ESMO PRECEPTORSHIP ON PANCREATIC ADENOCARCINOMA

Epidemiology, molecular characterisation and hereditary forms of pancreatic cancer

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Disclosures

Research grant: Halozyme

Travel grant: Novartis, Pfizer
Pancreatic cancer?

Adenocarcinoma (90%)
Pancreatic cancer?

Adenocarcinoma (90%)

Neuroendocrine lesions

Rare lesions: Acinar cell carcinomas....

Completely different morphology, biology, treatment (sometimes)....
We’re not out of the wood... Just getting in!
European cancer mortality predictions for the year 2014

M. Malvezzi¹,², P. Bertuccio¹, F. Levi³, C. La Vecchia²* & E. Negri¹

¹Department of Epidemiology, IRCCS-Istituto di Ricerche Farmacologiche ‘Mario Negri’, Milan. ²Department of Clinical Sciences and Community Health, Università Degli Studi di Milano, Milan, Italy; ³Cancer Epidemiology Unit, Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland

More deaths from pancreatic cancer than breast cancer in the EU by 2017

J. Ferlay⁴, C. Partensky⁵ and F. Bray⁴

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

Figure 2. Age-standardized (world population) total cancer mortality trends in quinquennia from 1970–1974 to 2005–2009 and predicted rates for 2014, for men (squares) and women (circles) in the EU.

V. Rebours
Incidence has been rising continuously in the last 30 years: France
Incidence is higher in the western world

Figure 1 Diagram of incidence of pancreatic cancer in both sexes throughout the world Adapted from Globocan\textsuperscript{[1]} 2018.
Pancreatic Cancer (C25), Average Number of New Cases per Year and Age-Specific Incidence Rates per 100,000 Population, UK, 2014-2016

Average Number of New Cases per Year

Incidence Rate per 100,000

Age at Diagnosis

From Cancer research uk
Pancreatic adenocarcinoma

- Smoking
  Smoking may cause about 20-30% of all exocrine pancreatic cancer cases.

- Family History
  Risk increases if multiple first-degree relatives had the disease, or any were diagnosed under 50.

- Pancreatitis
  Chronic pancreatitis increases risk. Risk is even higher for people with hereditary pancreatitis.

- Obesity
  Obese people have a 20% increased risk of developing the disease compared to people of a normal weight.

- Diabetes
  Long standing (over 5 years) diabetes increases risk.

V. Rebours
INFLAMMATION
- Tobacco
- Chronic pancreatitis
- Heavy alcohol intake
- Helicobacter Pylori

DNA DAMAGE
- Tobacco
- Oxidative stress

DNA REPAIR
- Mediterranean diet

IMMUNITY
- Allergies/Atopia
- O blood type

GENETIC
- Familial forms

CANCER

INSULINO-RESISTANCE
- Hyperglycemia
- Diabetes
- Overweight/Obesity
- Metabolic syndrome

GLYCEMIA CONTROL
- Metformine

V. Rebours
FOR GOOD DIAGNOSIS, GOOD RESEARCH STUDIES....

...WE NEED GOOD SAMPLES

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Poor EUS-FNA</th>
<th>Rich EUS-FNB / liver biopsy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Protein on Tum cells</th>
<th>OK</th>
<th>OK</th>
<th>OK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation on Tum cell</td>
<td>+/- OK</td>
<td>++/- OK</td>
<td>OK</td>
</tr>
<tr>
<td>Exp (mi)ARN (amount/purity)</td>
<td>+/- OK</td>
<td>+/- OK</td>
<td>+/- OK (amount/purity)</td>
</tr>
<tr>
<td>Protein in stroma</td>
<td>NO</td>
<td>NO</td>
<td>+/- OK</td>
</tr>
</tbody>
</table>
**USE PROPER SAMPLING TECHNIQUES AND GOOD FNB NEEDLES**

**HISTOPAN** (ClinicalTrials.gov ID: NCT03567863)  
Multicenter randomized control trial  
22-gauge Acquire® vs. 20-gauge Procore® (n=60)

<table>
<thead>
<tr>
<th>Diagnosis obtained, n (%)</th>
<th>Procore® 20G (n = 60)</th>
<th>Acquire® 22G (n = 60)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 (67%)</td>
<td>52 (87%)</td>
<td>&lt;0.02</td>
<td></td>
</tr>
<tr>
<td>Diagnosis of adenocarcinoma, n (%)</td>
<td>29/46 (63%)</td>
<td>38/46 (83%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diagnosis of neuroendocrine neoplasm, n (%)</td>
<td>9/11 (82%)</td>
<td>11/11 (100%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diagnosis of autoimmune pancreatitis, n (%)</td>
<td>1/2 (50%)</td>
<td>2/2 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis of chronic pancreatitis, n (%)</td>
<td>1/1 (100%)</td>
<td>1/1 (100%)</td>
<td>1</td>
</tr>
<tr>
<td>Core biopsy obtained, n (%)</td>
<td>49 (82%)</td>
<td>60 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cumulative length of tissue core biopsies per needle pass, mean (SD), mm</td>
<td>5.42 (6.3)</td>
<td>11.36 (9.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cumulative area of tissue core biopsies per needle pass, mean (SD), mm²</td>
<td>1.77 (2.0)</td>
<td>3.48 (3.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Karsenti et al. Submitted
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

Metastatic PDAC

Non-metastatic PDAC

What we treat....

Non-metastatic PDAC

Metastatic PDAC

What we know (biology)....
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

Treatments for which we need biomarkers

EUS FNA

Surgery

Chemo 1

Chemo 2 / TT

Chemo 3 / TT

Chemo 1

Chemo 2 / TT

Chemo 3 / TT
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

Samples on which we (try) to develop or test biomarkers...

EUS FNA

Surgery

Treatments for which we need biomarkers

Chemo 1

Chemo 2 / TT

Chemo 3 / TT

Chemo 1

Chemo 2 / TT

Chemo 3 / TT

This may impact clinical trials using biomarker-based patient stratification+++
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

- Tumor cells
- Stroma
- ECM
- Vessels
- Immune cells
- CAF
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

PDAC IS A HIGLY HETEROGEOUS TUMOR, PROBABLY WITH A HIGHLY PLASTIC BIOLOGY

Heterogeneity of the tumor cell – stroma ratio
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

Stroma abundance—pronostic role?

Bever et al. HPB 2015, 292

Heid et al. Clin can res 2017, 1461

Small sample (<100 pts)
MORPHOLOGICAL HETEROGENETITY

- ductal
- colloid
- intestinal

- Undifferentiated w/ giant cells osteocl-like
- adenosquamous
- micropapillary
### MORPHOLOGICAL HETEROGENETITY

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Frequency</th>
<th>%</th>
<th>Type of associated IPMN</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional ductal adenocarcinoma</td>
<td>91</td>
<td>51.4</td>
<td>2 gastric</td>
<td>22.7</td>
</tr>
<tr>
<td>Combined ductal adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with cribriform component</td>
<td>17</td>
<td>9.6</td>
<td></td>
<td>28.7</td>
</tr>
<tr>
<td>with papillary component</td>
<td>17</td>
<td>9.6</td>
<td></td>
<td>13.9</td>
</tr>
<tr>
<td>with clear-cell component</td>
<td>16</td>
<td>9.0</td>
<td>1 pancreatic-biliary</td>
<td>17.6</td>
</tr>
<tr>
<td>with complex component</td>
<td>12</td>
<td>6.7</td>
<td>1 gastric</td>
<td>10.7</td>
</tr>
<tr>
<td>with gyriform component</td>
<td>8</td>
<td>4.5</td>
<td></td>
<td>12.5</td>
</tr>
<tr>
<td>with micropapillary component</td>
<td>2</td>
<td>1.1</td>
<td></td>
<td>16.1</td>
</tr>
<tr>
<td>Variants and special carcinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosquamous carcinoma*</td>
<td>2</td>
<td>1.1</td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>Colloidal/mucinous carcinoma*</td>
<td>2</td>
<td>1.1</td>
<td>1 intestinal</td>
<td>&gt;64.3**</td>
</tr>
<tr>
<td>Medullary carcinoma*</td>
<td>1</td>
<td>0.5</td>
<td></td>
<td>&gt;75.1**</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>3</td>
<td>1.7</td>
<td></td>
<td>&gt;55.3**</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>6</td>
<td>3.4</td>
<td>2 pancreatic-biliary, 1 intestinal, 1 gastric</td>
<td>20.6</td>
</tr>
<tr>
<td>All tumors</td>
<td>177</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NGS/IHC KRAS/CDKN2A/SMAD4/TP53**

Schlitter et al. Sci reports 2017
More frequent MYC amplification?

More frequent GNAS mutation?

NGS/IHC KRAS/CDKN2A/SMAD4/TP53
No major difference

Schlitter et al. Sci reports 2017
NGS/IHC KRAS/CDKN2A/SMAD4/TP53
No major difference

Schlitter et al. Sci reports 2017
3 large datasets (ICGC (456 pts), TCGA (150 pts), Connor et al. (148 pts) – similar results

Connor et al. JAMA Oncol 2016
**GENOMIC CHARACTERIZATION**

![Diagram](Image)

- **Stable**
- **Scattered**
- **Unstable**
- **Locally rearranged**

- **Intra-chromosomal rearrangement**
- **Inter-chromosomal translocation**
- **Duplication**
- **Tandem duplication**
- **Inversion**
- **Foldback inversion**
- **Amplified inversion**
- **Deletion**

**Benefit from PARPi in maintenance therapy (POLO trial)**

### Table: Genomic Characterization

<table>
<thead>
<tr>
<th>Signature</th>
<th>Discovery (n)</th>
<th>Replication (n)</th>
<th>ESPAC (n)</th>
<th>Population [% 95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-Related</td>
<td>115*</td>
<td>59</td>
<td>NA</td>
<td>69.9% (64.2-75.6%)</td>
</tr>
<tr>
<td>DSBR, total</td>
<td>17**</td>
<td>10</td>
<td>NA</td>
<td>10.8% (6.98-14.7%)</td>
</tr>
<tr>
<td>DSBR, germline</td>
<td>9</td>
<td>2</td>
<td>NA</td>
<td>4.42% (1.9-6.97%)</td>
</tr>
<tr>
<td>DSBR, somatic</td>
<td>2</td>
<td>2</td>
<td>NA</td>
<td>1.6% (0.045-3.2%)</td>
</tr>
<tr>
<td>DSBR, occult</td>
<td>6</td>
<td>6</td>
<td>NA</td>
<td>4.8% (2.2-7.5%)</td>
</tr>
<tr>
<td>MMR</td>
<td>4</td>
<td>2</td>
<td>NA</td>
<td>1.7% (0.65-2.7%)</td>
</tr>
<tr>
<td>Signature 8</td>
<td>16</td>
<td>20</td>
<td>NA</td>
<td>14.5% (10.1-18.8%)</td>
</tr>
<tr>
<td>APOBEC</td>
<td>1***</td>
<td>4</td>
<td>NA</td>
<td>2.0% (0.27-3.8%)</td>
</tr>
<tr>
<td>Signature 17</td>
<td>1</td>
<td>2</td>
<td>NA</td>
<td>1.2% (0-2.56%)</td>
</tr>
<tr>
<td>Total sample sizes</td>
<td>154</td>
<td>95</td>
<td>342</td>
<td>NA</td>
</tr>
</tbody>
</table>

* there are 119 tumours from 115 cases in the Age Related discovery group
** there are 18 tumours from 17 cases in the DSBR discovery group
*** there are 2 tumours from 1 case in the APOBEC discovery group

---

**References**

- Waddell et al. Nature 2015
- Connor et al. JAMA Oncol 2016
MSI, DSBR Sensibility to immunotherapies?

Connor et al. JAMA Oncol 2016
2 main transcriptomic tumor subtypes with different prognosis
Molecular subtypes may have an important clinical utility.
True challenge! How to define (clearly) the molecular subtype in samples with few tumor cells???

There is no routine tool available (RNA signature, immunohistochemistry etc...)
Good old morphology may predict tumor subtypes...

### A. "Gland forming" component

<table>
<thead>
<tr>
<th>Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
</tr>
<tr>
<td>Tubulopapillary</td>
</tr>
</tbody>
</table>

### B. "Non-gland forming" component

<table>
<thead>
<tr>
<th>Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
</tr>
<tr>
<td>Squamous</td>
</tr>
</tbody>
</table>
Good old morphology may predict tumor subtypes...
Good old morphology may predict tumor subtypes...

« classical » tumors with a basal like subpopulation?
If tumor were pure, that would be too easy.....

A

<table>
<thead>
<tr>
<th>&quot;Gland forming&quot; component</th>
<th>Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional</td>
</tr>
</tbody>
</table>

B

- Composite
- Conventional
- Tubulopapillary
- Squamous

N=86
And the stroma is also heterogeneous...

*Moffitt et al. Nature genetics 2015*
NO CONSENSUS ON THE STROMA YET!

Puleo et al, Gastroenterology 2018
MOLECULAR CHARACTERISATION OF PANCREATIC ADENOCARCINOMA

- Metastatic PDAC
- Non-metastatic PDAC

What we treat....

- Non-metastatic PDAC
- Metastatic PDAC

What we know (biology)....
- Low heterogeneity of classical driver genes
- Most genomic events happen early
- No « metastasis » gene
- Physical and genomic spatialisation are different

Makohon-Moore et al. Nat Gen 2017
Yachida et al. Nature 2010
- Most genomic events happen before the first metastase
- 50% of tumours are not diploïd (T ou H)
- Multiples simultaneous genomic alterations

INTRA-TUMOR HETEROGENEITY – GENOMIC LEVEL

How to follow high risk patients???

**INTRA-TUMOR HETEROGENEITY - EPIGENOMIC**

**Genomic heterogeneity**

- **Catastrophic chromosomal event (1):** SMAD4/CDKN2A...
- **Catastrophic chromosomal event (2):** TP53, MYC...
- **Catastrophic chromosomal event (X):** Polyploidization

**Parental clone**

- **Liv M1**
- **Liv M2**

**Epigenetic remodeling**

- **Genetic/chromosomal alterations** *(Mutations in driver genes)*

**New drugs???
Pancreatic adenocarcinoma – hereditary forms

Mayo Clinic, 2000-2016
- Case control study:
- 3030 adults FamPa, 123,000 control subjects

Table 3. Comparisons of Mutation Carriers by Panel Gene Between Pancreatic Cancer Cases and gnomAD Controls

<table>
<thead>
<tr>
<th>Genes Significantly Associated With Pancreatic Cancer</th>
<th>Cases</th>
<th>Individuals Tested, No.</th>
<th>Carrier Frequency, %</th>
<th>gnomAD Controls</th>
<th>Individuals Tested, No.</th>
<th>Carrier Frequency, %</th>
<th>Cancer Riska</th>
<th>Odds Ratio (95% CI)</th>
<th>Adjusted P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A</td>
<td>9</td>
<td>2999</td>
<td>0.30</td>
<td>15</td>
<td>99,493</td>
<td>0.02</td>
<td>12.33</td>
<td>(5.43-25.61)</td>
<td>&lt;.001</td>
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<tr>
<td>TPS3</td>
<td>6</td>
<td>2999</td>
<td>0.20</td>
<td>25</td>
<td>104,162</td>
<td>0.02</td>
<td>6.70</td>
<td>(2.52-14.95)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MLH1</td>
<td>4</td>
<td>2999</td>
<td>0.13</td>
<td>25</td>
<td>103,526</td>
<td>0.02</td>
<td>6.66</td>
<td>(1.94-17.53)</td>
<td>.01</td>
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<tr>
<td>BRCAl</td>
<td>57</td>
<td>2999</td>
<td>1.90</td>
<td>313</td>
<td>102,739</td>
<td>0.30</td>
<td>6.20</td>
<td>(4.62-8.17)</td>
<td>&lt;.001</td>
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<tr>
<td>ATM</td>
<td>69</td>
<td>2999</td>
<td>2.30</td>
<td>386</td>
<td>104,016</td>
<td>0.37</td>
<td>5.71</td>
<td>(4.38-7.33)</td>
<td>&lt;.001</td>
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<tr>
<td>BRCAl</td>
<td>18</td>
<td>2999</td>
<td>0.60</td>
<td>208</td>
<td>104,122</td>
<td>0.20</td>
<td>2.58</td>
<td>(1.54-4.05)</td>
<td>.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes Not Significantly Associated With Pancreatic Cancer</th>
<th>Cases</th>
<th>Individuals Tested, No.</th>
<th>Carrier Frequency, %</th>
<th>gnomAD Controls</th>
<th>Individuals Tested, No.</th>
<th>Carrier Frequency, %</th>
<th>Cancer Riska</th>
<th>Odds Ratio (95% CI)</th>
<th>Adjusted P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>4</td>
<td>2999</td>
<td>0.13</td>
<td>31</td>
<td>103,812</td>
<td>0.03</td>
<td>3.70</td>
<td>(1.11-9.22)</td>
<td>.25</td>
</tr>
<tr>
<td>PALB2</td>
<td>12</td>
<td>2999</td>
<td>0.40</td>
<td>153</td>
<td>104,169</td>
<td>0.15</td>
<td>2.33</td>
<td>(1.23-4.01)</td>
<td>.09</td>
</tr>
<tr>
<td>CDH1</td>
<td>1</td>
<td>2999</td>
<td>0.03</td>
<td>15</td>
<td>102,110</td>
<td>0.01</td>
<td>2.30</td>
<td>(0.13-11.39)</td>
<td>&gt;.99</td>
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<tr>
<td>MSH6</td>
<td>6</td>
<td>2999</td>
<td>0.20</td>
<td>101</td>
<td>102,802</td>
<td>0.10</td>
<td>1.98</td>
<td>(0.77-4.14)</td>
<td>&gt;.99</td>
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<tr>
<td>FANCC</td>
<td>8</td>
<td>2999</td>
<td>0.27</td>
<td>129</td>
<td>104,042</td>
<td>0.12</td>
<td>1.69</td>
<td>(0.76-3.21)</td>
<td>&gt;.99</td>
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<tr>
<td>MSH2</td>
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<td>2999</td>
<td>0.03</td>
<td>16</td>
<td>103,327</td>
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<td>1.58</td>
<td>(0.09-7.54)</td>
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<tr>
<td>BARD1</td>
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<td>2999</td>
<td>0.13</td>
<td>86</td>
<td>102,189</td>
<td>0.08</td>
<td>1.32</td>
<td>(0.40-4.35)</td>
<td>&gt;.99</td>
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<tr>
<td>CHEK2</td>
<td>33</td>
<td>2999</td>
<td>1.10</td>
<td>572</td>
<td>102,856</td>
<td>0.56</td>
<td>1.31</td>
<td>(0.91-1.83)</td>
<td>&gt;.99</td>
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<tr>
<td>RAD51C</td>
<td>3</td>
<td>2999</td>
<td>0.10</td>
<td>94</td>
<td>104,128</td>
<td>0.09</td>
<td>1.11</td>
<td>(0.27-2.97)</td>
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<td>NBN</td>
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<td>2999</td>
<td>0.13</td>
<td>125</td>
<td>103,912</td>
<td>0.12</td>
<td>0.86</td>
<td>(0.27-2.04)</td>
<td>&gt;.99</td>
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<tr>
<td>BRIP1</td>
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<td>2999</td>
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<td>194</td>
<td>104,071</td>
<td>0.19</td>
<td>0.78</td>
<td>(0.28-1.71)</td>
<td>&gt;.99</td>
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<tr>
<td>MRE11A</td>
<td>2</td>
<td>2999</td>
<td>0.07</td>
<td>96</td>
<td>104,071</td>
<td>0.09</td>
<td>0.71</td>
<td>(0.12-2.23)</td>
<td>&gt;.99</td>
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<tr>
<td>PMS2</td>
<td>2</td>
<td>2999</td>
<td>0.07</td>
<td>86</td>
<td>101,976</td>
<td>0.08</td>
<td>0.70</td>
<td>(0.12-2.22)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviation: gnomAD, Genome Aggregation Database.
Who should we screen?

Multiple cases within a family (genes?)

Genetic syndrome

- BRCA 2
- Familial melanoma (CDKN2A/p16)
- Peutz-Jeghers (STK11/LKB1)
- Hereditary Pancreaticis (PRSS1)

Theoretical PDAC risk ≥ 5-10%

+ 1 PDAC case in the family
### Hereditary Pancreatic Cancer predisposition syndromes, their genetic findings and lifetime risk of pancreatic cancer by the age of 70

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Cumulative risk of pancreatic cancer at age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>PJS</td>
<td>STK11</td>
<td>20-60%</td>
</tr>
<tr>
<td>Hereditary Panreatitis</td>
<td>PRSS1/ SPINK1</td>
<td>40%</td>
</tr>
<tr>
<td>FAMMM</td>
<td>CDKN2A/p16</td>
<td>17%</td>
</tr>
<tr>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
<td>3-8%</td>
</tr>
<tr>
<td>ATM</td>
<td>ATM</td>
<td>5 %</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>CFTR</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Li Fraumeni</td>
<td>TP53</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>FAP</td>
<td>APC</td>
<td>2%</td>
</tr>
</tbody>
</table>

PJS – Peutz-Jeghers-Syndrome, FAMMM – familial atypical multiple mole melanoma, HBOC – hereditary breast and ovarian cancer, ATM – Ataxia teleangiectasia)
Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma


Overall: 35/834 (4.2%)

BRCA2: 12
ATM: 10
BRCA1: 3
PALB2: 2
MLH1: 1
CDKN2A:1
TP53:1

Who should we screen?
Who should we screen?

- Familial / personal history of neoplasia compatible with a genetic syndrome
  - Individuals with three or more affected blood relatives, with at least one affected
  - Individuals with at least two affected FDRs with PC, with at least one affected FDR
  - BRCA2/CDKN2A/PALB2 mutation carriers with one affected FDR
  - Hereditary pancreatitis
  - Peutz-Jeghers

- Excellent response to Pt-based treatment (to be proven)
  - Prolonged survival (many other reasons!!!)
TAKE HOME MESSAGES

- Pancreatic adenocarcinoma
  - Rising incidence
  - Role of systemic inflammation / metabolic syndrome

- Low heterogeneity at the mutational level
- High heterogeneity (space and time) at the epigenetic/transcriptomic level

- 2 main tumor subtypes with different prognosis
  + X stroma subtypes... = Y PDAC subtypes!

- Germline mutation (5-8%) (BRCA2/1++, MSI 1% max)