Defining Sensitivity and Specificity Targets for Pancreatic Cancer Surveillance

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Faces of Pancreatic Cancer in 2020
Pancreatic Cancer: Background

- **Incidence**
  - In the US in 2020: 57,600 new diagnoses
  - 47,050 deaths
  - ~1.6% life-time risk of developing PC
  - ~ 10% felt to be hereditary

- **Third leading cause of cancer related mortality in US**

- **Five-year survival rate of 10%**
  - Local disease(10%) with 5-yr survival rate of 37%

- **> 90% of tumors are adenocarcinomas**

- **Precursor lesions for Pancreatic Adenocarcinomas**
  - Pancreatic Intraepithelial Neoplasias (PanINs)  85% of PC
  - Intraductal Papillary Mucinous Neoplasms (IPMNs)
  - Mucinous cystic neoplasms
A PESSIMIST SEE THE DIFFICULTY IN EVERY OPPORTUNITY.

AN OPTIMIST SEES THE OPPORTUNITY IN EVERY DIFFICULTY

SIR WINSTON CHURCHILL
Why should we be optimistic?
Adapted from NCI’s SEER Cancer Statistics Review 2020

### Pancreatic Cancer 5-year Relative Survival by Stage at Diagnosis for 2009-2015, All Races, Both Sexes

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>% of Cases</th>
<th>5-year Relative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Regional</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Distant</td>
<td>53</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

### Colorectal Cancer 5-year Relative Survival by Stage at Diagnosis for 2009-2015, All Races, Both Sexes

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>% of Cases</th>
<th>5-year Relative Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>39</td>
<td>89.9</td>
</tr>
<tr>
<td>Regional</td>
<td>35</td>
<td>71.3</td>
</tr>
<tr>
<td>Distant</td>
<td>22</td>
<td>14.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>35.4</td>
</tr>
</tbody>
</table>

- Identifying the tumor at an earlier stage
- Better treatments
General Population

Familial PC Kindreds (FPC)

Asymptomatic Average Risk
Hereditary Syndromes

Asymptomatic High Risk
Familial PC Kindreds (FPC)

Symptomatic Abnormal Imaging
Pancreatic Cysts
New Onset DM

Screening

Surveillance

Diagnostic
High Risk Individuals as Defined in 2020

<table>
<thead>
<tr>
<th>Genes</th>
<th>Common name</th>
<th>Risk of pancreatic cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>STK11/LKB1</td>
<td>Peutz–Jeghers syndrome</td>
<td>RR, 132 (95% CI, 44–261)</td>
</tr>
<tr>
<td>PRSS1</td>
<td>Hereditary pancreatitis</td>
<td>SIR, 53 (95% CI, 23–105)</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Familial atypical multiple mole/melanoma syndrome</td>
<td>RR, 13–39</td>
</tr>
<tr>
<td>MLH1, MSH2, MSH6</td>
<td>Lynch syndrome</td>
<td>RR, 8.6–11</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni syndrome</td>
<td>RR, 7.3 (95% CI, 2–19)</td>
</tr>
<tr>
<td>ATM</td>
<td>NA</td>
<td>RR, 3.92 (95% CI, 0.44–14.2)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>Hereditary breast and ovarian cancer</td>
<td>RR, 2.26 (95% CI, 1.26–4.06)</td>
</tr>
<tr>
<td>BRCA2, PALB2</td>
<td>Familial pancreas cancer in 1 or 2 first-degree relatives</td>
<td>RR, 3.5–6.2 (95% CI 1.87–6.58)</td>
</tr>
<tr>
<td></td>
<td>Familial pancreas cancer</td>
<td>RR, 4–9.3</td>
</tr>
</tbody>
</table>

From Davee et al, adapted with permission. NA, not applicable; RR, relative risk; SIR, standardized incidence ratio.
Summary of Recommendations of the 2019 International CAPS Consortium: How

- **At Baseline**
  - MRI/MRCP + EUS + fasting blood glucose and/or HbA1c

- **During follow-up**
  - Alternate MRI/MRCP and EUS
    (no consensus if and how to alternate)
  - Routinely test fasting blood glucose and/or HbA1c

- **Intervals**
  - 12 months if no abnormalities, or only non-concerning abnormalities
  - 3 or 6 months if concerning abnormalities for which immediate surgery is not indicated
  - Surgery if positive FNA and/or a high suspicion of malignancy on imaging
Summary of pertinent findings after initial screening:
1. Cumulative incidence of invasive PDAC was 3.4% (12/354 HRI)
2. PDAC and high-grade precursor lesions develop in 7% of HRI at a rate of progression of 1.6% per year
3. Nine of 10 PDACs were resectable (stage I or II)
4. Three-year survival rate of 90%
Familial PC Kindred (FPC)

Asymptomatic High Risk

Hereditary Syndrome

Familial PC Kindred (FPC)

Imaging Study

Advanced Neoplasia

No Advanced Neoplasia

Surgery

Surveillance

BIOMARKER
Overall Strategy for Surveillance of High-Risk Groups

Target Performance:
Sensitivity > 95%
Specificity > 50-70%

General Population → Clinical Evaluation

Clinical Risk Groups
- Family History: Prevalence 1.6%
- Mucinous Cyst: Prevalence 2%
- NOD: Prevalence 0.8%
- Chronic Pancreatitis: Prevalence 1%

Biomarker Surveillance

Enriched Prevalence ~10%

Imaging Surveillance → Diagnostic Workup

If positive

Adapted from Liu et al. Cancer Epidemiol Biomarkers Prev. 2020
Pancreatic Cyst Management

- Who should you resect?
- Treatment
- Who should you follow?
- Surveillance
- Who should you forget?
  No further management required
# Common Pancreatic Cysts

<table>
<thead>
<tr>
<th>No Malignant Potential</th>
<th>Malignant Potential</th>
</tr>
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<tbody>
<tr>
<td>Pseudocyst</td>
<td>Intraductal papillary mucinous neoplasm</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>Mucinous cystic neoplasm</td>
</tr>
<tr>
<td>Retention Cyst</td>
<td>Cystic neuroendocrine tumor</td>
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<tr>
<td>Lymphoepithelial cyst</td>
<td>Solid pseudopapillary neoplasm</td>
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**Are any of the following high-risk stigmata of malignancy present?**
- i) obstructive jaundice in a patient with cystic lesion of the head of the pancreas, ii) enhancing solid component within cyst, iii) main pancreatic duct ≥10 mm in size

**Yes**
- Consider surgery, if clinically appropriate

**No**
- **Are any of the following worrisome features present?**
  - **Clinical:** Pancreatitis
    - Imaging: i) cyst ≥3 cm, ii) thickened/enhancing cyst walls, iii) main duct size 5-9 mm, iii) non-enhancing mural nodule iv) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy.

**Yes**
- If yes, perform endoscopic ultrasound

**No**
- **Are any of these features present?**
  - i) Definite mural nodule(s)
  - ii) Main duct features suspicious for involvement
  - iii) Cytology: suspicious or positive for malignancy

**Yes**
- What is the size of largest cyst?
  - ≤1 cm
    - CT/MRI in 2-3 years
  - 1-2 cm
    - CT/MRI yearly x 2 years, then lengthen interval if no change
  - 2-3 cm
    - EUS in 3-6 months, then lengthen interval alternating MRI with EUS as appropriate. Consider surgery in young, fit patients with need for prolonged surveillance
  - >3 cm
    - Close surveillance alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients

**No**
- Inconclusive

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a. Pancreatitis may be an indication for surgery for relief of symptoms.
b. Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue
c. Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is inconclusive.
d. Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.
Performance of International Consensus Fukuoka Guidelines for the management of suspected asymptomatic BD-IPMN
(Xu et al. Medicine 2017 96:35)

- Multi-center study of 405 patients undergoing resection for an asymptomatic pancreatic cyst.
- Patients with main duct IPMN defined as >1 cm, symptomatic cysts and presence of solid pancreatic masses were excluded.
- Total of 269 eligible patients
  - 228 (85%) with benign or low-grade cystic neoplasms
  - 41 (15%) malignant: 14 HGD, 27 invasive cancer

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<tr>
<td>Sensitivity for HGD/CA</td>
<td>73.2%</td>
</tr>
<tr>
<td>Specificity for HGD/CA</td>
<td>45.6%</td>
</tr>
<tr>
<td>PPV for HGD/CA</td>
<td>19.4%</td>
</tr>
<tr>
<td>NPV for HGD/CA</td>
<td>90.4%</td>
</tr>
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</table>
### Who to Resect?

<table>
<thead>
<tr>
<th></th>
<th>Current Guidelines</th>
<th>Proposed</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity for HGD/CA</td>
<td>62-73%</td>
<td>80-85%</td>
</tr>
<tr>
<td>Specificity for HGD/CA</td>
<td>46-79%</td>
<td>90%</td>
</tr>
<tr>
<td>PPV for HGD/CA</td>
<td>19-52%</td>
<td>80%</td>
</tr>
<tr>
<td>NPV for HGD/CA</td>
<td>82-90%</td>
<td>95%</td>
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Xu *et al.* Medicine 2017 and Singhi *et al.* GIE 2015
Both optimists and pessimists contribute to society. The optimist invents the aeroplane, the pessimist the parachute.

— George Bernard Shaw —
Questions to Address

1. Considering the topics covered in your session, what are the most important takeaways?
2. What actions should be taken to implement them?
3. Can the topics discussed in the session be implemented by the EDRN? YES
4. Should the topics discussed be written up as a manuscript for the community engaged in biomarker research? ALREADY HAS THIS YEAR!!