PANGEN-FAM STUDY: THE SPANISH FAMILIAL PANCREATIC CANCER (FPC) REGISTRY: GENETIC ANALYSIS OF FAMILIES AND SCREENING OF AT RISK INDIVIDUALS.

DR. CARMEN GUILLÉN PONCE
DR. ALFREDO CARRATO MENA
DR. JULIE EARL
DR. EVELINA MOCCI
DR. NURÍA MALATS
PANCREATIC CANCER

• The 10th most frequent cancer. 4\textsuperscript{th} cause of cancer related death. \textit{Incidence almost equals mortality:}

• \textbf{Overall 5 year survival 5.4%}

• 80\% of patients present with locally advanced or metastatic disease

• Resistant to chemotherapy, gemcitabine ± nab-paclitaxel standard of care.

• \textbf{5-10\% of cases have a family history} (Breast/ovarian, Peutz Jeghers Syndrome (PJS), Familial Atypical Multiple Mole Melanoma (FAMMM), HNPCC, hereditary pancreatitis (PRSS1)

• \textbf{15–20\% of families carry germline mutations} in \textit{BRCA2, PALB2} and \textit{ATM}
OBJECTIVES OF PANGEN-FAM

• Established in 2009, coordinated by Drs Alfredo Carrato and Carmen Guillen, H RyC, Madrid.
• Identification and creation of a national registry of families with FPC.
• Characterization of the phenotype of families
• Whole exome sequencing of individuals in order to identify novel genes and/or variants associated with FPC.
• Establish a screening program for at risk individuals in order to detect a Pancreatic Cancer (PC) at a potentially curative stage.
INCLUSION CRITERIA

• ≥ 2 cases of 1st degree relatives or ≥ 3 cases independent of relationship.
• Families that present with other criteria of other hereditary cancer syndromes:
  • Peutz-Jeghers Syndrome (SPJ), Familial Atypical Multiple Mole melanoma (FAMMM)* and Hereditary Breast and Ovarian Cancer (HBOC)*.
  • Families that present with a young case of PC (<=50 years old)**.
  • Families with Hereditary Pancreatitis (HP) or chronic pancreatitis (CP) with PC

*For these syndromes only families that present with at least one case of PC will be included.

**These families will only undergo genetic analysis and not screening.
STUDY PROTOCOL

• Generate a family tree with a minimum of 3 generations.
• Completion of an epidemiological questionnaire: demographic data, smoking, alcohol consumption and clinical data.
• Collection of biological samples: peripheral blood and tumor tissue (fresh or paraffin embedded, depending upon the availability).
• Routine genetic analysis: BRCA1/2, CDKN2A
• Screening program for at risk individuals.
# Families Registered in PAN-GEN-FAM

<table>
<thead>
<tr>
<th>Family phenotype</th>
<th>Number of families registered</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPC</td>
<td>10</td>
</tr>
<tr>
<td>FPC &gt;= 3 PC</td>
<td>3</td>
</tr>
<tr>
<td>PC &lt;= 50 years</td>
<td>4</td>
</tr>
<tr>
<td>HBOC + PC</td>
<td>5</td>
</tr>
<tr>
<td>HBOC+ PC &lt;= 50 year</td>
<td>6</td>
</tr>
<tr>
<td>unclassified</td>
<td>5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>33</td>
</tr>
</tbody>
</table>
## BRCA GERMLINE MUTATION SCREENING

<table>
<thead>
<tr>
<th>Family Phenotype</th>
<th>BRCA1 mutation positive</th>
<th>BRCA1 mutation negative</th>
<th>BRCA1 variant of unknown significance</th>
<th>BRCA2 mutation positive</th>
<th>BRCA2 mutation negative</th>
<th>BRCA2 variant of unknown significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPC</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPC &gt;= 3 PC</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PC &lt;= 50 Years of age</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBOC + PC</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBOC + PC &lt;= 50 Years of age</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unclassified</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
MINIMALLY INVASIVE TUMOR MARKERS

CTC detection in peripheral blood

- Tumor cells shed into the blood stream from the primary tumor

- Clinically detectable metastases

- Clinically undetectable micrometastases

Primary tumor

Circulating Tumor Cells (CTC) are isolated from peripheral blood

miRNA profiling in serum

Screening of a panel of 742 miRNA markers.
SCREENING PROTOCOL

EUS + CT conventional/diffusion
CTC/miRNA detection

EUS + CT Normal

Repeat imaging annually

EUS + CT Abnormal

RMI

Evaluation by a multidisciplinary team
41 at risk individuals in 11 families (1-12 participants per family) participating in the imaging screening program (CT/EUS/RMI).

The majority of anomalies identified are consisted with changes associated with pancreatitis. 6 cystic lesions and 1 NET.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Number of Pancreatic abnormalities</th>
<th>Abnormalities detected</th>
<th>Number of Extra pancreatic lesions</th>
<th>Abnormalities detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>5/38</td>
<td>cysts, steatosis</td>
<td>21/38</td>
<td>hepatic and biliary cysts</td>
</tr>
<tr>
<td>EUS</td>
<td>17/39</td>
<td>pancreatic heterogeneity, cysts, parenchymal lobulation, hyperechoic areas</td>
<td>4/39</td>
<td>gallstones, fatty liver, hiatal hernia</td>
</tr>
<tr>
<td>RMI</td>
<td>4/12</td>
<td>cysts</td>
<td>7/12</td>
<td>renal, biliary, hepatic cysts</td>
</tr>
</tbody>
</table>
SUMMARY

• PANGEN-FAM: Identification and creation of familial pancreatic cancer registry.
• Routine genetic analysis (BRCA1/2 CDKN2A)
• Screening of high risk individuals: imaging techniques: CT, EUS, RMI
• Whole exome sequencing to identify novel genes or variants involved in FPC
• Minimally invasive markers: CTC y miRNA

CONTACT:
CARMENGUILLENPONCE@GMAIL.COM
ACARRATO@TELEFONICA.NET
JULIE.EARL@LIVE.CO.UK

Unidad de Cáncer Familiar. Servicio de Oncología Médica, Hospital Universitario Ramón y Cajal, Madrid
Teléfono: 0034 913369085
ACKNOWLEDGEMENTS

Pan-Gen-FAM:
- Dra Carmen Guillen
- Dr Alfredo Carrato
- D Carme Guerrero-Arroyo
- Dra Evelina Mocci
- Dra Nuria Malats
- Dra Mirari Marquez
- Dr Francisco Real

miRNA profiling in serum/tumor pancreatic cancer:
- Dra Laura Garcia Bermejo
- Dra Elisa Conde Moreno
- D Edurne Ramos Muñoz
- Dra Elia Aguado

Research Nurses:
- Andreia, Maite