Biomarkers in Pancreatic Cancer

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Biomarker
What it is – what it can be

Diagnostic
Prognostic
Predictive
Biomarker role in diagnosis

**Clinical information**

**Enzymes activity**
- e.g. beta-glucocerebrosidase

**Proteins**
- e.g. Troponin I

**Nucleic acids**
- e.g. RNA, DNA

**Metabolites**
- e.g. sphingolipids

**Genetic variants**
Changing the Way We Do Business: Recommendations to Accelerate Biomarker Development in Pancreatic Cancer

Margaret A. Tempero¹, David Klimstra³, Jordan Berlin⁴, Tony Hollingsworth⁷, Paula Kim⁵, Nipun Merchant⁶, Malcolm Moore⁸, Doug Pleskow⁹, Andrea Wang-Gillam¹⁰, and Andrew M. Lowy²

• Position statement of ASCO
Points of discussion – OPEN questions

- Defining the real “window of opportunity” for PC screening
- Understanding the catastrophic progression of PC
- Evaluating screening protocols for biomarkers for early detection of pancreatic cancer and its precursors
- Listing and prioritizing biomarkers, upon the availability of evidences, for their validation in well-characterized common resources
- Estimating cost/efficient screening interventions in high-risk populations
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Figure 1  “Early” pancreatic cancer—definitions.
Window of opportunity

Carcinoma in situ | Minute | Small | Locally unresectable

Histology
- Normal
- Normal or Dilated duct
- Small mass
- Mass + vascular invasion

Imaging
- Normal
- Dilated duct
- Normal
- Or Liver metastases

Symptoms
- No
- No
- May be
- Yes

Radiologic Window-of-opportunity to Diagnose Resectable Pancreatic Cancer
Is early detection possible?
Defining the window of opportunity for PC screening

- Incipient, intraductal, in situ neoplasia
  → BEFORE
  - Onset of symptoms
  - Radiological evidence

- In
  → Individuals at risk (IAR(FPC))
  - Regardless of lesion

- Sporadic IPMN
  - Main duct
Defining the window of opportunity for PC screening

- Biomarkers for incipient neoplasia may NOT be present in later stages of overt (radiologically positive) disease
Early marker ≠ late marker

- Early marker
  - Host response
    - Immunological
    - Metabolom/microbiom

- Late marker
  - Tumor product
    - CA 19-9, MUC
Metabonomic intraepithelial adenocarcinoma of biomarkers of pancreatic cancer

Xianchao Lin, Bohan ZL, Jianghua Feng

Fig. 3 Two-dimensional PCA (A) and PLS-DA (B) score plots based on the $^1$H NMR spectra of serum samples from control, PanIN and PDAC rats.
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Understanding the catastrophic progression of PC

- NO specific early signs
- NO screening
- NO biomarker
  - \( \rightarrow \) LATE diagnosis
  - \( \rightarrow \) SYSTEMIC disease
- LOW resection rate
- LOW R0 group
  - \( \rightarrow \) LOW surgical eradication
- LOW response to chemotherapy
- LOW response to targeted therapy
- LOW/NO response to radiation therapy
  - \( \rightarrow \) Rapid progress, SHORT survival time
The long way to diagnosis

Fig. 1. Model for pancreatic cancer development and biomarkers status.
Pancreatic cancer = Medical emergency

We MUST do something about it!

“The greatest oncological challenge” results partly from delays to diagnosis and treatment, writes J-Matthias Löhr

Figure 1. Recorded (2001–2010) and projected (up to 2025) number of breast and pancreatic cancer deaths (both males and females) in the EU.
Understanding the catastrophic progression of PC

- There is NO lack of understanding …

Hidalgo, Löhr et al., Panreatology 2015, 15: 8-18
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Screening protocols for biomarkers for early detection

- TWO questions
  - WHO – patient group
  - WHAT marker(s)

  - WHEN
  - HOW
WHOM to screen?

DEF Screening Model for Sporadic Pancreatic Cancer

**General Population**

- **First Sieve**
  - **DEFINE:** at risk population
  - High Risk Group

- **Second Sieve**
  - **ENRICH:** at risk cohort
  - Phenotype, Serologic Biomarker, Non-Invasive Imaging

- **FIND:** “early” lesion
  - Localize “Early” Lesion

**FIGURE 2.** Define, enrich, and find approach to screening for sporadic PDAC (Chari, 2014).
WHOM to screen?

Box 1
High-risk individuals for pancreatic cancer screening

- Individuals with 3 or more affected blood relatives with PC, including at least 2 related by first degree (familial PC), with at least one of the affected related to the at-risk relative by first degree (parent, sibling, child)
- Individuals with at least 2 affected FDRs with PC
- All patients with Peutz–Jeghers syndrome should be screened, regardless of family history of PC
- p16 (CDKN2A) gene mutation carriers with 1 affected FDR
- BRCA2 gene mutation carriers with 1 affected FDR
- BRCA2 gene mutation carriers with 2 affected family members (no FDR) with PC
- PALB2 gene mutation carriers with 1 affected FDR
- ATM gene mutation carriers
- Mismatch repair gene mutation carriers (Lynch syndrome) with 1 affected FDR

### WHOM to screen?

#### Table 1
Inherited cancer syndromes associated with increased risk of pancreatic cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Locus</th>
<th>Lifetime Risk of PC, Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast/ovarian cancer</td>
<td>BRCA2, BRCA1</td>
<td>13q</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>PALB2</td>
<td>16p</td>
<td>Unknown</td>
</tr>
<tr>
<td>Familial atypical multiple mole melanoma syndrome</td>
<td>CDKN2A</td>
<td>9p</td>
<td>10–19</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK 11</td>
<td>19p</td>
<td>11–36</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>5q</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch II)</td>
<td>DNA mismatch repair genes</td>
<td>2p, 3p, 7p</td>
<td>4</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1, SPINK1</td>
<td>7q, 5q</td>
<td>25–40</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>11q</td>
<td>Unknown</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>P53</td>
<td>17p</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Individuals at risk in FPC

Table 1. Characteristics of Patients With Positive Findings on Screening

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y/Sex</th>
<th>Total Affected</th>
<th>First Degree</th>
<th>Second Degree</th>
<th>Genetic Mutation</th>
<th>Time to First Detection, mo</th>
<th>Diagnosis at First Detection</th>
<th>Cyst Size at First Detection, mm</th>
<th>Pancreatic Duct Size at First Detection, mm</th>
<th>Progression Under Follow-up (Yes/No)</th>
<th>Type of Progression</th>
<th>Surgery (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPC 1/54/F</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>p16</td>
<td>0</td>
<td>BD-IPMN</td>
<td>5</td>
<td>Normal</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>FPC 2/75/M</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>5</td>
<td>Normal</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>FPC 3/48/F</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>0</td>
<td>Mixed-type IPMN</td>
<td>8</td>
<td>5</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>FPC 4/47/M</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>MD-IPMN</td>
<td>5</td>
<td>Normal</td>
<td>Yes</td>
<td>Increased cyst size (15 mm)</td>
<td>No</td>
</tr>
<tr>
<td>FPC 5/62/F</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>10</td>
<td>Normal</td>
<td>Yes</td>
<td>Mixed-type IPMN + PDAC</td>
<td>Yes</td>
</tr>
<tr>
<td>FPC 6/49/M</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>10</td>
<td>Normal</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>FPC 7/61/M</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>9</td>
<td>Normal</td>
<td>Yes</td>
<td>Increased cyst size (12 mm)</td>
<td>No</td>
</tr>
<tr>
<td>FPC 8/49/F</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>0</td>
<td>MD-IPMN</td>
<td>5</td>
<td>Normal</td>
<td>No</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of the Patients Who Underwent Surgery During the Surveillance Program

<table>
<thead>
<tr>
<th>Patient</th>
<th>Operation Performed</th>
<th>IPMN</th>
<th>IPMN Grade of Dysplasia</th>
<th>PDAC (Yes/No)</th>
<th>PDAC Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPC 5</td>
<td>Total pancreatectomy</td>
<td>Mixed type</td>
<td>High</td>
<td>Yes</td>
<td>T3N0M0</td>
</tr>
<tr>
<td>FPC 11</td>
<td>Distal pancreatectomy</td>
<td>Mixed type</td>
<td>Intermediate</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>FPC 13</td>
<td>Pancreatoduodenectomy</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>FPC 15</td>
<td>Total pancreatectomy</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
<td>T4N1M0</td>
</tr>
<tr>
<td>FPC 16</td>
<td>3 Enucleations</td>
<td>Branch duct IPMN</td>
<td>Intermediate</td>
<td>No</td>
<td>NA</td>
</tr>
</tbody>
</table>

Original Investigation

Short-term Results of a Imaging-Based Swedish for Individuals at Risk for

Marco Del Chiario, MD, PhD; Caroline S. Verbeke, MD, PhD; N Peter Gustafsson, MD, PhD; Johan Hansson, MD, PhD; Steopl Åke Andren-Sandberg, MD, PhD; J.-Matthias Löh, MD, PhD

Figure 3. Patient Undergoing Multiple Enucleations for Branch Duct Intraductal Papillary Mucinous Neoplasia
WHOM to screen?

<table>
<thead>
<tr>
<th>Years</th>
<th>IPMN Risk (%)</th>
<th>PDAC Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>16.7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>31.4</td>
<td>6.2</td>
</tr>
<tr>
<td>4</td>
<td>64.8</td>
<td>6.2</td>
</tr>
<tr>
<td>5</td>
<td>88.3</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Del Chiaro, Löh, unpublished
WHOM to screen?

Risk of progression in IPMNs

<table>
<thead>
<tr>
<th>Years</th>
<th>IPMN Sporadic (%)</th>
<th>IPMNs Familial (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>27.5</td>
<td>16.7</td>
</tr>
<tr>
<td>3</td>
<td>42.5</td>
<td>31.4</td>
</tr>
<tr>
<td>4</td>
<td>50.7</td>
<td>64.8</td>
</tr>
<tr>
<td>5</td>
<td>67.9</td>
<td>88.3</td>
</tr>
</tbody>
</table>

p=NS

# 307  # 24
WHAT to screen

- Pending confirmation in
  - Prospective studies
  - IAR/FPC cohorts
  - IPMN cohorts
Table 2. Biomarker panel performance in the TexGen cohort

<table>
<thead>
<tr>
<th>Assay</th>
<th>Stage I/IIA (n = 30) vs controls (n = 30)</th>
<th>Stage IIB (n = 22) vs controls (n = 30)</th>
<th>Stage II (n = 57) vs controls (n = 30)</th>
<th>All early-stage (n = 85) vs controls (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (95% CI)</td>
<td>P*</td>
<td>AUC (95% CI)</td>
<td>P*</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>0.72 (0.57 to 0.86)</td>
<td>1.00</td>
<td>0.87 (0.76 to 0.96)</td>
<td>1.00</td>
</tr>
<tr>
<td>TFPI</td>
<td>0.71 (0.57 to 0.84)</td>
<td>.91</td>
<td>0.91 (0.81 to 0.98)</td>
<td>.58</td>
</tr>
<tr>
<td>TNC-FN III-C</td>
<td>0.54 (0.39 to 0.69)</td>
<td>.08</td>
<td>0.87 (0.77 to 0.95)</td>
<td>.97</td>
</tr>
<tr>
<td>TNC-FN III-C, CA 19-9</td>
<td>0.82 (0.71 to 0.92)</td>
<td>.27</td>
<td>0.95 (0.89 to 0.99)</td>
<td>.14</td>
</tr>
<tr>
<td>TFPI, CA 19-9</td>
<td>0.82 (0.70 to 0.91)</td>
<td>.29</td>
<td>0.98 (0.93 to 1.00)</td>
<td>.06</td>
</tr>
<tr>
<td>TNC FN III-C, TFPI, CA19-9</td>
<td>0.84 (0.74 to 0.93)</td>
<td>.17</td>
<td>0.98 (0.95 to 1.00)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*P values were two-sided and calculated based on bootstrapping. AUC = area under the curve; CI = confidence interval.
Discrimination of pancreatic cancer and pancreatitis metabolomics

Anna Lindahl² · Rainer Heuchel³ · Jenny Forsheid² · Janne Lehtio² · Matthias Lohr³
Anders Nordström¹,²,³

Table 1 Clinical data

<table>
<thead>
<tr>
<th></th>
<th>Discovery cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PDAC</td>
<td>CP</td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>21/20¹</td>
<td>18/5</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>67 (30–102)²</td>
<td>36 (31–93)</td>
</tr>
</tbody>
</table>

Diagram:

- Hexanoyl carnitine
- N-palmitoyl glutamic acid
- Glycocholic acid
WHAT to screen

Biology of Human Tumors

Identification of a Three-Biomarker Par for Early Detection of Pancreatic Adeno

### What to screen?

- Will need some kind of liquid biopsy (ct-DNA; CTC)

### Table 1. Genes targeted (mutated) in the most common precursor and cystic lesions in the pancreas

<table>
<thead>
<tr>
<th>Gene</th>
<th>IPMN-LG</th>
<th>IPMN-HG</th>
<th>MCN-LG</th>
<th>MCN-HG</th>
<th>PanIN-1 and -2</th>
<th>PanIN-3</th>
<th>SCA</th>
<th>SPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>P16/CDKN2A</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>TP53</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>RNF43</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>GNAS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTNNB1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>VHL</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Abbreviations: HG, high grade; LG, low grade.*
Applications of liquid biopsy

Early detection and monitoring

Brain tumor DNA blocked by blood-brain barrier

Breast cancer
Pancreatic cancer
Colon cancer

Many tumors release DNA fragments that circulate in the bloodstream

Detection of resistance mutations

Targeted therapy
Response to therapy
Selective pressure
Resistance mutation #1
Resistance mutation #2

Analysis of ctDNA

ctDNA of resistance mutations collected in blood sample

Fig. 1. Potential applications of ctDNA.
Detection of Circulating Pancreas Epithelial Cells in Patients With Pancreatic Cystic Lesions

Andrew D. Rhim,1,2,3 Fredrik I. Thege,4 Steven M. Santana,5 Timothy B. Lannin,5 Trisha N. Saha,1,2 Shannon Tsai,2,3 Lara R. Maggs,2,3 Michael L. Kochman,2,3,8 Gregory G. Ginsberg,2,3,8 John G. Lieb,2,3 Vinay Chandrasekhara,2,3 Jeffrey A. Drebin,3,6 Nuzhat Ahmad,2 Yu–Xiao Yang,2 Brian J. Kirby,5,7 and Ben Z. Stanger2,3,8
A CANcer Development mOnitor “CanDo”

www.fp7cando.eu

4M€, 2014-2017

10 partners

Contact: Prof. Andres Cantarero (Andres.Cantarero@uv.es)
The how-to in PDAC biomarkers

Figure 1. Pancreatic cancer biomarker development, including the challenges, possible cohorts of samples, sample types that have been used in biomarker discovery, the confounding factors that have to be taken into account and some of the marker types that have been documented.

CP: Chronic pancreatitis; FPC: Familial pancreatic cancer; HP: Hereditary pancreatitis; PDAC: Pancreatic ductal adenocarcinoma.
Where to go?

- The EU can help!
How long does it take?

- Time frame > 10 years!

EMERGING OPPORTUNITIES FOR SCIENTIFIC ADVANCEMENT

Progress has been achieved in each of the 4 components of the Strategic Map for Innovation during the past year. Current priorities focus on identifying emerging opportunities for scientific advancement that hold the greatest promise for the future of early detection in PDAC. A roadmap of action items for the next 10 years includes:

1. Identifying existing and novel biomarkers of early PDAC:
   - Timeline: 1 to 10 years
2. Validating promising existing and new biomarkers in retrospective samples:
   - Timeline: 1 to 3 years
3. Assembling a prospective high-risk cohort for sporadic PDAC:
   - Timeline: 1 to 10 years
4. Initiating a prospective screening study:
   - Timeline: 1 to 10 years
Screening protocols for biomarkers for early detection

Prioritize
- Germline sequencing
- Pancreatic cysts
- Other risk factors

Detect
- Pancreatic imaging
- Cyst aspiration
- Pancreatic juice

Distinguish
- Low-grade dysplasia
- High-grade dysplasia
- Early invasive cancer

Intervene
- Surgery for suspicious lesions
- Surveillance for other lesions
- Surveillance when possible

Cancer Research Reviews

Lennon et al., Cancer Res 2014, 74: 3381-3389
Another myth in early biomarker business

Hits during screening may be random

Points of discussion – OPEN questions

- Defining the real “window of opportunity” for PC screening
- Understanding the catastrophic progression of PC
- Evaluating screening protocols for biomarkers for early detection of pancreatic cancer and its precursors
- Listing and prioritizing biomarkers, upon the availability of evidences, for their validation in well-characterized common resources
- Estimating cost/efficient screening interventions in high-risk populations
Screening protocols for biomarkers for early detection

- TWO questions
  - WHO – patient group
  - WHAT marker(s)

- WHEN
- HOW
96% accuracy for Pancreatic cancer stage I and II

Training set 666 controls, 111 Stage I+II
Test set 222 controls, 37 Stage I+II
3. IMMray™ PanCan-d Pancreatic Cancer Test status

**CLINICAL USE 1**
- HEREDITARY
  - High risk groups
    - Familiar autosomal
      - stratified ≥ 2 close fam
        - members
    - Familiar non-autosomal
    - ≥ 3 close fam members
    - BRCA1/2 Hereditary
    - PanCan/Breast/Ovarian
    - FAMMM p16, CDKN2A
    - Peutz Jeghers
    - Lynch Syndrome with
      - PC history (HNPCC)
    - Hereditary pancreatitis

**CLINICAL USE 2**
- NEW ONSET DIABETES TYPE II AFTER 50 YRS OF AGE

**CLINICAL USE 3**
- VAGUE SYMPTOMS
  - Depression
  - Indigestion
  - Jaundice
  - Midback pain
  - Upper abdominal pain
  - Pain on eating
  - Fatigue
  - Unexplained weight loss
  - Diabetes

**CLINICAL USE 4**
- CONFIRMATORY DIAGNOSIS/MONITORING

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Prospective (longitudinal) validation clinical study PanFAM-1

Retrospective & Prospective Studies planning
Ongoing

Prospective Studies planning ongoing

To start at a later stage

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Diagnostic assessment studies for IPMNs (pre-cancer lesions) & different pancreatic diseases
Different tests for ONE disease

- There is (still) a market for SINGLE (as in simple) tests
  → $$$$$
  → TAT

www.grandviewresearch.com
Points of discussion – OPEN questions

- Defining the real “window of opportunity” for PC screening
- Understanding the catastrophic progression of PC
- Evaluating screening protocols for biomarkers for early detection of pancreatic cancer and its precursors
- Listing and prioritizing biomarkers, upon the availability of evidences, for their validation in well-characterized common resources
- Estimating cost/efficient screening interventions in high-risk populations
Cost-efficient screening in high-risk populations

- **WHAT to use in screening?!**
  - Imaging
    - MRI, EUS, …
  - Blood tests
    - Conventional marker
    - ct-DNA, CTC

- **WHAT to compare to?**
  - Surgery
  - Chemotherapy
  - Preventive surgery

- **HOW long?!**
  - QUALY, …
Imaging

- MRI
The costs

- MRI screening
  → Short protocol

- Preventive Surgery
  → In IAR (FPC, IPMN)

- Novel biomarker
  → tbd

- Therapy costs
  → Surgery + adjuvant therapy
  → Palliative therapy + BSC

<table>
<thead>
<tr>
<th>Item</th>
<th>cost</th>
<th>Σ 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>250</td>
<td>2 500</td>
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<tr>
<td>Prev Sx</td>
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<td>20 000</td>
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<tr>
<td>Biomarker</td>
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<td>1 000</td>
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<td>Sx + Tx</td>
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<td>130 000</td>
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<tr>
<td>Tx</td>
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<td>100 000</td>
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EXISTING biomarkers
- Confirmatory prospective studies in well-characterized patient cohorts

NEW biomarkers
- to be identified with novel methods
  - Liquid biopsy
  - Metabolomics
- In selected risk groups
  - IAR/FPC
  - IPMN
Looking Out Of the Box
What are the 3 top challenges?

- Prevention
- Diagnosis
- Therapy

Diagram:
- Diagnostic
- Prognostic
- Predictive
Top 3 challenges

PREVENTION

- As we cannot heal PDAC in its later stages, prevention is mandatory

- Preneoplastic conditions
  - Chronic (hereditary) pancreatitis
  - Cystic lesions/tumors
  - IMPN
  - FPC – “individuals at risk”
Top 3 challenges

DIAGNOSIS

- ANY kind of marker is missing
  - Screening
  - Diagnosing
  - Follow-up/monitoring
  - Response/resistance to therapy
  - Prognosis
Top 3 challenges

DIAGNOSIS

- The problem with biomarkers:
  - Promising initial results, highly recognized in the scientific community
  - The necessary follow-up studies fall into a hole
    - No funding schemes
Top 3 challenges

DIAGNOSIS

▪ Proposed actions

→ Create funding schemes for follow-up studies of verified biomarkers (panels, profiles)

→ Make this an obligatory alliance with industry
  ▪ Ensure QC/QA and SOP’s, GLP etc.
  ▪ IMI scheme?!
General Population

First Sieve
- Hereditary pancreatic cancer kindreds
- New-onset Diabetes

Second Sieve
- Symptoms
- Smokers
- ? New-onset diabetes
- Phenotype, Serologic Marker, Non-invasive Imaging

- Symptoms
- Serologic biomarker of PaCDM
- Abnormal non-invasive imaging

Confirm diagnosis: Endoscopic ultrasonography
Pancreatic Cancer Growth and Dissemination

1. Estimation of growth and dissemination rates

2. Prediction of numbers and sizes of metastases at autopsy as well as patient survival, and validation of these quantities in an independent database

3. Identification of optimum therapeutic interventions to prolong patient survival
Markers and timelines

Normal epithelium → PanIN → PDAC → Metastasis

- PanIN-1 → PanIN-3
- Telomere shortening → Kras → p16INK4A → CDKN2A → TP53/SMAD4/BRCA2

- ~12 years: Tumorigenesis onset
- ~7 years: Invasiveness
- ~3 years: Metastatic spread
- Death

CAF → Cancer cell → MDSC → Extracellular matrix
Fibrocytes → Macrophage → Neutrophil → Tregs → CD8+ T cell

Fokas et al., BBA 2015 (1855): 61-82
PDAC – early systematic spread?

Fig. 1 Flow diagram for the study
PDAC – early systematic spread?

Ansari et al BJS 2017, 104: 600-607
### Table 4. Potential Predictive Biomarkers in Pancreatic Cancer

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Treatment Biomarker Is Potentially Predictive For</th>
<th>Evidence/Comments</th>
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<tbody>
<tr>
<td>EGFR, KRAS</td>
<td>Erlotinib</td>
<td>No association with survival benefit identified in patients in PA.3 trial with available tumor samples treated with gemcitabine/erlotinib(^{76})</td>
</tr>
</tbody>
</table>
| hENT1                     | Gemcitabine                                      | RTOG 9704 trial: hENT1 expression associated with improved overall survival in postresection patients receiving adjuvant gemcitabine (hazard ratio, 0.40), but not fluorouracil\(^{73}\)  
No survival difference between high and low hENT1 subgroups in trial of gemcitabine-treated patients with metastatic pancreatic cancer\(^{74}\)   |
| SPARC                     | Nab-paclitaxel                                   | SPARC expression in stroma correlated with improved survival in phase I/II gemcitabine plus nab-paclitaxel trial\(^{29}\)                                                                                           
Findings not corroborated in larger sample size (phase III MPACT trial)\(^{75}\)                                                                 |
| DPC4 (SMAD4)              | Radiation                                        | Rapid autopsy series: loss of DPC4 associated with higher rates of metastatic dissemination\(^{77}\)                                                                                                                  
Current RTOG 1201 trial: patients with locally advanced disease to be stratified according to DPC4 expression                                                                 |
| C-reactive protein (in serum) | Ruxolitinib                                      | Randomized phase II trial data suggest benefit to ruxolitinib specifically in patients with higher levels of C-reactive protein\(^{66}\)                                                                           
Ongoing phase III trials enriched exclusively for patients with high C-reactive protein                                                                                                             |

Abbreviations: EGFR, epidermal growth factor receptor; hENT1, human equilibrative nucleoside transporter 1; MPACT, Metastatic Pancreatic Adenocarcinoma Clinical Trial; nab, nanoparticle albumin-bound; RTOG, Radiation Therapy Oncology Group; SPARC, secreted protein acidic and rich in cysteine.
## Family History

### FHx melanoma

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### FHx Breast/Ovarian

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