling is an in-depth discussion that includes collecting information, educating the person and assisting him or her in making decisions.

VC: Let’s talk about the genes involved in pancreatic cancer. Which genes are known to be associated with the development of the disease?

HF: Today, we know of only a handful of genes that are responsible for or associated with pancreatic cancer. Of all inherited (familial) pancreatic cancer cases, only about 20% have a gene that is either the cause of the cancer or is associated with the cancer. Since inherited pancreatic cancers account for approximately 15% of all cases, you can see that the numbers of people affected by inherited genetic mutations is small. Nevertheless, there are known gene mutations that significantly increase one’s risk for developing pancreatic cancer.

The gene most commonly discussed in relation to pancreatic cancer is PRSS1, which is responsible for hereditary pancreatitis. A mutation in the PRSS1 gene causes severe pancreatitis at a very early age. Hereditary pancreatitis is a painful syndrome, which ultimately places individuals at high risk for pancreatic cancer (up to 40% of individuals with this mutation will develop the disease). Fortunately, mutations of this gene are uncommon, accounting for less than 1% of all inherited pancreatic cancers.

Another uncommon hereditary syndrome associated with the development of pancreatic cancer is PJS (Peutz-Jeghers Syndrome). Peutz-Jeghers Syndrome is caused by an abnormality in the STK11 gene, which is associated with breast cancer, polyps of the bowel and cancers of the small bowel, and also pancreatic cancer. In fact, of all the known inherited syndromes, Peutz-Jeghers Syndrome probably poses the highest risk for pancreatic cancer; people with this Syndrome have about a 40% lifetime risk of pancreas cancer. Fortunately, it is a very rare disorder.

FAMMM (Familial Atypical Multiple Mole Melanoma) Syndrome is a skin mole syndrome related to a CDKN2A (p16) gene abnormality. FAMMM Syndrome is associated with melanoma, and also increases the risk of developing pancreas cancer.

“We do not routinely test an individual who does not have pancreatic cancer to look for a gene abnormality...”

HNPCC (Hereditary Non-Polyposis Colorectal Cancer) Syndrome presents another genetic risk for pancreatic cancer. HNPCC is primarily a colon cancer syndrome but includes endometrial and pancreas cancer.

The fifth known gene associated with pancreatic cancer is BRCA, which causes Familial Breast and Ovarian Cancer Syndrome. There are two BRCA genes that we know about, BRCA1 and BRCA2. Up to 15% of all families with an inherited risk of pancreatic cancer will have a BRCA1 or BRCA2 gene abnormality, making it the most common of all mutations, especially in individuals of Ashkenazi Jewish descent. It is likely that other breast cancer genes will be identified, and that there is an association of pancreas cancer with closely related genes of the Fanconi Anemia pathway of disease.

Other genes have been found in pancreas cancer families for which we’re not quite sure of the relationship. For example, the Palladin gene that was found by Dr. Brentnall may play a role in inherited risk, and also the PALB2 gene, which was identified by Johns Hopkins researchers, will likely prove important to pancreatic cancer because it interacts with the BRCA gene.

VC: Many times, people turn to The Lustgarten Foundation when they’ve had a family member affected by pancreatic cancer and are concerned about their own risk for developing the disease. Are these individuals eligible for genetic testing, and/or would screening be an option?

HF: Genetic counseling/testing is an adjunct that should be used in parallel with early detection and screening programs for pancreas cancer. Certainly, if somebody has a family history of pancreatic cancer but either is not a good candidate for genetic testing, or doesn’t want genetic testing, the information that we get from the personal and family history alone will allow us to risk stratify that individual. When informative, genetic testing can more precisely estimate an individual’s risk for pancreas cancer and will also, importantly, identify other cancer risks associated with the gene mutation. Many of these other cancers have clear screening guidelines that exist and are covered by insurance. A non-informative genetic test would not exclude any of the other screening or detection modalities that we would apply.

We do not routinely test an individual who does not have pancreatic cancer to look for a gene abnormality, because even if she or he comes from a family where there’s a lot of pancreas cancer, a negative test does not tell us whether she or he either didn’t inherit the gene, or if we’re testing for the right gene in that particular family. One situation where we might recommend genetic testing is for an individual who does not have pancreas cancer, but who is of Ashkenazi Jewish descent and has a family member with pancreas cancer.
DNA

DNA (deoxyribonucleic acid) is the basic genetic material (“building block”) of living organisms. A single DNA molecule consists of two separate strands, wound into a double helix (spiral structure). Each strand is made up of four chemical components known as nucleotides.

**These nucleotides are:**
- adenine (A)
- cytosine (C)
- guanine (G)
- thymine (T)

A single DNA sequence may stretch for millions of nucleotides.

**GENETIC CODE**

Genes are defined segments of DNA, made up of groupings of three nucleotides. (Ex., TAG-TTA-TTG). The order of nucleotides in DNA is determined by patterns that stretch back millions of years, and astonishingly, this order is usually accurately preserved. Changes that occur in the nucleotide sequence are known as mutations, and these are also copied with a high degree of accuracy.

An example of a genetic mutation is:

**TAG-TTA-TTG**

**Gets copied (mutated) as:**

**TCG-TTA-TTG**

Mutations can affect the likelihood of a certain trait or disease.

**Inherited mutations** are those passed down through families.

**Acquired mutations** are those that develop during a person’s lifetime, either randomly or in response to DNA injury from harmful environmental factors, such as exposure to radiation or chemicals.

Many times, mutations to DNA are harmless, and do not impact the likelihood of one’s developing a certain disease. These kinds of mutations are called **polymorphisms**.

**DISEASE AS GENETIC MUTATIONS**

Genetic disease occurs because of a mutation in genetic material. In cases where mutations are inherited, they may be autosomal dominant or autosomal recessive. In **autosomal dominant inheritance**, the mutation appears in every generation, and each child of an affected family member has a 50% chance of inheriting the trait or disease. In **autosomal recessive inheritance**, parents of the child may not show the trait or disease. The child’s chances of having the trait are 1 in 4 (25%). In order for the trait or disease to show in autosomal recessive inheritance, the child must receive the recessive (mutated) gene from **both** parents.

**fast facts:**

Approximately 15% of all pancreatic cancers result from hereditary factors. Not everyone who has an inherited and/or acquired mutation will develop pancreatic cancer.

**Sources:**

In this case, we would test for the BRCA gene mutation. This is because BRCA is the most common gene mutation identified in Jewish families with pancreas cancer, and is carried by 1/40 Jewish individuals regardless of family history.

There are real costs associated with genetic testing. For example, comprehensive sequencing of the BRCA 1 and 2 genes is an expensive test, costing more than $3,000. However, we know that in Ashkenazi Jews, there are three particular mutations that account for 95% to 98% of the mutations in these two genes. We can test just for those three sites at a cost of less than $550, which makes it much more affordable. Again, for people who don’t have cancer, we would avoid testing for a gene abnormality unless we knew specifically which abnormality to look for, based on genetic test results of another family member.

In other words, we want to know what we are looking for before we test a family member without pancreas cancer.

Whether or not someone is eligible for screening depends on more than simply the number of relatives affected by the disease. For example, someone with only one relative who developed pancreas cancer, but at a young age, would be considered high risk. So we wouldn’t necessarily exclude those individuals from screening programs. (For more about screening, see Interview With An Expert: Screening & Early Detection). However, we might not offer them genetic testing if they did not have a known family history indicative of an inherited syndrome. In this case, we would have them join a Pancreatic Cancer Registry, which would provide access to up-to-date information and opportunities on research relating to hereditary pancreatic cancer.

VC: For people with no known family history of pancreatic cancer, but who do have environmental risk factors, could the information gained from genetic testing help influence behavior? For example, might a smoker who undergoes genetic testing for pancreatic cancer decide to quit if a genetic abnormality is revealed?

HF: Interestingly, the risk factor you are referring to (cigarette smoking) is an environmental risk factor, and certain people are more susceptible to them than others, based on genetic metabolic variations or how their bodies deal with environmental toxins. When an environmental factor alters your DNA, it is called an acquired mutation. Although environmental toxins can interact with existing genetic abnormalities, they’re actually separate issues.

Genetic predisposition to a disease is by definition innate, but may be something that can be changed through the modification of one’s behavior. Genetic predisposition involves inherited mutations, the effects of which may be altered by how much you drink alcohol, smoke or other lifestyle choices and environmental risk factors. The genetic abnormality can predispose you to cancer, including pancreas cancer and/or other cancers. Environmental risk factors likely compound or otherwise modify your inherited risk for developing pancreatic cancer. Genetic testing seeks to understand whether an individual has an inherent risk of developing a disease based on known family history, regardless of whether they also face any environmental risk factors. So, a history of smoking would not by itself drive a decision to undertake genetic testing.

Also, changing people’s behavior is one of the most difficult things that we as physicians encounter, and this has been going on for many years and with many diseases, such as heart disease, colon cancer, and breast cancer, to name a few. It’s extremely difficult to get somebody to modify his or her behavior, and especially to change things like diet and exercise. Considering the fact that smoking increases your risk of pancreas

Can Blood Type Determine Risk for Pancreatic Cancer?

The results of a study released online August 2, 2009 in Nature Genetics linked ABO blood type to an increased risk of pancreatic cancer, based on an association with common variants of the gene that determines human blood type. The study was part of PanScan, a genome-wide association study conducted by the Pancreatic Cancer Cohort Consortium. Researchers discovered that genetic variation in a region of chromosome 9 (which contains the gene for human blood type) was associated with risk for pancreatic cancer.

Further studies are needed to determine whether these initial findings could offer implications for diagnostic and therapeutic interventions.
cancer two to three-fold, anybody who comes into a pancreas cancer screening and early detection program and declares him or herself a smoker will be encouraged to quit; people who do smoke may actually develop a more aggressive and earlier form of the disease. We invite anybody at any risk of pancreatic cancer to quit smoking, because that’s one thing they can do to greatly reduce their risk of the disease.

VC: Earlier you mentioned costs associated with genetic testing. Is genetic testing for pancreatic cancer typically covered by insurance? If not, what’s the average cost?

HF: Costs vary depending on the genetic test. If somebody is being tested for a gene abnormality that’s already known, the cost can approximate $450 – $550. At the other end of the spectrum are the BRCA and HNPCC tests, which run between $3,000 and $3,500. Most of the other test costs fall somewhere in the middle. For example, the FAMMM Syndrome test costs approximately $900, but the actual cost to individuals depends on the laboratory conducting the test. Not all tests are available at all labs. For example, the test for HNPCC is widely available, as is the heredity pancreatitis gene test. However, not as many labs conduct the test for Peutz-Jegher Syndrome, so it could be harder to shop around for a good price.

Insurance companies have come a long way with regard to covering costs associated with genetic testing. There are now guidelines for coverage of some of these tests. For example, insurance companies tend to cover the BRCA test in individuals with a family history of breast and ovarian cancer, and in our experience, insurance seems to be covering more testing for FAMMM Syndrome, Peutz-Jegher Syndrome and HNPCC. Overall, however, genetic testing for pancreas cancer is relatively new and there are no uniform testing guidelines, so coverage tends to be insurance policy and/or company specific.

VC: What is DNA banking, and when, if ever, should individuals consider it?

HF: DNA banking involves extracting and storing samples. The purpose of DNA banking is two-fold: for research purposes and for personal use. Most DNA banking is done for research purposes. For example, if somebody in your family has pancreatic cancer and you bank their DNA, researchers can “pull” the DNA in the future for research on pancreatic cancer, such as testing for new pancreatic cancer genes when they are discovered. This makes banking a very useful tool for research purposes, because once new developments are identified, it allows researchers to do retrospective work on DNA they’ve already banked.

There are also personal reasons for banking DNA. For example, somebody with pancreatic cancer who has an extensive family history of the disease may wish to bank his or her DNA for future testing, which can help family members determine their risk now, and also as the science of pancreatic cancer genetics continues moving forward. Family members may also wish to bank their own DNA based on a family history of a known genetic syndrome.

VC: Let’s turn to personal genomic testing. Today, there are medical screening tests available for purchase for in-home use. The kits allow people to collect and send away samples for testing with the aim of determining genetic risk profiles. Is it advisable for people concerned about their risk for pancreatic cancer to consider any of these tests?

HF: The issue of personal genomic tests is a complicated and difficult one. The reason is because we’ve been discussing genetic testing for well-defined disorders that significantly increase cancer risk due to a mutation in a single gene within a family. The genes and genetic variants tested by the personal (in-house) genomic tests confer a much more modest risk of cancer, and the risk is likely determined by a complex combination of genetic variations as well as environmental exposures, as we discussed earlier. This is known as multifactorial causation. Doctors and scientists do not yet know enough about all the modifiers of cancer risk to accurately predict the risk of cancer based upon these genomic tests. Someday this will likely be possible, but these tests are not yet accurate enough to clarify the risk of pancreas cancer beyond the current risk factors of family history, smoking, drinking, and pancreatitis that we already use.

VC: Is genetic counseling and genetic testing for pancreas cancer susceptibility genes available throughout the United States?

HF: Genetic counseling and genetic testing for pancreas cancer susceptibility genes is available throughout the United States. To find a genetic counselor or other health professional in your area with an expertise in cancer genetics, visit the National Society of Genetic Counselors’ website at www.nsgc.org/resourcelink.cfm or the National Cancer Institute’s website at www.cancer.gov/search/geneticservices.
GENETIC COUNSELING & TESTING
what to expect during

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Preparing for Your Counseling Session
Prior to a genetic counseling consultation, an individual should obtain information about his or her medical and family histories. Information about both sides of the person’s family, maternal and paternal, are important because a detailed family tree or pedigree will be elicited during the consultation. Therefore, before the consultation the person should get as much information as possible about any diagnosis of cancer in his or her family and the age at which the family member was diagnosed with the cancer. Information about the type of treatment a family member diagnosed with cancer received is also helpful (i.e. surgery, radiation therapy, or chemotherapy). To ensure the most accurate cancer risk assessment, we like to get information on family members as far back as the person’s maternal and paternal grandparents, if possible. The family’s ethnic origin is also useful. For those who have a family history of pancreas cancer, we would also like to know if their affected family member(s) smoked cigarettes, suffered with pancreatitis, or were ever diagnosed with diabetes, as these factors may have influenced their family member(s)’ risk to develop pancreas cancer.

During Your Counseling Session
Genetic counseling is an essential component of cancer risk assessment and the genetic testing process. It involves a medical records review, a discussion of a person’s medical and family histories, a brief discussion about the role genes may play in the development of pancreas cancer, an assessment of a person’s risk(s) to develop cancer based on his or her medical and family histories, an assessment of a person’s risk to carry an inherited change or mutation in a pancreas cancer susceptibility gene, a discussion of the risks, benefits, and limitations of genetic testing, and recommendations for cancer screening based on family history and/or genetic test results. At Columbia’s Pancreatic Cancer Prevention & Genetics Program, most genetic counseling consultations are 45 minutes to one hour long, and include a physical examination. We find that this amount of time allows us to gather all of the necessary information, as well as to facilitate a truly informed decision about genetic testing.

If someone decides to undergo genetic testing, the results are usually given in person at a second visit with the doctor and the genetic counselor. Depending on the genetic test ordered and the laboratory used, the turnaround time for results can be anywhere from 10 days to three or four months. Regardless of the result, the implications for the person and his or her family are discussed in detail and a plan for medical follow-up is mapped out with our team.

Genetic Counselors and Genetic Testing
A genetic counselor is a health professional with a Master’s Degree in genetic counseling, medical genetics, human genetics or other related field from an accredited genetic counseling program who is either board eligible or board certified by the American Board of Genetic Counseling. Some states require licensure for the provision of genetic counseling. Physicians, nurses, or nurse practitioners with a specialty in genetics can also provide genetic counseling. Genetic counselors who deal with patients at-risk of an inherited pancreas cancer susceptibility syndrome generally work as part of a team of geneticists, gastroenterologists, surgeons, oncologists, nurses, nurse practitioners, and mental health professionals to provide patients with information about the genetics of pancreas cancer. Genetic testing itself is just a simple blood test. Most genetic tests require just one or two tubes of blood. However, the implications of genetic testing are complex and far-reaching, and should be discussed with the patient prior to undergoing testing in the context of a genetic counseling consultation. Such a consultation is an essential component of cancer risk assessment and the genetic testing process.
Confidentiality and Costs

Because of the perceived possibility of genetic discrimination by health insurers, confidentiality and privacy of genetic test results is a concern for many individuals contemplating genetic counseling and genetic testing. The experience of cancer genetic programs over the past several years suggests that there have not been any reported cases of individuals being dropped from their insurance or having premiums raised solely based on genetic test results. Federal legislation in the form of the Federal Health Insurance Portability Accountability Act of 1996 or HIPAA and the recently passed Genetic Information Non-discrimination Act or GINA states that genetic information cannot be considered a pre-existing condition and cannot be used to determine coverage or set individual coverage rates. However, no such regulations exist for life and disability insurances. Interested parties can check the website www.nhgri.nih.gov to keep up to date on public policy regarding genetic testing.

Like any doctor’s visit, the information discussed during a genetic counseling consultation at Columbia’s Pancreatic Cancer Prevention & Genetics Program is strictly confidential. However, if a person wishes, we will send a consultation note with the details of the visit to the referring physician and any additional doctors that are specified. Additionally, if someone undergoes genetic testing, those results will remain confidential. We will send a copy of the genetic test results to whomever the person specifies or he or she can give a copy of the results directly to their a doctor.

At this time, most insurers are covering either all or part of the cost of genetic testing as appropriate. The majority of private insurers, as well as Medicaid and Medicare, have developed specific guidelines for the provision of and reimbursement for genetic testing. If a person is interested in genetic testing and wants to know if their insurer will cover it, she or he can contact the insurer directly and/or speak with a genetic counselor.

Sources:
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VIRGINIA CRAVOTTA
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About The Lustgarten Foundation
The Lustgarten Foundation is the nation’s largest private supporter of pancreatic cancer research. Founded in 1998, The Lustgarten Foundation was named after Cablevision executive Marc Lustgarten, who died from pancreatic cancer. The Foundation is dedicated to advancing scientific and clinical research related to the diagnosis, treatment, cure and prevention of pancreatic cancer. The Foundation concentrates on stimulating the scientific community to conduct the research necessary to find early detection methods, better treatments and a cure for the disease. Toward this end, The Lustgarten Foundation sponsors an annual scientific conference and supports promising pancreatic cancer research. The Foundation also provides free informational materials to patients and caregivers, and airs public service announcements (PSAs) that appear on major television and cable networks nationwide.

In 2008, The Lustgarten Foundation and leading media and entertainment company Cablevision Systems Corporation launched curePC, a public awareness campaign in support of the fight against pancreatic cancer. The campaign is made possible through the support of Cablevision, who has committed to underwriting all of The Lustgarten Foundation’s administrative costs to ensure that 100 percent of every dollar donated to the Foundation will go directly to pancreatic cancer research. Visit www.curePC.org to learn more.