Webinar Objectives

- Review role of pancreatic cancer in hereditary cancer syndromes
- PANEXIA™ Overview
  - Product description
  - Background on the PALB2 gene
  - Identifying patients
  - Cancer risks in mutation carriers
  - Medical management options
Pancreatic Cancer Statistics

10th most common cancer in the U.S.
- 43,140 new cases and 36,800 deaths in 2010
- Equal risk for men and women

4th leading cause of cancer-related death in men and women of all ages
- Lowest 5-year survival rate of any cancer
Risk Factors for Pancreatic Cancer

There is less than 1% risk of pancreatic cancer by age 80 in the general population

- **Age:** >70% are over age 65
  - Average age at diagnosis 72 y
- **Smoking:** 2-3x higher risk, up to 20-30% of cases
- **Diabetes,** mostly type 2
- **Chronic pancreatitis**
Family History as a Risk Factor

- Several studies have shown that relatives of patients who have pancreatic cancer (ductal adenocarcinoma) have an increased risk for pancreatic cancer.
- The magnitude of risk increases with the number of affected relatives.
- 32-fold increase in individuals with three affected first-degree relatives.

Klein, 2004
Tersmette, 2001
Rulyak, 2003
# Genetic Syndromes and Pancreatic Cancer

<table>
<thead>
<tr>
<th>Pancreatic Cancer AND</th>
<th>Consider</th>
<th>Genes</th>
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<tbody>
<tr>
<td>Breast, Ovarian</td>
<td>HBOC</td>
<td>BRCA1, BRCA2</td>
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<tr>
<td>Melanoma</td>
<td>FAMMM</td>
<td>p16</td>
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<tr>
<td>Colon, Endometrial, Ovarian</td>
<td>Lynch</td>
<td>MMR genes</td>
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<tr>
<td>Colon, adenomatous polyps</td>
<td>FAP, AFAP</td>
<td>APC</td>
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<td>Hamartomatous polyps, Breast, skin findings</td>
<td>Peutz-Jeghers</td>
<td>STK11</td>
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<tr>
<td>Pancreatitis</td>
<td>Hereditary pancreatitis</td>
<td>PRSS1, SPINK1</td>
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<tr>
<td>Pancreatic</td>
<td>Hereditary Pancreatic Cancer</td>
<td>BRCA2, PALB2, ??</td>
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PANEXIA™

- A test for hereditary pancreatic and related cancers
- Full sequencing of PALB2 and BRCA2 genes
  - Concurrent or reflex testing of BRCA1 gene and/or p16 gene depending on family history

- Comprehensive PANEXIA™: $3025
- PALB2 single-gene analysis: $1435
PALB2
Partner and Localizer of BRCA2

- PALB2 co-localizes with BRCA2 in nuclear foci
  - promotes its localization and stability in key nuclear structures
  - enables its recombinational repair and checkpoint functions

- PALB2 part of same DNA repair pathway as BRCA1 and BRCA2, along with a large number of other proteins
PALB2

- Biallelic PALB2 mutations associated with Fanconi anemia (FANCN)
  - Bone marrow failure, congenital malformations, childhood embryonal tumors

- Monoallelic truncating PALB2 mutations associated with cancer risk
  - Pancreatic cancer
  - Breast cancer

Reid, 2007
Rahman, 2007
Xia, 2007
Jones, 2009
**PALB2 and Familial Pancreatic Cancer (FPC)**

- **Jones et al, 2009**
  - Tumor sequencing of a FPC patient identified *PALB2* as a pancreatic cancer susceptibility gene.
  - 3/96 (3%) FPC patients had *PALB2* truncating mutations in *BRCA2*-negative familial PC patients.
  - 1/3 did not have family history of breast cancer.

- **Slater et al, 2010**
  - 81 FPC patients.
  - 3/81 (3.7%) positive for a *PALB2* mutation.
  - All 3 families had a history of breast cancer.
**PALB2 and Familial Breast Cancer**

**PALB2 mutations are present in approximately 0.6 to 2.7% “familial breast cancer” patients**

- 10/923 (1.1%) British women with breast cancer and 2 or more relatives with breast cancer (0/1084 controls) (Rahman 2007)
- 3/113 (2.7%) Finnish women with “familial breast cancer,” 18/1918 (0.9%) unselected Finnish breast cancer patients – founder mutation (Erkko 2007)
- 4/203 (2.0%) German and Russian women with bilateral breast cancer (Bogdanova 2010)
- 3/360 (0.8%) Chinese women with breast cancer, either diagnosed under age 35 or a family history of breast cancer (Cao 2009)
BRCA2 and Familial Pancreatic Cancer

BRCA2 most commonly mutated known gene in FPC

- 3/41 (7.3%) unselected PC patients (Goggins 1996)
- 2/41 (4.9%) unselected PC patients (Ozcelik 1997)
  - 1/13 (7.7%) AJ & 4.6% (1/26) non-AJ
  - 4/39 (10%) unselected AJ patients, only 6174delT tested
- 5/29 (17%) families with ≥3 affected relatives. (Murphy 2002)
  - 3/5 (60%) AJ with founder mutation
  - 2/24 (8%) non-AJ
- 3/26 (12%) non-AJ families with ≥2 affected FDRs (Hahn 2003)
- 5/151 (3%) families with ≥2 affected FDRs or SDRs (Couch 2007)
- 3/70 (4.3%) non-AJ families with ≥2 affected FDRs (Slater 2010)
BRCA2 and Familial Pancreatic Cancer

Conclusions

- Most recent studies indicate that BRCA2 mutations account for 3-17% of moderate and high-risk PC families.

- Current data does not support BRCA2 testing in pancreatic cancer patients who do not have a family history of pancreatic cancer, except for.....

- AJ pancreatic cancer patients, unselected for family history, have approximately a 10% chance of testing positive for the 6174delT mutation.
Summary of Data from Familial Pancreatic Cancer - Germany Case Collection

- 94 German families with at least two 1st-degree relatives with pancreatic cancer, not meeting criteria for another hereditary cancer condition

- Probands (with pancreatic cancer) tested for:
  - BRCA2, PALB2, p16 (CDKN2a), RNASEL, STK11, NOD2, CHEK2, PALLD

- 4.9% for mutations in PALB2 and 4.3% positive for BRCA2 mutations—nothing found in any of the other genes

**Conclusion** – This data supports PALB2 and BRCA2 testing as appropriate for FPC patients, with a possible positive rate of just under 10%

Schneider et al., 2011
PANEXIA™ Red Flags

- Pancreatic cancer patient with at least one close relative\(^\wedge\) with pancreatic cancer
- Individual with two or more close relatives\(^\wedge\) with pancreatic cancer
- Individual of Ashkenazi Jewish ancestry with a personal history of or a first-degree relative with pancreatic cancer\(^\ast\)
- A previously identified *PALB2* or *BRCA2* mutation in the family

\(^\wedge\)close relative = first- or second-degree relative  
\(^\ast\)order MultiSite 3 BRACAnalysis\(^\circledR\) as an initial test

Assessment criteria based on scientific literature and expert opinion. For a list of references, go to: www.myriadpro.com/references
PANEXIA™ Test Request Form

<table>
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<tr>
<th>ANCESTRY AND CLINICAL HISTORY</th>
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<tr>
<td>☐ WESTERN/NORTHERN EUROPE</td>
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<td>☑ CENTRAL/EASTERN EUROPE</td>
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<td>☐ ASHKENAZI</td>
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<td>☐ LTX AMERICAN/ CARIBBEAN</td>
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<td>☐ AFRICA</td>
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<td>☐ NEAR EAST/ MIDDLE EAST</td>
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<td>☐ ASIA</td>
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<td>☐ NATIVE AMERICAN</td>
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<table>
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<tr>
<th>PATIENT PERSONAL HISTORY OF CANCER</th>
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<tr>
<td>☐ NO PERSONAL HISTORY OF CANCER</td>
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<tr>
<td>☑ BREAST, INVASIVE/AGE AT Dx: 64</td>
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<td>☐ BREAST, DCIS/AGE AT Dx:</td>
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<td>☐ OVARY/AGE AT Dx:</td>
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<tr>
<td>☐ MELANOMA: # OF PRIMARIES:</td>
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<td>☐ BONE MARROW TRANSPLANT RECIPIENT</td>
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<th>FAMILY HISTORY OF CANCER</th>
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<tr>
<td>☐ NO KNOWN FAMILY HISTORY</td>
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<tr>
<td>☑ RELATIONSHIP</td>
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<td>☑ FATHER</td>
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<td>☐ MATERNAL</td>
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<td>☐ PATERNAL</td>
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<tr>
<td>☐ CANCER SITE</td>
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<tr>
<td>☑ PANCREAS</td>
</tr>
<tr>
<td>☑ AGE AT Dx: 70</td>
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<tr>
<th>TESTS REQUESTED</th>
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<tr>
<td>☑ Comprehensive PANEXIA – PALB2 and BRCA2 gene sequence analysis for susceptibility to hereditary pancreatic and related cancers.</td>
</tr>
<tr>
<td>☐ Perform the following gene analysis AT THE SAME TIME as PANEXIA: ☐ BRCA1* ☐ p16*</td>
</tr>
<tr>
<td>☐ REFLEX to the following if Comprehensive PANEXIA is negative: ☐ BRCA1* ☐ p16*</td>
</tr>
<tr>
<td>☐ Single Site PANEXIA – Mutation-specific analysis for individuals with a known mutation in their family. Specify Gene: ☐ BRCA2 ☐ PALB2 ☐ BRCA1 ☐ p16</td>
</tr>
<tr>
<td>☐ Specify Variant (Mutation):</td>
</tr>
<tr>
<td>☐ Relationship of known mutation carrier to patient (e.g., sister):</td>
</tr>
<tr>
<td>☐ Multisite 3 BRACAnalysis® – Three-mutation BRCA1 and BRCA2 analysis for individuals of Ashkenazi Jewish ancestry (187delAG, 5385insC, 6174delIT)</td>
</tr>
<tr>
<td>☐ REFLEX if the Multisite 3 is negative to: ☐ Comprehensive PANEXIA ☐ Other:</td>
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<td>☐ Other: ____________________________</td>
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PANEXIA™ Results - BRCA2 Positive

... The results of this analysis are consistent with the germline BRCA2 mutation S1970X, resulting in premature truncation of the BRCA2 protein at amino acid position 1970. Although the exact risk of breast and ovarian cancer conferred by this specific mutation has not been determined, ... Additionally, studies have shown that BRCA2 mutations confer as much as a 7% risk of pancreatic cancer by age 80 (J Med Genet 42:711-9, 2005); however, this risk may be higher in families in which pancreatic cancer has previously been diagnosed.
The results of this analysis are consistent with the germline PALB2 mutation 509delGA, resulting in premature truncation of the PALB2 protein at amino acid position 183. The exact risks of pancreatic and/or breast cancer conferred by this specific mutation have not been determined. However, studies indicate that deleterious mutations in PALB2 may confer a 2-4 fold increased risk for breast cancer (Nat Genet 39:165-167, 2007; Nature 446:316-319, 2007). Deleterious mutations in PALB2 have also been identified in families with multiple cases of pancreatic cancer (Science 324:217-218, 2009; Clin Genet 78:490-494, 2010), but the exact risk for pancreatic cancer conferred by PALB2 mutations has not been established. …
Clinical Utility of PANEXIA™ Testing

For pancreatic cancer patients and their families:

• Pancreatic cancer risk for unaffected family members
• Risks for other cancers associated with these genes
• Explanation for their cancer history
• Possibility of targeted therapy
Pancreatic Cancer Surveillance

- Consensus practice recommendations for screening in the context of a clinical trial
  - High-risk patients (10X increased risk):
    - >3 FDRs, SDRs, or TDRs with PC in same lineage
    - >2 relatives with PC, at least 1 FDR
    - Diagnosis of hereditary pancreatitis
    - Diagnosis of Peutz-Jehgers
    - BRCA1, BRCA2, or p16 carrier with >1 FDR or SDR with PC
  - No standard protocol for clinical screening -- ultimately depends on knowledge level of provider, facility protocol, and technology available

Brand, 2007
Tempero, 2010
Pancreatic Cancer Surveillance

- 45y or 15 years before earliest diagnosis in family
  - Evidence of genetic anticipation
  - Smoking lowers age of onset

Endoscopic Ultrasound (EUS)
- Most sensitive, no radiation exposure, sample lesions for diagnosis
- Expensive, invasive, operator-dependent

Endoscopic Retrograde Cholangiopancreatigraphy (ERCP)
- Highly sensitive
- Invasive, significant morbidity

Magnetic Resonance Cholangiopancreatigraphy (MRCP)
- Sensitive, no radiation exposure
- Expensive, limited availability, time-consuming

CT
- Not sensitive for smaller lesions or background pancreatitis

Brand, 2007
Risk Management for Other Cancers

**BRCA2: NCCN Guidelines for HBOC**
- Breast and ovarian cancer risks

**PALB2: Breast Cancer Risk Management**
- Formal surveillance guidelines not established
- Given lifetime breast cancer risk, guidelines for family history
  - Initiate screening at younger ages
  - Increased frequency of screening
  - Use of MRI, mammography, BSE, CBE
- No guidelines regarding chemoprevention or RRPM in PALB2 carriers

Bevers, 2009
Daly, 2010
Treatment Considerations

- Certain chemotherapeutic agents may be especially effective in patients with mutations in genes that are part of the Fanconi Anemia/BRCA DNA repair pathway
  - *PALB2, BRCA2* and *BRCA1* are part of this pathway
- PC in mutation carriers may be particularly sensitive to
  - DNA damaging agents, including mitomycin C, platinum-based
  - PARP inhibitors
- NCCN guidelines suggest certain patients with inherited forms of PC, including *PALB2* or *BRCA1/BRCA2* mutations, may benefit from gemcitabine in combination with a platinum agent

Tempero, 2010
**PALB2 and Familial Breast Cancer**

- **BRCA1 and BRCA2** mutations most frequent cause of HBOC
- Mutations in several other genes such as, *PTEN, p53, CHEK2, ATM, CDH1, BRIP1, RAD51* and **PALB2**, are also associated with an increased risk of breast cancer
- Mutations in some of these genes also increase risks for various other cancers
- Clinical utility of identifying mutations in these genes for management of breast cancer risk based on:
  - consideration of their relative frequency as a cause of hereditary breast cancer
  - their overall impact on breast cancer risk
  - access to clinical testing and
  - the availability of guidelines for medical management of mutation carriers
Summary

- Pancreatic cancer is a feature of many hereditary cancer syndromes
- PANEXIA™ (sequencing of PALB2 and BRCA2) is a test for patients with a significant personal and/or family history of pancreatic cancer who do not fit into another syndrome
- Results from PANEXIA™ testing can provide patients and their families with information about risks for pancreatic cancer, as well as other cancers, most notably breast and ovarian cancer
Summary

- Initially, there will be uncertainty about the best medical management strategy for patients who test positive, much as there was uncertainty when testing began for BRCA1 and BRCA2.
- PALB2 gene sequencing is available for patients who test negative for mutations in BRCA1 and BRCA2, and may be considered appropriate for some patients at high risk for inherited breast cancer risk.
- Myriad will initially focus our marketing and educational efforts on cancer genetic and pancreatic cancer specialists.
Thank you for your time and attention

Any questions regarding PANEXIA™
Please contact Myriad Genetic Laboratories Medical Services at 800-469-7423, X 3850
or
helpmed@myriad.com
or
your local Regional Medical Specialist