Objectives

- Recognize those cancer susceptibility genes that are associated with an increased risk for PC development
- Understand the rationale for performing genetic risk assessment in a PC patient
- Identify those patients who are candidates for genetics referral
- Understand how to incorporate genetic testing into clinical practice
Pancreatic Cancer: Background

- Incidence
  - In the US in 2014: 46,420 new diagnoses
  - About 1.4% life-time risk of developing
- Fourth leading cause of cancer related mortality in the United States
- Over 90% of tumors are adenocarcinomas
- Hereditary Disorders associated with PC
  - Recognized genetic syndromes with a known germline mutation associated with PC development
  - 2 or more cases of PC (with at least a pair of FDR)
    - Known as “Familial Pancreatic Cancer”
Five to 10% of PC Related to Hereditary Factors

- Study in French Canadians (Ghadirian et al. 1991)
  - 13-fold difference
    - 7.8% of PC patients with positive FH
    - 0.6% of controls with positive FH
- UPMC PC registry (unpublished data from 2004-13)
  - 962 pancreatic adenocarcinoma cases
    - 58 with PC FDR: 6%
  - No significant differences were found in age, gender, race and overall stage

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Relative Risk of PC</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Atypical Multiple Mole Melanoma (FAMMM)</td>
<td>13 to 39-fold</td>
<td>p16</td>
</tr>
<tr>
<td>Familial Breast and Ovarian</td>
<td>2-fold and 3 to 9-fold</td>
<td>BRCA1 and 2</td>
</tr>
<tr>
<td>Fanconi Anemia, Breast CA</td>
<td>Unknown</td>
<td>PALB2</td>
</tr>
<tr>
<td>FAP</td>
<td>5-fold</td>
<td>APC</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>9 to 11-fold</td>
<td>MLH1, MSH6 MSH2, PMS2</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>132-fold</td>
<td>STK11/LKB1</td>
</tr>
<tr>
<td>Hereditary Pancreatitis</td>
<td>53-fold</td>
<td>PRSS1</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>7-fold</td>
<td>p53</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>~3-fold</td>
<td>ATM</td>
</tr>
</tbody>
</table>
Risk for Developing Pancreatic Cancer in “Familial Pancreatic Cancer” by Family History, Age and Smoking History

<table>
<thead>
<tr>
<th></th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.79 (4.54 to 9.75)*</td>
</tr>
<tr>
<td>Three or more FDR</td>
<td>17.02 (7.34 to 33.5)*</td>
</tr>
<tr>
<td>Two FDR</td>
<td>3.97 (1.59 to 8.2)*</td>
</tr>
<tr>
<td>One FDR</td>
<td>6.86 (3.75 to 11.04)*</td>
</tr>
<tr>
<td>Young-onset kindred</td>
<td>9.31 (3.42 to 20.28)*</td>
</tr>
<tr>
<td>Late-onset kindred</td>
<td>6.34 (4.02 to 9.51)*</td>
</tr>
<tr>
<td>Smokers</td>
<td>9.09 (4.97 to 15.25)*</td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>6.38 (3.02 to 11.15)*</td>
</tr>
</tbody>
</table>

* p < 0.005

Brune, et al. JNCI 2010

Rationale for Genetic Risk Assessment for PC Patients

• PRO
  – Can provide a reason for their cancer diagnosis
  – May provide information that guides therapy
    • PARP inhibitors and use in BRCA1/2 mutation carriers
  – Address concerns over passing risk to their family

• CON
  – No benefit of knowing future associated cancer risks
  – Issues of variant of unknown significance (VUS)
Importance of Genetic Testing: Family Members

- Specific (single-site) testing if pathogenic mutation has been identified
  - Don’t need to be concerned about VUS
- If found to be mutation carrier
  - Undergo surveillance and/or prevention for associated cancers
  - Decreased false positive rate due to higher disease prevalence
  - EUS- based on expert opinion should be done in centers with active research (Canto et al 2013 GUT)
- If not a mutation carrier
  - Can follow general cancer screening guidelines

Who are Candidates for Genetic Referral?
Evaluation

• Obtain pedigree
  – Three generation (children, siblings, parents, aunts, uncles and grandparents)

• Review pedigree
  – For excess number of cancers
  – Cancers associated with known hereditary syndromes that predispose to PC
  – Early age-onset cancers

Genetic Predisposition to Pancreatic Cancer

1. Murphy et al Cancer Research 2012
6. Nicholas et al Cancer Discovery 2012
7. Lichtenstein et al. NEJM 2000

**Unknown for Lynch syndrome, FAP, Hereditary Pancreatitis, Peutz-Jeghers, Li-Fraumeni Syndrome
**Syndromes Associated with Pancreatic Adenocarcinoma**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Major non-PC Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Atypical Multiple Mole Melanoma (FAMMM)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Familial Breast and Ovarian</td>
<td>Breast, Ovary</td>
</tr>
<tr>
<td>Fanconi Anemia (PALB2)</td>
<td>Breast</td>
</tr>
<tr>
<td>FAP</td>
<td>Colon</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>Colon, Endometrial</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>GI malignancies, Breast</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>Sarcomas, Breast, Brain, Adrenocortical</td>
</tr>
<tr>
<td>Ataxia -telangiectasia</td>
<td>Breast, colon</td>
</tr>
</tbody>
</table>

**Candidates for Genetic Risk Assessment**

- If melanoma is present consider FAMMM
- Look for Amsterdam/Bethesda Guidelines for Lynch Syndrome
- Determine if meets HBOC NCCN guidelines
- Strong family or personal history of acute or chronic pancreatitis (Hereditary Pancreatitis)
- Meet criteria for Familial Pancreatic Cancer
Incorporating Genetic Testing for Pancreatic Cancer in Clinical Practice

- Obtain personal and family history with emphasis on cancer history
- Develop a relationship with a certified genetic counselor/ genetic program
- Limited use in past for pancreatic cancer
  - Unless criteria for one of the well described hereditary syndromes associated with PC
  - Change in practice since 2013
    - Supreme court ruling (*Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U. S. 12-398)
    - Advances in technology like next-generation sequencing (NGS)
Incorporating Genetic Testing in Clinical Practice for Pancreatic Cancer: Cancer Panels

<table>
<thead>
<tr>
<th>Commercial Lab</th>
<th>Genes on Panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>APC, ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53, VHL, XRCC2</td>
</tr>
<tr>
<td>#2</td>
<td>APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, STK11, TP53</td>
</tr>
<tr>
<td>#3</td>
<td>APC, ATM, BRCA1, BRCA2, CDKN2A, EPCAM, FANCC, MEN1, MLH1, MSH2, MSH6, PALB2, PALLD, PMS2, STK11, TP53, VHL</td>
</tr>
</tbody>
</table>

[Family tree diagram]
UPMC Experience with Cancer Panels
(manuscript submitted)

• First 18 NGS panels obtained on PC affected patients
  – 15 met criteria for FPC
  – 2 with SDR with PC
  – One with early age onset PC
• Results
  – Two deleterious mutations in ATM gene (11%)
  – 39% variant rate (VUS) without a concurrent deleterious mutation
  – 50% no mutations or VUS

Summary
• The possibility now exists to identify candidates for genetic testing based on family history
• Usefulness of genetic testing is not known outside of known hereditary syndromes associated with an increased PC risk
  – Unknown role for early age-onset PC patients
• No guidelines currently available for genetic testing for Pancreatic Cancer
• Expanding role of genetics in personalizing cancer treatment
• Worthwhile to involve genetic professional(s) when evaluating for hereditary cancer predisposition and disclosing genetic testing results