Familial Pancreatic Cancer Families
(and other high-risk people)

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Risk, Early Detection

• Subjects at increased risk include:
  – Familial cancer syndromes
  – Chronic pancreatitis
  – Tobacco smoking

• Screening: generally not recommended outside of a research study

• Most early detection is incidental
  – Malignant cystic lesions
  – IPMN
Familial Pancreatic Cancers: defining high-risk patients

- Strong Family History (10% sporadic)
- Early Age of Onset
- Often Associated With Syndromes
  - HNPCC (MLH1, MSH2 and MSH6) +Korean, - Dutch
  - FAMMM (p16, CDKN2A) heterogeneity!
  - Peutz-Jeghers Syndrome (STK11/LKB1)
  - Breast cancer (BRCA2)
  - Hereditary Pancreatitis (PRSS1 - trypsinogen)
  - Fanconi Anemia (FANCC and FANCG)
  - Family X

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A New Susceptibility Locus for Autosomal Dominant Pancreatic Cancer Maps to Chromosome 4q32-34

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Identification of the PALLID Gene

A new approach to identify a cancer gene in 4q32:
Check expression of all genes in normal and abnormal tissue


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Cytoskeletal Proteins

Cell Migration Assay

HeLa + Wt

HeLa + FX mutation

Screening High Risk Families: CAPS2

- A prospective controlled study of screening EUS and CT followed by ERCP in 78 at-risk relatives and 149 control subjects
- High prevalence of CP-like changes
  - 72% by EUS
  - 68% by ERCP
- 10% treated by subtotal pancreatectomy:
  - IPMNs
  - carcinoma-in-situ (1 pt)

Candidates for PC Screening*

- ≥ 3 first-degree, second degree or third degree relatives with PC in the same linage
- Known mutation carrier in BRAC1, BRCA2 or p16 with at least one first-degree or second degree relative with pancreatic cancer.
- A member, ideally a verified germline carrier, of a PJS kindred.
- Two relatives in the same linage (directly connected) affected with pancreatic cancer, at least one a first-degree relative of the candidate.
- An affected individual with hereditary pancreatitis.

* Brand et al, Gut 2007;56:1460-1469
Real Challenges

• Refer patients with early diagnosis to expert pancreatic cancer centers.
    • Stage I - 71% did NOT undergo surgery
    • 38% not offered surgery
    • >65y, black, Medicare, head lesions, low income, low education, small centers.

• Much better risk models are needed to identify patients for risk reduction strategies and possible surveillance.

• Better methods to evaluate lesions identified on high quality imaging studies.
# Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses*

**Table 2.** Core signaling pathways and processes genetically altered in most pancreatic cancers

<table>
<thead>
<tr>
<th>Regulatory Process or Pathway</th>
<th>Number of genetically altered genes detected</th>
<th>Fraction of tumors with genetic alteration of at least one of the genes</th>
<th>Representative altered genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis</td>
<td>9</td>
<td>100%</td>
<td>CASP10, VCP, CAD, HIP1</td>
</tr>
<tr>
<td>DNA damage control</td>
<td>9</td>
<td>83%</td>
<td>ERCC4, ERCC6, EP300, RANBP2, TP53</td>
</tr>
<tr>
<td>Regulation of G1/S phase transition</td>
<td>19</td>
<td>100%</td>
<td>CDKN2A, FBXW7, CHD1, APC2</td>
</tr>
<tr>
<td>Hedgehog signaling</td>
<td>19</td>
<td>100%</td>
<td>TBX5, SOX3, LRP2, GLI1, GLI3, BOC, BMPR2, CREBBP</td>
</tr>
<tr>
<td>Homophilic cell adhesion</td>
<td>30</td>
<td>79%</td>
<td>CDH1, CDH10, CDH2, CDH7, FAT, PCDH15, PCDH17, PCDH18, PCDH9, PCDHB16, PCDHB2, PCDHGA1, PCDHGA11, PCDHGC4</td>
</tr>
<tr>
<td>Integrin signaling</td>
<td>24</td>
<td>67%</td>
<td>ITGA4, ITGA9, ITGA11, LAMA1, LAMA4, LAMA5, FN1, ILK</td>
</tr>
<tr>
<td>JNK signaling</td>
<td>9</td>
<td>96%</td>
<td>MAP4K3, TNF, ATP2, NFATC3</td>
</tr>
<tr>
<td>KRAS signaling</td>
<td>5</td>
<td>100%</td>
<td>KRAS, MAP2K4, RASGRP3</td>
</tr>
<tr>
<td>Regulation of invasion</td>
<td>46</td>
<td>92%</td>
<td>ADAM11, ADAM12, ADAM19, ADAM5220, ADAMTS15, DPP6, MEPIA, PCSK6, APG4A, PRSS23</td>
</tr>
<tr>
<td>Small GTPase-dependent signaling (other than KRAS)</td>
<td>33</td>
<td>79%</td>
<td>AGHGEF7, ARHGEF9, CDC42BPA, DEPDC2, PLCB3, PLCB4, RP1, PLXNB1, PRKCG</td>
</tr>
<tr>
<td>TGF-β signaling</td>
<td>37</td>
<td>100%</td>
<td>TGFBR2, BMPR2, SMAD4, SMAD3</td>
</tr>
<tr>
<td>Wnt/Notch signaling</td>
<td>29</td>
<td>100%</td>
<td>MYC, PPP2R3A, WNT9A, MAP2, TSC2, GATA6, TCF4</td>
</tr>
</tbody>
</table>

*A complete listing of the gene sets defining these signaling pathways and processes and the statistical significance of each gene set are provided in table S8.*