The lifetime risk of pancreatic cancer among men and women in the United States is ~1.4% and most cases of pancreatic cancers are sporadic (1). However, an estimated 10% of cases may be due to an underlying hereditary cause (2,3). Although our knowledge and the genetic testing options for hereditary pancreatic cancer have increased in recent years, the underlying genetic cause for clusters of pancreatic cancer in many families is still unclear.

Hereditary pancreatic cancer can be divided into several distinct categories: 1) known hereditary cancer syndromes mainly defined by risk for other cancers which include > risk of PC; 2) known hereditary disease which causes inflammation of the pancreas leading to > risk of PC; 3) familial pancreatic cancer (a clustering of pancreatic cancer in 2 or more first degree relatives) in which the underlying genetic cause is not yet known (4).

Genetic testing is available for the genes associated with categories 1 and 2 as follows:

1. Hereditary Cancer Syndromes
   - Hereditary Breast and Ovarian Cancer (HBOC)
     - BRCA1 and BRCA2 genes; autosomal dominant.
     - Clinical features include significantly increased risks of breast, ovarian, and prostate cancer.
     - The general population incidence of BRCA1/2 mutations is ~1/800-1/2500 in non-Jewish individuals and ~1/40 individuals of Ashkenazi Jewish ancestry (5).
     - BRCA2 mutations are the most common identifiable germline mutation in familial pancreatic cancer (6).
     - BRCA2 mutations have been identified in ~17-19% of familial pancreatic cancer families (even in the absence of a family history of breast and/or ovarian cancer). ~7% of apparently sporadic pancreatic cancers and ~10% of Ashkenazi Jewish individuals with pancreatic cancer (2,3,6).
     - BRCA2 mutations are associated with a ~4-8% lifetime risk of PC (7). Therefore, the vast majority (92-96%) of BRCA2 carriers never develop PC.
     - The association between BRCA1 mutations and pancreatic cancer is less clearly defined. However, some studies have shown an increased risk of pancreatic cancer in families with BRCA1 mutations (2,3,8).

   - PALB2 gene
     - The PALB2 gene was identified in recent years and its protein product interacts with the protein products of the BRCA1 and BRCA2 genes (9,10).
     - Germline mutations in the PALB2 gene have been identified in ~1-3% of familial breast cancer cases and ~3-4% of familial pancreatic cancer cases (9,10,11).
     - Mutations in the PALB2 gene are associated with an increased risk of pancreatic and female breast cancers and perhaps male breast cancer. The exact cancer risks associated with PALB2 mutations are not well defined at this time (9,10,11).

   - Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)
     - CDKN2A (p16) gene; autosomal dominant (2,3).
     - Clinical features include multiple nevi, increased risk of melanoma including melanoma at an earlier than average age and multiple primary melanomas.

There are a variety of hereditary cancer syndromes that involve endocrine cancers and tumors. Some of these syndromes also involve non-malignant, non-endocrine findings. These findings are critical when obtaining a family history and can help guide the determination of which genetic test to order (1). To follow is a summary of the currently known hereditary endocrine cancer syndromes for which genetic testing is available, arranged according to the clinical endocrine finding. Since there are a number of hereditary cancer syndromes that include risk for endocrine tumors, our coverage of these syndromes will be split into two articles. In this issue we will cover hereditary endocrine cancer syndromes involving the thyroid and parathyroid glands. In the next...
Welcome to autumn! This year fall will bring not only cooler temperatures, back-to-school, and the beginning of our academic calendar, but many new changes in our Program.

As you will read in the coming pages, we have added an Assistant Director to our Program. Our own Danielle Campfield Bonadies, MS, CGC, with whom many of you have worked, has been promoted to this position and will be pivotal in our upcoming expansion.

Yes, that is correct, we are expanding! Our Program began exactly 15 years ago this fall and has since expanded to one of the largest Programs in the country, with 3 additional genetic counselors, an office manager, a phlebotomist, and many students. We will now be adding a 5th dedicated cancer genetic counselor to our team. This counselor will enable us to better serve your needs and the needs of your patients. We have also added an outreach clinic at the Center for Cancer Care at Griffin Hospital in Derby, CT, which will allow many of your patients to be seen in their own neighborhood.

In this issue of our newsletter, you will read about the many non-cancer related findings that should be considered when taking a detailed family history for endocrine-related malignancies. You, the clinician, are critical in determining when your patients need a referral for cancer genetic counseling and testing. This often requires some investigative history-taking on your part and we appreciate your assistance in this process. You will also read about hereditary pancreatic cancer, the role of breast MRI in BRCA carriers, the meaning of triple-negative breast cancer in genetic screening, and phenotype/genotype correlations in Lynch syndrome. If there is an area of interest to you that you’d like to see us cover in our next issue, please contact us at karina.brierley@yale.edu.

Thank you for working with us over the past 15 years in offering your patients accurate risk assessment, genetic counseling, and testing. We look forward to the exciting changes ahead in the next 15 years.

Sincerely,
Ellen T. Matloff, MS
Director, Cancer Genetic Counseling
Referral for Genetic Counseling:
A referral to genetic counseling for hereditary pancreatic cancer should be considered for individuals with a personal and/or family history that includes any of the following risk factors:

- Multiple cases of pancreatic cancer on the same side of the family.
- A combination of related cancers on the same side of the family (e.g., pancreatic/breast/ovarian, pancreatic/melanoma, or pancreatic/colon/uterine/ovarian).
- Multiple related primary cancers in one individual (e.g., pancreatic/melanoma, pancreatic/breast).
- Ashkenazi Jewish ancestry and pancreatic cancer.
- Pancreatic cancer and multiple and/or early onset gastrointestinal polyps including greater than 15 gastrointestinal polyps or greater than 5 hamartomatous polyps.

Screening for Individuals at Increased Risk:
Routine population screening for pancreatic cancer is not of practical use due to the rarity of the disease and the limitations of the available screening (2,3). However, some data suggest that screening may prove valuable in individuals at high risk by detecting lesions at an earlier, treatable stage (2,3). The optimal screening method for pancreatic cancer is still unclear due to the ultrasound (EUS), endoscopic retrograde cholangiopancreatogram (ERC P), and computed tomography (CT) (3). However, consideration of screening, particularly in the setting of a research protocol, is recommended for individuals with a greater than 10-fold increased risk to develop pancreatic cancer beginning at age 40-45 or 10-15 years younger than the youngest relative with pancreatic cancer on the same side of the family including at least one first degree relative of the individual having screening.

Screening should be considered for individuals meeting the following criteria (2,3):

- Diagnosis of PJS or hereditary pancreatitis.
- A known BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, or PMS2 mutation and one or more first or second degree relatives with pancreatic cancer.
- A family history of 2 or more relatives with pancreatic cancer on the same side of the family including at least one first degree relative of the individual having screening.

References:
issue we will cover syndromes involving the adrenal and pituitary glands, and paragangliomas.

**THYROID**

**Cowden disease (PTEN gene)**
(also known as multiple hamartoma syndrome and Bannayan-Riley-Ruvalcaba) Individuals with Cowden disease are at increased risk for florid parathyroid and thyroid cancer, thyroid nodules and goiters, breast/uterine/renal cancer, hamartomatous polyps, and benign lesions of the breast and uterus. Macroglossy, trichilemmomas (a hallmark feature of this syndrome), mental retardation/developmental delay/autism, and pigmented macules of the penis can also be seen with Cowden disease (2).

**FAP (APC gene)**
A higher incidence of papillary thyroid cancer has been reported in some families with Familial Adenomatous Polyposis. The primary features associated with FAP include adenomatous polyposis, desmoids tumors, early-onset colon and stomach cancers, congenital hypertrophy of the retinal pigment epithelium (CHRPE), and osteomas of the mandible (3).

**MEN2 (RET gene)**
Individuals with Multiple Endocrine Neoplasia 2a are at an increased risk to develop medullary thyroid cancer (70-100% lifetime risk), pheochromocytoma, and hyperparathyroidism. Individuals with MEN2 are also at increased risk for cutaneous lichen amyloidosis and Hirschsprung’s disease (4).

Individuals with MEN2b are also at increased risk for medullary thyroid cancer, pheochromocytoma, and mucosal-intestinal ganglioneuromas (not hyperparathyroidism). MEN2b is associated with a distinct clinical presentation with enlarged lips, ‘Marfanoid’ habitus and an increased risk for mucosal-intestinal ganglioneuromas.

In some families with a RET mutation, hereditary medullary thyroid cancer is the only feature. This syndrome is known as Familial Medullary Thyroid Cancer (FMTC).

**PARATHYROID GLANDS**

**FHH (CASR)**
Familial Hypocalciuric Hypercalcemia/Familial isolated hypoparathyroidism/autosomal dominant hypocalcemia/neonatal severe primary hyperparathyroidism is due to mutations in the CASR gene. Individuals with a CASR mutation typically present with hypercalcemia and relative hypocalciuria. Some individuals may experience pancreatitis, gall stones, renal stones, or chondrocalcinosis (deposits of a chemical compound in the connective tissue). A severe neonatal form exists when an individual inherits two copies of the CASR gene (5).

**Hyperparathyroidism-Jaw Tumor Syndrome (HRPT2/CDC73)**
In addition to hyperparathyroidism and jaw tumors, parathyroid adenomas and carcinomas and renal tumors have also been seen in individuals with this syndrome (6).

**MEN1 (MEN gene)**
Individuals with Multiple Endocrine Neoplasia Type 1 are at increased risk for hyperparathyroidism (100% by age 50), parathyroid adenomas (approximately 95%), pituitary tumors, gastrinomas, insulinomas, foregut carcinoids, and pheochromocytoma. Facial angiofibromas, collagenomas, meningiomas, and leiomyomas have also been reported in MEN1 families (7).

**MEN 2a**
The lifetime risk for hyperparathyroidism in individuals with MEN2a is 20-30% (4).

References:

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**Staff Announcements**

**NEW TEAM PSYCHOLOGIST**
We are pleased to welcome Terry Eicher, PhD as our new Team Psychologist. Dr. Eicher has a diversified background, earning a master’s degree in divinity followed by a master’s degree in public health. He then went on to earn a PhD in Clinical Psychology from Yale University and has practiced as a psychologist in the New Haven area for many years. If you would like to make an appointment with Dr. Eicher, please contact him at (203) 772-4066.

**ASSISTANT DIRECTOR**
Danielle Campfield Bonadies, MS, CGC has been promoted to Assistant Director of the Cancer Genetic Counseling Program. Ms. Bonadies interned in the program before graduate school and completed our summer fellowship during her training. She has been a genetic counselor with the program for seven years and will play a pivotal role in our expansion.
IMPROVEMENTS IN TESTING FOR HEREDITARY COLON CANCER (LYNCH SYNDROME/HNPCC)

In 2011, several of the major genetic testing laboratories updated their testing panels for hereditary colon cancer associated with Lynch Syndrome. These advances may help identify genetic mutations in individuals whose previous testing was uninformative and will now allow us to offer more comprehensive testing to families who are at risk for Lynch Syndrome.

For patients who previously tested negative for Lynch Syndrome/HNPCC mutations, these additional tests will require a new blood sample and will be associated with additional charges that may be covered by insurance. The identification of families with Lynch syndrome provides a unique opportunity to tailor their medical management options through screening and prevention. Therefore, individuals with a significant personal and/or family history suggestive of hereditary colon cancer whose previous testing (performed prior to 2011) did not identify a mutation may wish to consider additional testing using these new techniques.

Previous testing:

- Full sequencing and large rearrangement analysis of the MLH1 and MSH2 genes
- Full sequencing of MSH6

Additions to testing as of 2011:

- Full sequencing and large rearrangements of PMS2. Studies suggest that as much as 15% of Lynch syndrome is attributable to mutations in the PMS2 gene.

- Large rearrangement analysis of MSH6 and EPCAM. The EPCAM gene is a recently discovered contributor to Lynch syndrome, accounting for an estimated 1-3% of all detectable Lynch syndrome mutations.

If your patients are interested in pursuing testing for Lynch syndrome, have previously tested negative and are interested in additional testing, or have any questions about this testing, please have them contact our program at (203) 764-8400.

Journal Clips

PREVALENCE OF BRCA1 AND BRCA2 MUTATIONS IN TRIPLE NEGATIVE BREAST CANCER


Approximately 15% of all breast cancers are triple negative breast cancers (TNBC) and we’ve long suspected that these cancers are overrepresented in BRCA1 mutation carriers. This study compared the prevalence of BRCA1 and BRCA2 mutations in several published TNBC cohorts. In one study of 63 isolated cases of TNBC diagnosed <41 years, 8/63 (12.7%) carried a BRCA1 mutation. In another study of 43 isolated TNBC diagnosed <41 years, 5/43 (11.3%) were BRCA1+. The percentage of both BRCA1 and BRCA2 mutations increased with positive family history of breast and/or ovarian cancer, earlier age of onset, and Jewish ancestry. The majority of TNBC cases are not due to an underlying BRCA mutation. However, the NCCN has expanded their genetic counseling and testing guidelines to include all women diagnosed with TNBC before the age of 60.

CANCER RISKS ASSOCIATED WITH GERM LINE MUTATIONS IN MLH1, MSH2, AND MSH6 GENES IN LYNCH SYNDROME


This French study of 537 Lynch syndrome families analyzed cancer prevalence and age of diagnoses in known carriers of the genes MLH1 (248), MSH2 (256), and MSH6 (33). They found that colorectal cancer risk by age 70 was highest in MSH2 (48%) and MLH1 (41%) carriers, and lowest in MSH6 carriers (12%). Endometrial cancer risks by age 70 were 54% in MLH1 carriers, and lower for MSH2 (21%) and MSH6 (16%). The risk of ovarian cancer by age 70 was highest for MSH2 (24%) and MLH1 (20%) carriers, and lower for MSH6 (1%). Although these data are interesting in pointing out genotype/phenotype correlations in Lynch syndrome, they are not conclusive and should not change screening and risk reduction recommendations for Lynch syndrome at this time; particularly because early stage ovarian cancer is so difficult to detect with surveillance.

PROSPECTIVE STUDY OF BREAST CANCER INCIDENCE IN WOMEN WITH A BRCA1 OR BRCA2 MUTATION UNDER SURVEILLANCE WITH AND WITHOUT MAGNETIC RESONANCE IMAGING


Canadian researchers followed 1275 female BRCA1 or BRCA2 carriers for a mean of 3.2 years in this surveillance study. A total of 445 BRCA carriers were enrolled in the MRI screening trial and 830 were in the comparison group and instructed to receive annual clinical breast examination and mammography (although their compliance was not controlled or monitored). Of note, breast ultrasound was discontinued in 2005 because it was not found effective in surveillance. Within the follow-up time, there were 41/445 (9.2%) cases of breast cancer in the MRI group and 76/830 (9.2%) in the comparison group. The percentages of DCIS or stage I breast cancer at 6 years was 13.8% in the MRI group vs. 7.2% in the comparison group. The incidence of stages II to IV breast cancer was 1.9% in the MRI group vs. 6.6% in the comparison group. These data support the hypothesis that annual surveillance with MRI is associated with a significant reduction in advanced-stage breast cancer in BRCA1 and BRCA2 carriers.
You, the clinician, are critical in determining when your patients need a referral for cancer genetic counseling and testing.

Please visit our new website to learn the facts about genetic testing and to refer a patient for counseling at yalecancercenter.org/genetics.