Pancreatic screening for high risk familial syndromes

John A Windsor
Professor of Surgery, University of Auckland
Surgeon, HBP/Upper GI Unit, Auckland City Hospital
Director, Surgical and Translational Research Centre
No disclosures
No conflicts of Interest
‘Melancholie’
(Geneva)
The best chance of reducing the high mortality of pancreatic cancer is the **identification of individuals at risk** and the development of **screening tests** for early diagnosis and treatment.

*Rieder and Bartsch*  
Familial Cancer 2004
EDITORIAL

Is Screening for Pancreatic Cancer in High-Risk Individuals One Step Closer or a Fool’s Errand?

- Problems with screening
  - Varying definitions of high risk individual
  - Different testing modalities

- Screening average risk population is futile
  - Age adjusted incidence of 37/100,000 for > 50 years
  - Using screening test has 99% sensitivity and specificity
  - Will detect nearly all pancreatic cancers (n=36), but falsely identify another 1000 patients.

Hart and Chari, Clin Gastro Hepat 2019
To overcome this challenge need to apply filters to enrich a high-risk population for screening

Potential filters
- Family history ✓
- Genetic profile ✓
- New onset diabetes ?
- Biomarkers ?

Hart and Chari
Clin Gastro Hepat 2019
Individuals at risk

- family history of pancreatic cancer
Definitions

- **Familial pancreatic cancer**
  - used to describe families with at least 2 first degree relatives with pancreatic cancer

- **Hereditary pancreatic cancer**
  - used to describe pancreatic cancer due to an underlying genetic predisposition

- **Inherited cancer syndromes**
  - Used to describe inherited profiles with known genetic defects that increase the cumulative life time risk of developing pancreatic cancer
Family history

- Recognized as risk factor in 1967 by Henry Lynch
- Population-based case-control studies
  - Canada (Ghadirian et al. IJP 2001)
    - positive family history of pancreatic cancer in 7.8% cases and 0.6% controls
  - USA (Silverman et al. TCM 2001)
    - 3.2 fold increased risk if a FDR had PC
- Genetic basis is unknown for the vast majority (~80%) of familial pancreatic cancers
### Risk of pancreatic cancer in FPC

- Prospective study of 838 kindreds with FPC on National Familial Pancreas Tumour Registry

<table>
<thead>
<tr>
<th>First Degree Relatives</th>
<th>Standardized Incidence Ratio (95% CI)</th>
<th>Lifetime Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or more</td>
<td>32.0 (10.4-74.7)</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>6.4 (1.8-16.4)</td>
<td>8-12</td>
</tr>
<tr>
<td>1</td>
<td>4.5 (0.54-16.3)</td>
<td>6</td>
</tr>
</tbody>
</table>
Individuals at risk

- family history of pancreatic cancer
- long standing cigarette smoking
The effect of smoking

- Smoking - independent and significant risk factor
- Interaction between family history and smoking
  - Schenk et al. 2001
  - Tersmette et al. 2001

- Smoking increases risk of FPC 4 x
- Hastens the onset of the disease by 10 years
  - Rulyak, Lowenfels, et al.
  - Gastroenterology 2003
Rulyak, Lowenfels, et al.
Gastroenterology 2003
Individuals at risk

▪ family history of pancreatic cancer
▪ long standing cigarette smoking
▪ new onset (adult) diabetes
Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes

Ayush Sharma, Harika Kandlakunta, Sajan Jiv Singh Nagpal, Ziding Feng, William Hoos, Gloria M. Petersen, and Suresh T. Chari

1Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; 2Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas; 3Pancreatic Cancer Action Network, Manhattan Beach, California; and 4Department of Health Science Research, Mayo Clinic, Rochester, Minnesota

- NOD + >50 yrs = 1% diagnosed with PC in 3 years
- ‘DEF approach’ (define, enrich, find) to screening pool
- ENDPAC score
  - Change in weight
  - Change in blood glucose
  - Age at onset of diabetes
Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes

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### CLINICAL—PANCREAS

**Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes**

Ayush Sharma,¹ Harika Kandlakunta,¹ Sajan Jiv Singh Nagpal,¹ Ziding Feng,² William Hoos,³ Gloria M. Petersen,⁴ and Suresh T. Chari¹

¹Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota; ²Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas; ³Pancreatic Cancer Action Network, Manhattan Beach, California; and ⁴Department of Health Science Research, Mayo Clinic, Rochester, Minnesota

- **ENDPAC SCORE >3**
  - Prevalence of PC was 4.4x higher in patients with NOD
  - Identified 7 of 9 patients with PC in validation cohort
  - False positives tended to be on steroids or other cancers

- **ENDPAC SCORE 0**
  - 49% of patients
  - Extremely low risk of PC
ENDPAC model determines risk of PC in patients with NOD based on glycaemic status.

Still requires independent prospective validation

Could contribute to early detection of PC
Individuals at risk

- family history of pancreatic cancer
- long standing cigarette smoking
- new onset adult diabetes
- known syndrome with risk
Prevalence of Hereditary Pancreatic Cancer

USA (10%: Lynch 1996 & Hruban 1999), but Sweden (2.7%), Germany (1.9%)
<table>
<thead>
<tr>
<th>INHERITED CANCER SYNDROMES</th>
<th>Involved Gene</th>
<th>Gene Function</th>
<th>Lifetime Risk for Panc Ca (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Pancreatitis</td>
<td>PRSS1, SPINK, CFTR</td>
<td>Cationic trypsinogen</td>
<td>40 % by 70 yrs</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11, LKB1</td>
<td>Tumour suppressor Serine threonine kinase</td>
<td>36 %</td>
</tr>
<tr>
<td>FAMMM (familial atypical multiple mole melanoma)</td>
<td>P16-Leiden, CDKN2A</td>
<td>Tumour suppressor</td>
<td>17 % by 75 yrs</td>
</tr>
<tr>
<td>HOBC (hereditary ovarian and breast cancer)</td>
<td>BRCA2, BRCA1</td>
<td>Tumour suppressor</td>
<td>3.6 %</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal carcinoma</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Mismatch repair</td>
<td>3.7 %</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>Tumour suppressor</td>
<td>2 %</td>
</tr>
</tbody>
</table>
Screening

- Routine screening has limited utility given
  - low incidence of pancreatic cancer (9/100,000)
  - low cumulative life time risk (1.5%)
  - lack of low cost, non-invasive, accurate tests

- Screening has proven utility for individuals from certain high risk subgroups to detect precursor lesions
  - But much uncertainty exists regarding the optimal screening approach (and management of pancreatic lesions found in these populations)
Precursor lesions

- Potential targets for screening and for early intervention

- A number are well described
  - **PanIN’s** are microscopic non-invasive neoplasms involving ducts of columnar cells of varying atypia
  - **IPMN** are epithelial neoplasms with grossly visible mucous arising from main, branch duct (or mixed)
  - **Mucinous cystadenomas** are macrocystic, peripheral calcification and normal duct
PanIN’s

- Number increase with age
- Often multi-centric
- Often in pancreatic head
- More frequent in FPC kindreds
- More common in association with other pathologies
  - 3x more common associated with pancreatic ca
  - 82% of pancreatic ca associated with PanIN’s
- Frequently associated with lobular parenchymal atrophy – which can often be detected by EUS
PanIN’s

- Normal
- PanIN-1A
- PanIN-1B
- PanIN-2
- PanIN-3

- Telomere shortening
- K-ras
- PSCA, Mucin5, Fascin
- p16
- Mucin 1
- Cyclin D1
- p53, DPC4, BRCA2
- KI-67, Topollα, 14-3-3σ
- Mesothelin

Invasion
Sequential Inactivation in PanIN vs. IPMN Development

Pancreatic Ductal Adenocarcinoma (More Common)

IPMN related Adenocarcinoma (Less Common)
The **natural history** (proportion and rate of progression) to invasive malignancy **not well known**

**Prevalence of invasive carcinoma**
- In Main Duct IPMN 50 - 60%
- In Branch Duct IPMN 25%
- In MCN 6 - 36%
International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

Marcia Irene Canto,1 Femme Harinck,2 Ralph H Hruban,3 George Johan Offerhaus,4 Jan-Werner Poley,2 Ihab Kamel,5 Yung Nio,6 Richard S Schulick,7 Claudio Bassi,8 Irma Kluijt,9 Michael J Levy,10 Amitabh Chak,11 Paul Fockens,12 Michael Goggins,1 Marco Bruno,2 on behalf of the International Cancer of the Pancreas Screening (CAPS) Consortium
International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

“A successful screening program should detect and treat:

- T1N0M0 margin-negative PC (asymptomatic)
- High-grade dysplastic precursor lesions (PanINs, IPMNs and MCNs)”

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary Pancreatitis</td>
<td>No recommendation</td>
<td>40 % by 70 yrs</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Yes, regardless of FHx</td>
<td>36 %</td>
</tr>
<tr>
<td>FAMMM (familial atypical multiple mole melanoma)</td>
<td>Yes, if one FDR affected</td>
<td>17 % by 75 yrs</td>
</tr>
<tr>
<td>HOBC (hereditary ovarian and breast cancer)</td>
<td>Yes, if one or two FDR affected</td>
<td>3.6 %</td>
</tr>
<tr>
<td>HNPCC (hereditary nonpolyposis colorectal carcinoma)</td>
<td>Yes, if one FDR affected</td>
<td>3.7 %</td>
</tr>
<tr>
<td>FAP (familial adenomatous polyposis)</td>
<td>No recommendation</td>
<td>2 %</td>
</tr>
<tr>
<td>* Familial pancreatic cancer</td>
<td>Yes, if 2 or more FDR affected</td>
<td>8 -12 % (2 FDR) 16-30 % (3FDR)</td>
</tr>
</tbody>
</table>
Consensus was NOT reached
- on age to initiate screening or to stop surveillance
- on optimal screening modalities
- on frequency of imaging
- on screening abnormalities that warrant surgery

Canto et al. Gut 2013
<table>
<thead>
<tr>
<th></th>
<th>Number of affected relatives</th>
<th>1</th>
<th>≥1 FDR</th>
<th>≥2 FDR</th>
<th>≥3 FDR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No germline mutation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (92% if 2 FDRs and 78% if 1 FDR)</td>
<td>Yes</td>
</tr>
<tr>
<td>BRCA1</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes 78%</td>
<td>—</td>
</tr>
<tr>
<td>BRCA2</td>
<td>Indeterminate 69%</td>
<td>—</td>
<td>—</td>
<td>Indeterminate 69%</td>
<td>—</td>
</tr>
<tr>
<td>PALB2</td>
<td>No</td>
<td>Yes 78%</td>
<td>—</td>
<td>Yes 90%</td>
<td>—</td>
</tr>
<tr>
<td>STK11</td>
<td>Yes 96%</td>
<td>Yes 96%</td>
<td>Yes 96%</td>
<td>Yes 96%</td>
<td>—</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Indeterminate 57%</td>
<td>Yes 88%</td>
<td>Indeterminate 57%</td>
<td>Indeterminate 57%</td>
<td>—</td>
</tr>
<tr>
<td>Lynch syndrome*</td>
<td>No</td>
<td>Yes 88%</td>
<td>No</td>
<td>Indeterminate 53%</td>
<td>—</td>
</tr>
</tbody>
</table>


NOTE. The percentages represent the proportion of international experts (among 49 voting participants) in the International Cancer of the Pancreas Screening Consortium who agreed with screening for the respective combination. Blank boxes indicate no vote was reported for the combination. Color coding reflects the strength of support for screening (green, ≥75%; yellow, 50%–74%; red, <50%).

FDR, first-degree relative.

*Associated with MLH1, MSH2, MSH6, or PMS2 gene mutations.
<table>
<thead>
<tr>
<th>Screening modalities</th>
<th>Disadvantages</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT Scan</td>
<td>Lowest accuracy</td>
<td>Non invasive</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ducts not well seen</td>
<td></td>
</tr>
<tr>
<td>ERCP</td>
<td>Invasive</td>
<td>Duct well seen</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Operator dependent</td>
<td></td>
</tr>
<tr>
<td>MR/ MRCP</td>
<td>Poor accuracy for PanIN</td>
<td>Noninvasive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duct well seen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No radiation</td>
</tr>
<tr>
<td>EUS</td>
<td>Availability</td>
<td>High accuracy</td>
</tr>
<tr>
<td></td>
<td>Operator dependent</td>
<td>Duct well seen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mural nodules</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FNA possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No radiation</td>
</tr>
</tbody>
</table>
Diagnostic yield depends on genetic background and screening modality

- Median diagnostic yield 12% (range 1.3 – 50%)

<table>
<thead>
<tr>
<th>Study</th>
<th>High-risk group</th>
<th>Imaging tests</th>
<th>Diagnostic yield* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentnall 1999 (1) n=14</td>
<td>FPC</td>
<td>EUS + ERCP + CT</td>
<td>7/14 (50)†</td>
</tr>
<tr>
<td>Kimmey 2002 n=46‡</td>
<td>FPC</td>
<td>EUS; ERCP§</td>
<td>12/46 (26)†</td>
</tr>
<tr>
<td>Canto 2004 (2) n=38</td>
<td>FPC, PJS</td>
<td>EUS; ERCP§, EUS-FNA§, CT§</td>
<td>2/38 (5.3)†</td>
</tr>
<tr>
<td>Canto 2006 (3) n=78</td>
<td>FPC, PJS</td>
<td>EUS; CT§, EUS-FNA§, ERCP§</td>
<td>8/78 (10.3)¶,†</td>
</tr>
<tr>
<td>Poley 2009 (4) n=44</td>
<td>FPC, BRCA, PJS, p16, p53, HP</td>
<td>EUS; CT§, MRI§</td>
<td>10/44 (23)</td>
</tr>
<tr>
<td>Langer 2009 (5) n=76</td>
<td>FPC, BRCA</td>
<td>EUS + MRCP; EUS-FNA§</td>
<td>1/76 (1.3)¶,†</td>
</tr>
<tr>
<td>Vema 2010 (6) n=51</td>
<td>FPC, BRCA, p16</td>
<td>EUS and/or MRCP</td>
<td>6/51 (12)†</td>
</tr>
<tr>
<td>Ludwig 2011 n=109</td>
<td>FPC, BRCA</td>
<td>MRCP; EUS§, EUS-FNA§</td>
<td>9/109 (8.3)¶</td>
</tr>
<tr>
<td>Vasen 2011 (7) n=79</td>
<td>p16</td>
<td>MRI/MRCP</td>
<td>14/79† (18)</td>
</tr>
<tr>
<td>Al-Sukhni 2011 (8) n=262</td>
<td>FPC, BRCA, PJS, p16, HP</td>
<td>MRI; CT§, EUS§, ERCP§</td>
<td>19/262¶ (7.3)</td>
</tr>
<tr>
<td>Schneider 2011 (9)** n=72</td>
<td>FPC, BRCA, PALB2</td>
<td>EUS + MRCP</td>
<td>11/72 (15)¶</td>
</tr>
<tr>
<td>Canto 2012 (10) n=216</td>
<td>FPC, BRCA, PJS</td>
<td>CT, MRI/MRCP; EUS; ERCP§</td>
<td>5/216 (2.3)† – 92/216 (43)</td>
</tr>
</tbody>
</table>
Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals

Multi-centre prospective (largest) study

216 high-risk individuals

Visualization of detectable lesions:
- CT 13.8 %
- MR/MRCP 77 %
- EUS 79 %

NS
Screening: when to start

Fourth International Symposium of Inherited Diseases of the Pancreas (Gut 2007) included investigators from both University of Washington and John Hopkins

- Familial Pancreatic Cancer
  - at 40-45 years (mean age onset 60 years), or
  - 10-15 years younger than youngest affected FDR

- Peutz-Jegher’s syndrome
  - at 30 years

- Smoker
  - 10 years earlier
Fourth International Symposium of Inherited Diseases of the Pancreas (Gut 2007) included investigators from both University of Washington and John Hopkins

- Annual screening in high risk individuals seems reasonable
- Screening programs should be centralised in specialized centres and linked with genetic services
Prospective cohort studies (>20 patients)
Asymptomatic adults at > 5% lifetime risk including genetic associated conditions (CAPS Consortium)
19 studies with 7085 individuals
Primary outcome ‘high risk pancreatic lesions’
Summary estimates - incidence rates per 100 pt-years
1660 (23%) had EUS ± MRI
257 (15%) underwent pancreatic surgery
59 (23%) had ‘high risk’ lesions
   - 43 adenocarcinomas; 28 primary, 15 secondary
Detection rate: 0.74/100 patient years (1:135)
The Auckland approach

- Patients at increased risk are referred to Regional Genetic Services or clinicians
- Formal pedigree analysis and genetic testing discussed/done by Regional Genetic services
- Referred to Pancreas Clinic for discussion about screening. Was MR/MRCP then EUS, now prefer EUS first (in experienced hands)
- Starting age as discussed, annual interval, until too frail for pancreatic resection, smoking cessation
The future

- Better evidence needed for improved survival in screen positive high risk individuals
- Natural history of precursor lesions better defined
- Frequency of screening to be tailored
- Optimisation of screening protocols, including FNA
- Discovery of biomarkers, especially in pancreatic fluid, through proteomic analysis/bioinformatics
- Major gene defects in FPC/HPC to be elucidated
- Genetic testing better defined
- Role for chemoprevention developed
Thank-you.
Pancreatic cysts
Managing the ‘at risk’ individual

- Medical history and examination to detect PC
- Careful pedigree analysis over 3 generations looking for inherited predisposing conditions and to define relative risk of pancreatic cancer
- Smoking cessation program
- Genetic counseling regarding risks and benefits of screening, gene testing of relatives, storage of serum for later testing, and other issues
- Screen if indicated
- Consider submission to Registry
CONCLUSIONS

- FPC is an established, heterogeneous and poorly defined hereditary tumour entity
- Major gene defect(s) remains unknown
- FPC (like sporadic cancer) usually diagnosed with symptomatic and advanced disease
- High risk individuals can be identified by pedigree analysis (but no agreed definition)
PancPRO: Risk Assessment for Individuals With a Family History of Pancreatic Cancer

Wenyi Wang, Sining Chen, Kieran A. Brune, Ralph H. Hruban, Giovanni Parmigiani, and Alison P. Klein

- Mendallian risk prediction tool for pancreatic cancer
- Uses full pedigree data (those affected and those not affected) + age of family members + knowledge of genetic transmission
- Successfully validated against prospective (incident) data from large National Family Pancreatic Tumor Registry (NFPTR) at John Hopkins
Uses family history to

- Estimate probability that an individual carries a pancreatic cancer susceptibility gene
- Estimate probability that asymptomatic individual will develop pancreatic cancer for specified age interval
- Discriminate between high risk and low risk individuals when they have same number of affected family members
Figure 3.2: Age-standardised five year relative survival rate, by sex, pancreatic cancer, England and Wales 1971-2006

% survival

Period of diagnosis


* England only
Screening modalities

- **Tumour markers** (CEA, Ca19-9)
  - inadequate sensitivity for screening
- **CT / MR / US**
  - inadequate resolution to detect pancreatic dysplasia
- **ERCP**
  - too invasive for primary screening?
- **EUS**
  - most promising screening tool
Diagnostic Yield From Screening Asymptomatic Individuals at High Risk for Pancreatic Cancer: A Meta-analysis of Cohort Studies

Juan E. Corral,† Karl F. Mareth,† Douglas L. Riegert-Johnson,† Ananya Das,‡ and Michael B. Wallace†

Findings
We estimate that screening 135 high-risk individuals can identify one case with adenocarcinoma or high-grade dysplasia. EUS and MRI identified similar number of high-risk pancreatic lesions. Diagnostic yield depends largely on patients’ genetic background.

Implications for patient care
Pancreatic cancer surveillance in high-risk individuals is comparable with other preventive services. Questions regarding harms of screening and surgery, and cost-effectiveness need to be answered before scale-up implementation.
Linkage analysis

- Aims to establish a linkage between genes
- Is a way of gene hunting and testing
- To find the rough position of disease gene relative to known genetic markers
- It is a statistical estimate of whether the two gene loci lie near each other on a chromosome, and therefore if likely to be inherited together
Some questions ....

- What age and co-morbidity should exclude a person from primary screening?
- Is invasive ERCP justified as a primary screening tool?
- What degree of dysplasia warrants a pancreatectomy (PanIN1, 2, 3)?
- Can less than total pancreatectomy be justified for potentially multi-focal disease?
International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with familial pancreatic cancer

Marcia Irene Canto, Ferran Jan-Werner Polei, Ihab Irma Kluijft, Michael J L Marco Bruno, on behalf of the Pancreas Screening (CAPS) Consortium

Objective To develop consortium statements on screening, surveillance and management of high-risk individuals with an inherited predisposition to PC.

Methods A 49-expert multidisciplinary international consortium met to discuss pancreatic screening and vote on statements. Consensus was considered reached if ≥75% agreed or disagreed.

Results There was excellent agreement that, to be successful, a screening programme should detect and treat T1NOOMO margin-negative PC and high-grade dysplastic precursor lesions (pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm). It was agreed that the following were candidates for screening: first-degree relatives (FDRs) of patients with PC from a familial PC kindred with at least two affected FDRs; patients with Peutz–Jeghers syndrome; and p16, BRCA2 and hereditary non-polyposis colorectal cancer (HNPCC) mutation carriers with ≥1 affected FDR. Consensus was not reached for the age to initiate screening or stop surveillance. It was agreed that initial screening should include endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography not CT or endoscopic retrograde cholangiopancreatography. There was no consensus on the need for EUS fine-needle aspiration to evaluate cysts. There was disagreement on optimal screening modalities and intervals for follow-up imaging. When surgery is recommended it should be performed at a high-volume centre. There was great disagreement as to which screening abnormalities were of sufficient concern to for surgery to be recommended.

Conclusions Screening is recommended for high-risk individuals, but more evidence is needed, particularly for how to manage patients with detected lesions. Screening and subsequent management should take place at high-volume centres with multidisciplinary teams, preferably within research protocols.
Screening recommendations

Fourth International Symposium of Inherited Diseases of the Pancreas (Gut 2007)

- Included investigators from both University of Washington and John Hopkins Hospital

Anyone considered to have a risk of pancreatic cancer that is 10 fold greater than the general population
Screening recommendations

- Familial Pancreatic Cancer (unknown mutation)
  - 3 or more relatives (first, second or third degree) with pancreatic cancer, with at least one FDR
- Inherited cancer syndrome (known mutation)
  - BRCA2, p16 known mutations, and also BRCA1, MLH1, MSH2, MSH6, PMS2 (less data available)
- Peutz-Jeghers syndrome
- Hereditary pancreatitis
## Biomarker screening

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Biofluid</th>
<th>Marker</th>
<th>PDAC</th>
<th>Metastatic</th>
<th>Normal</th>
<th>CP</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koopman</td>
<td>2006</td>
<td>Serum</td>
<td>CA19-9 glycoprotein</td>
<td>50</td>
<td>0%</td>
<td>50</td>
<td>50</td>
<td>62%</td>
<td>80%</td>
</tr>
<tr>
<td>Gold</td>
<td>2006</td>
<td>Serum</td>
<td>MUC-1 glycoprotein</td>
<td>53</td>
<td>n.a.</td>
<td>43</td>
<td>90</td>
<td>77%</td>
<td>100%</td>
</tr>
<tr>
<td>Koopman</td>
<td>2006</td>
<td>Serum</td>
<td>MIC-1 protein</td>
<td>50</td>
<td>0%</td>
<td>50</td>
<td>50</td>
<td>90%</td>
<td>94%</td>
</tr>
<tr>
<td>Ishizone</td>
<td>2006</td>
<td>Serum</td>
<td>a4nT RNA</td>
<td>55</td>
<td>60%</td>
<td>70</td>
<td>10</td>
<td>76%</td>
<td>82%</td>
</tr>
<tr>
<td>Hoffmann</td>
<td>2007</td>
<td>Serum</td>
<td>CK-19 RNA</td>
<td>37</td>
<td>30%</td>
<td>16</td>
<td>20</td>
<td>65%</td>
<td>65%</td>
</tr>
<tr>
<td>Yamada</td>
<td>1998</td>
<td>Serum</td>
<td>Mutant k-ras DNA</td>
<td>21</td>
<td>62%</td>
<td>4</td>
<td>10</td>
<td>43%</td>
<td>100%</td>
</tr>
<tr>
<td>Wang</td>
<td>2009</td>
<td>Serum</td>
<td>microRNA Panel</td>
<td>19</td>
<td>43%</td>
<td>28</td>
<td>0</td>
<td>64%</td>
<td>89%</td>
</tr>
<tr>
<td>Koopman</td>
<td>2004</td>
<td>Serum</td>
<td>Seldi Proteomic Profile</td>
<td>60</td>
<td>n.a.</td>
<td>60</td>
<td>60</td>
<td>78%</td>
<td>97%</td>
</tr>
<tr>
<td>Bhattacharya</td>
<td>2004</td>
<td>Serum</td>
<td>Seldi Proteomic Profile</td>
<td>49</td>
<td>50%</td>
<td>54</td>
<td>0</td>
<td>100%</td>
<td>93%</td>
</tr>
<tr>
<td>Farrell</td>
<td>2010</td>
<td>Saliva</td>
<td>mRNA</td>
<td>30</td>
<td>0%</td>
<td>30</td>
<td>30</td>
<td>93%</td>
<td>100%</td>
</tr>
</tbody>
</table>
International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

Objective To develop consortium statements on screening, surveillance and management of high-risk individuals with an inherited predisposition to PC.

Methods A 49-expert multidisciplinary international consortium met to discuss pancreatic screening and vote on statements. Consensus was considered reached if ≥75% agreed or disagreed.

Results There was excellent agreement that, to be successful, a screening programme should detect and treat T1NOM0 margin-negative PC and high-grade dysplastic precursor lesions (pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm). It was agreed that the following were candidates for screening: first-degree relatives (FDRs) of patients with PC from a familial PC kindred with at least two affected FDRs; patients with Peutz–Jeghers syndrome; and p16, BRCA2 and hereditary non-polypsis colorectal cancer (HNPCC) mutation carriers with ≥1 affected FDR.

Consensus was not reached for the age to initiate screening or stop surveillance. It was agreed that initial screening should include endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography not CT or endoscopic retrograde cholangiopancreatography. There was no consensus on the need for EUS fine-needle aspiration to evaluate cysts. There was disagreement on optimal screening modalities and intervals for follow-up imaging. When surgery is recommended it should be performed at a high-volume centre. There was great disagreement as to which screening abnormalities were of sufficient concern to for surgery to be recommended.

Conclusions Screening is recommended for high-risk individuals, but more evidence is needed, particularly for how to manage patients with detected lesions. Screening and subsequent management should take place at high-volume centres with multidisciplinary teams, preferably within research protocols.
### Table 1  Summary of diagnostic yield of familial pancreatic cancer screening and surveillance programmes

<table>
<thead>
<tr>
<th>Study</th>
<th>High-risk group</th>
<th>Imaging tests</th>
<th>Diagnostic yield* n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentnall 1999 (1) n=14</td>
<td>FPC</td>
<td>EUS+ERCP+CT</td>
<td>7/14 (50)†</td>
</tr>
<tr>
<td>Kimmey 2002 n=46‡</td>
<td>FPC</td>
<td>EUS; ERCP§</td>
<td>12/46 (26)†</td>
</tr>
<tr>
<td>Canto 2004 (2) n=38</td>
<td>FPC, PJS</td>
<td>EUS; ERCP§, EUS-FNA§, CT§</td>
<td>2/38 (5.3)†</td>
</tr>
<tr>
<td>Canto 2006 (3) n=78</td>
<td>FPC, PJS</td>
<td>EUS; CT§, EUS-FNA§, ERCP§</td>
<td>8/78 (10.3)¶,†</td>
</tr>
<tr>
<td>Poley 2009 (4) n=44</td>
<td>FPC, BRCA, PJS, p16, p53, HP</td>
<td>EUS; CT§, MRI§</td>
<td>10/44 (23)</td>
</tr>
<tr>
<td>Langer 2009 (5) n=76</td>
<td>FPC, BRCA</td>
<td>EUS+MRCP; EUS-FNA§</td>
<td>1/76 (1.3)¶,†</td>
</tr>
<tr>
<td>Vema 2010 (6) n=51</td>
<td>FPC, BRCA, p16</td>
<td>EUS and/or MRCP</td>
<td>6/51 (12)‡</td>
</tr>
<tr>
<td>Ludwig 2011 n=109</td>
<td>FPC, BRCA</td>
<td>MRCP; EUS§, EUS-FNA§</td>
<td>9/109 (8.3)¶</td>
</tr>
<tr>
<td>Vasen 2011 (7) n=79</td>
<td>p16</td>
<td>MRI/MRCP</td>
<td>14/79† (18)</td>
</tr>
<tr>
<td>Al-Sukhni 2011 (8) n=262</td>
<td>FPC, BRCA, PJS, p16, HP</td>
<td>MRI; CT§, EUS§, ERCP§</td>
<td>19/262 (7.3)</td>
</tr>
<tr>
<td>Schneider 2011 (9)** n=72</td>
<td>FPC, BRCA, PALB2</td>
<td>EUS + MRCP</td>
<td>11/72 (15)¶</td>
</tr>
<tr>
<td>Canto 2012 (10) n=216</td>
<td>FPC, BRCA, PJS</td>
<td>CT, MRI/MRCP, EUS; ERCP§</td>
<td>5/216 (2.3)†−92/216 (43)</td>
</tr>
</tbody>
</table>

*Yield is defined as the detection of any pathologically proven (pre)malignant lesion (≥PanIN-2/IPMN and pancreatic adenocarcinoma) and lesions that are morphologically suspicious for branch-duct IPMNs.
†Includes only pathologically proven pancreatic neoplasms (histology or cytology).
‡Continuation of Brentnall 1999, included 14 high-risk individuals from Brentnall 1999.
§Test performed only as an additional test for detected abnormalities.
¶Includes baseline and follow-up.
**Continuation of Langer 2009, includes high-risk individuals from this series.
ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasm; MRCP, magnetic resonance cholangiopancreatography; PJS, Peutz−Jeghers syndrome; PanIN, pancreatic intraepithelial neoplasia.
Perspective

Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States

Lola Rahib¹, Benjamin D. Smith², Rhonda Aizenberg¹, Allison B. Rosenzweig¹, Julie M. Fleshman¹, and Lynn M. Matrisian¹

Abstract

Cancer incidence and deaths in the United States were projected for the most common cancer types for the years 2020 and 2030 based on changing demographics and the average annual percentage changes in incidence and death rates. Breast, prostate, and lung cancers will remain the top cancer diagnoses throughout this time, but thyroid cancer will replace colorectal cancer as the fourth leading cancer diagnosis by 2030, and melanoma and uterine cancer will become the fifth and sixth most common cancers, respectively. Lung cancer is projected to remain the top cancer killer throughout this time period. However, pancreas and liver cancers are projected to surpass breast, prostate, and colorectal cancers to become the second and third leading causes of cancer-related death by 2030, respectively. Advances in screening, prevention, and treatment can change cancer incidence and/or death rates, but it will require a concerted effort by the research and healthcare communities now to effect a substantial change for the future. Cancer Res; 74(11); 2913–21. ©2014 AACR.
Screening: EUS + ERCP

- 35 members of 13 FPC families
- EUS + ERCP: 12 / 35 had abnormal findings
- Prophylactic (partial) pancreatectomy
- Histology:
  - 0 / 12 had pancreatic cancer
  - 12 / 12 had dysplasia (mostly PanIN2)

Rulyak and Brentnall. Pancreatology 2001
Screening: EUS

- Screening EUS
- If abnormal then EUS-FNA, ERCP and CT scan
- High risk asymptomatic individuals (n = 38)
  - 31 with ≥ 3 FDR’s with PC
  - 6 with 2 FDR’s with PC
  - 1 with Peutz-Jeghers syndrome

*Canto et al. Clin Gastroenter & Hepatology 2004*
Screening: EUS

- Findings - 6 masses
  - 1 invasive ductal adenocarcinoma
  - 1 benign IPMN
  - 2 serous cystadenoma
  - 2 non neoplastic masses
- Diagnostic yield of clinically significant pancreatic neoplasia is 5.3% (2 / 38) or 1 : 20
- Incidental symptomatic GI findings in 18.4 %

*Canto et al. Clin Gastroent & Hepatology 2004*
EUS screening - guidelines

- Screening should not be done unless pancreatectomy would be considered for dysplasia / early cancer
- Less useful if concurrent chronic pancreatitis or significant ETOH history
- Initiate at 50 years or 10 years before the earliest onset of family member or smoker
- Annual surveillance is reasonable
- Best done in consultation with expert centre
EUS based screening of FPC kindreds is cost-effective, although the benefit appears to be limited to populations with a pre-test probability of pancreatic dysplasia of 16 % or greater.

Rulyak et al. Gastrointestinal Endoscopy 2003
- KEY ARTICLE - PROBABLY ALL I NEED
  - Corral et al SR and MA in Clin Gastro Hepat

- Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer
  - Celeste A. Shelton, Chandraprakash Umapathy, Kimberly Stello, Dhiraj Yadav & David C. Whitcomb
  - The American Journal of Gastroenterology 2018 113 :1376 - 1384; July 18, 2018; 10.1038/s41395-018-0194-5

- See Shelton et al (Whitcomb) Am J Gastro September 2018 113:1385-

- VERY IMPORTANT PUBLICATION - EUS CAN DETECT
Precursor lesions

- Normal duct
- PanIN Ia
- PanIN Ib
- PanIN II
- PanIN III
- MCN low grade
- Intermediate grade
- High grade
- IPMN low grade
- Cancer
Advances in screening, prevention and treatment can change cancer incidence and/or death rates, but it will require a concerted effort to effect a substantial change for the future.
Risk factors and relative risk for developing pancreatic cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial pancreatic cancer:</td>
<td></td>
</tr>
<tr>
<td>2 first-degree relatives affected</td>
<td>18</td>
</tr>
<tr>
<td>3 first-degree relatives affected</td>
<td>57</td>
</tr>
<tr>
<td>Hereditary pancreatic cancer syndromes:</td>
<td></td>
</tr>
<tr>
<td>BRCA2 mutation</td>
<td>5.9</td>
</tr>
<tr>
<td>Familial atypical multiple mole melanoma</td>
<td>16</td>
</tr>
<tr>
<td>Peutz-Jeghers Syndrome</td>
<td>36</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>50</td>
</tr>
<tr>
<td>Cigarette smoking:</td>
<td></td>
</tr>
<tr>
<td>Positive family history of pancreatic cancer</td>
<td>3.7</td>
</tr>
<tr>
<td>Diabetes &gt; 20 years</td>
<td>2</td>
</tr>
</tbody>
</table>
Algorithm for managing patients at risk of hereditary pancreatic cancer

Review Article

Hereditary Pancreatic and Hepatobiliary Cancers

Ashraf Haddad,1 Gopal C. Kowdle,1 Timothy M. Pawlik,2 and Steven C. Cunningham1

1 Department of Surgery, Saint Agnes Hospital, Baltimore, MD 21229, USA
2 Department of Surgery, The Johns Hopkins Hospital, Baltimore, MD 21231, USA
≥10x risk, ≥10 years earlier than earliest affected relative
≥10× risk, ≥10 years earlier than earliest affected relative

Pancreas-protocol CT or MRI/MRCP
CEA, Ca19-9, liver and pancreas labs, genetic testing?
≥10x risk, ≥10 years earlier than earliest affected relative

Pancreas-protocol CT or MRI/MRCP
CEA, Ca19-9, liver and pancreas labs, genetic testing?

Recent alcohol
Abstain ≥1 month

No recent alcohol
EUS

Haddad et al. 2011
≥10x risk, ≥10 years earlier than earliest affected relative

Pancreas-protocol CT or MRI/MRCP
CEA, Ca19-9, liver and pancreas labs, genetic testing?

Recent alcohol

- Abstain ≥1 month
- Normal

No recent alcohol

- EUS
- Abnormal

Haddad et al. 2011
≥10x risk, ≥10 years earlier than earliest affected relative

Pancreas-protocol CT or MRI/MRCP
CEA, Ca19-9, liver and pancreas labs, genetic testing?

Recent alcohol
- Abstain ≥1 month
  - Normal
    - Repeat EUS 1–3 y
  - Abnormal
    - ERCP

No recent alcohol
- EUS
  - Normal
  - Abnormal
≥10x risk, ≥10 years earlier than earliest affected relative

Pancreas-protocol CT or MRI/MRCP
CEA, Ca19-9, liver and pancreas labs, genetic testing?

Recent alcohol
- Abstain ≥1 month
  - Normal
    - Repeat EUS 1–3 y
  - Abnormal
    - ERCP
      - Normal
      - Abnormal
        - Consider resection

No recent alcohol
- EUS
  - Normal
  - Abnormal
Prophylactic pancreatectomy cannot be recommended in asymptomatic high-risk individuals without evidence of dysplastic pancreatic lesions, given the significant morbidity of the procedure and the unknown penetrance in the different settings of hereditary pancreatic cancer.

Rieder and Bartsch. Review. Familial Cancer 2004
Two surgical approaches have been proposed

- Radical: total pancreatectomy, for multi-centric dysplastic precancerous lesions

- Conservative: partial pancreatectomy ± completion depending on histology
Genetic testing

- Genetic counselling is of key importance in managing individuals with an inherited predisposition
- Genetic testing may be associated with significant consequences/risks – psychological, social, employment and insurance coverage
- In selected individuals in early adulthood
- In all those with inherited cancer syndromes
- Should be done by genetic service to manage the recognised risks of genetic testing
Genetic testing

- Familial cancer syndromes - yes
- Hereditary pancreatitis - yes
- Cystic fibrosis - yes
- Familial pancreatic cancer - no

“Because of the current limitations in our knowledge about FPC, testing outside of controlled studies should be avoided”

Rieder and Bartsch
Familial Cancer 2004
CONCLUSIONS

- Genetic counselling imperative to discuss gene testing, storage of serum, screening
- No established protocol for gene testing
- No established screening method for high risk individuals (EUS, then EUS-FNA, CT and ERCP)
- Prevention
  - Stop smoking
  - Chemoprevention - the future?
Early detection, improved survival?

Hypothesis
Undergoing EUS associated with improved survival, probably related to early detection of pancreatic cancer, accurate preoperative staging, and improved stage appropriate treatment.

Study
SEER – Medicare linked database (Jan 1994 - Dec 2002)

Results
4,236 patients - EUS (12 %), no EUS (88 %)
Average overall survival – EUS (9/12), no EUS (5/12)

Ngamruengphong, GIE 2010
During our appointment recently, I discussed the fact that pancreatic cancer is associated with 25% of pancreatic cancer and that diabetes is also a risk for developing cancer. After confirming the family history of pancreatic cancer, I discussed this with Susan Parry. She confirmed that no pancreatic genetic testing is currently present and advised that I discuss with you advice for surveillance for your close relatives. I have stored DNA from Colin should pancreas cancer become available in the future.

I appreciate your advice regarding this family

Yours sincerely

Jenny Warrington (MSc)
Genetic Associate
Komudi Siriwardena
Clinical Geneticist
NORTHERN REGIONAL GENETIC SERVICE
Important

- Presents opportunity for early detection by screening higher risk individuals, and therefore increase likelihood of curative treatment
- Study of the high risk families will enable better understanding of pancreatic carcinogenesis and will enable discovery of improved biomarkers and new gene mutations
- Reminder of the importance of family history
Researchers are fervently searching for new, improved technologies that could either detect pancreatic cancer earlier or treat it once it's detected. Endoscopic ultrasound (EUS) is an expensive treatment, but shows great promise in helping to improve patient outcomes after a diagnosis with pancreatic cancer. Researchers for this study sought to learn about the association between EUS performance and pancreatic cancer survival. To achieve this, investigators reviewed the SEER-Medicare database of patients receiving treatment between January 1994 and December 2002. In all, the records of 4,236 patients with pancreatic cancer were assessed, and broken into two groups - those who received EUS (only 12 percent of the sample) and those who did not (88 percent).

Researchers found that after they controlled for age, race, gender and comorbidities, those who did receive EUS at the time of diagnosis had a longer average survival time (nine months) than those who did not receive EUS (five months).
Early involvement of genetic service for those considered at increased risk of pancreatic cancer
Recognizing those who have an increased risk of pancreatic cancer

Develop a practical approach to screening of these higher risk cases

Involve Genetic Service for pedigree analysis

This is a pragmatic talk, not from someone with a research program, these experts are in the audience and their views will no doubt be helpful
During our appointment today I was informed that about 25% of pancreatic cancer and that diabetes is also a risk for confirming the family history of pancreatic cancer. I discussed with Susan Parry. She confirmed that no pancreatic genetic testing is present and advised that I discuss with you advice for surveillance of degree relatives. I have stored DNA from Colin should pancreatic cancer become available in the future.

I appreciate your advice regarding this family.

Yours sincerely

Jenny Warrington (MSc)
Genetic Associate
Komudi Siriwardena
Clinical Geneticist
NORTHERN REGIONAL GENETIC SERVICE
NHI #: NJG0678
Our reference number: A18731

Mr John Windsor
Consultant
General Surgery
AUCKLAND CITY HOSPITAL

Dear Mr Windsor

Re: Michael [REDACTED] – d.o.b. 30.07.64

I would appreciate your advice regarding screening recommendations for the following family. I met a family at Genetic Services who reported a strong family history of pancreatic cancer. Out of five siblings, the oldest, Jack is still living at 85 years of age, his brother, William is still living at 82 years of age, a sister, Ruth was diagnosed with pancreatic cancer at aged 54 years and died at age 55 years (she was reported to have smoked for approximately 15 years). The other sister, Marie has a confirmed head of pancreas cancer diagnosed at age 77 years (she was reported to have smoked for 10 years) and Colin was diagnosed with pancreatic cancer at age 72 years and he smoked for approximately 50 years. The family were wanting to discuss their risk of pancreatic cancer.
Figure 3.2: Age-standardised five year relative survival rate, by sex, pancreatic cancer, England and Wales 1971-2006
I would appreciate your advice regarding screening recommendations for the following family. I met a family at Genetic Services who reported a strong family history of pancreatic cancer. Out of five siblings, the oldest, Jack is still living at 85 years of age, his brother, William is still living at 82 years of age, a sister, Ruth was diagnosed with pancreatic cancer at aged 54 years and died at age 55 years (she was reported to have smoked for approximately 15 years). The other sister, Marie has a confirmed head of pancreas cancer diagnosed at age 77 years (she was reported to have smoked for 10 years) and Colin was diagnosed with pancreatic cancer at age 72 years and he smoked for approximately 50 years. The family were wanting to discuss their risk of pancreatic cancer.
Principles of screening program

**Principles**
- Reasonable yield is expected
- The most sensitive/specific screening tool is used
- Screening is voluntary
- Results are appropriately interpreted
- Supportive care is offered
- Screening improves survival
- Benefits of screening outweigh risks
Screening

- **RATIONALE**
  Improved survival by detection of early pancreatic cancer

- **JUSTIFICATION**
  Long term survival is possible for very small favourable cases (usually fortuitously diagnosed)

 59% 5YS for <2cm and node negative PC

  *Furukawa et al Cancer 1966*
Evidence for Screening

- Early lesions can be detected and treated
- Recommendations regarding screening and surveillance are still in evolution
- Brentnall (see old presentation and p5 G&S)
- Canto
- The yield from screening has not been uniformly high.
IPMN and MCN
Genetic defect undefined, although an autosomal dominant inheritance with variable penetrance is suggested from segregation analysis

Smoking
Risk factors for pancreatic cancer

- Positive family history
- Hereditary pancreatic cancer syndromes
- Cigarette smoking
- Long standing diabetes
five-year survival rates

- Lung: 6%
- Colon: 50%
- Breast: 5.1%
- Pancreas: 100%
- Prostate: (Bar not labeled)
Endoscopic pancreatoscopy
NB: Evidence that current approaches to early detection prolongs survival is not strong.
<table>
<thead>
<tr>
<th>STAGE</th>
<th>5 YS</th>
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<tbody>
<tr>
<td>Ia</td>
<td>14 %</td>
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<tr>
<td>Ib</td>
<td>12 %</td>
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<td>IIa</td>
<td>7 %</td>
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<td>5 %</td>
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<td>III</td>
<td>3 %</td>
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<td>IV</td>
<td>1 %</td>
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