Outline

• General concepts
• Hereditary cancer syndromes associated with gynecological cancers
  • Common Syndromes
    • Hereditary Breast and Ovarian Cancer Syndrome (HBOC)
    • Lynch Syndrome
  • Rare Syndromes
    • Cowden Syndrome
    • Peutz-Jeghers Syndrome
  • New Genes
• Assessment for a hereditary cancer syndrome
• Changing landscape of genetic testing
• Case vignette

GENERAL CONCEPTS
Cancer prevalence in 2012 (SEER):
- 622,000 (Endometrial ca)
- 192,000 (Ovarian ca)

Approximate prevalence of Hereditary Endometrial/Ovarian Ca cases:
- ~81,000

Flags for Hereditary Cancers
- Ovarian, fallopian tube, peritoneal cancer at any age
- Uterine cancer diagnosed at age 50 or under
- Multiple primary cancers in one person
- Multiple close family members with ovarian/uterine & other cancer types in the same side of the family

Common Features of Hereditary Cancer Genes
- NOT sex-linked
- Normal functions: tumor suppression, DNA mismatch repair, cell division checkpoint
- Heterozygous mutation status (only one gene copy, or allele, bears a mutation) usually results in increased lifetime risks for cancer
- Homozygous mutation status (both gene copies, or alleles, bear a mutation) usually results in rare clinical features
- Inheritance is usually autosomal dominant
- High penetrance and variable expressivity
HEREDITARY CANCER SYNDROMES

Common Syndromes: Hereditary Breast and Ovarian Cancer Syndrome (HBOC)

HEREDITARY CANCER SYNDROMES

HBOC

- Caused by germline mutations in BRCA1 and BRCA2
- Accounts for as much as 20% of all invasive ovarian cancer cases and the majority of hereditary breast cancer (Castera 2014, Zhang 2011)
- Associated with increased lifetime risks for breast, ovarian, prostate, pancreatic cancer (Mono-allelic mutations)
  - BRCA2 bi-allelic mutations: Fanconi anemia
- Penetrance: Incomplete
- Prevalence: 1/300-1/800
- Founder mutations in specific populations (Ashkenazi Jewish (Unselected carrier rate 1/40; Breast ca carrier rate: ~1/10), Bahamian (Unselected carrier rate: 1/1000; Breast ca cases carrier rate: ~1/5) (Akkari et al 2013, Rubinstein et al 2004, Trotier 2015)
- Genotype-phenotype correlations are complex but present
### Lifetime Cancer Risks Through Age 70 for HBOC vs. General Population

(Adapted from NCCN 2015)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>BRCA1+ Risk</th>
<th>BRCA2+ Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>12%</td>
<td>50-80%</td>
<td>40-70%</td>
</tr>
<tr>
<td>Second Primary Breast</td>
<td>11%</td>
<td>Up to 64%</td>
<td>Up to 64%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>&lt;2%</td>
<td>24-40%</td>
<td>11-18%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1%</td>
<td>1-3%</td>
<td>2-7%</td>
</tr>
<tr>
<td>Male Breast</td>
<td>&lt;1%</td>
<td>1-2%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Prostate</td>
<td>&lt;15%</td>
<td>&lt;30%</td>
<td>&lt;40%</td>
</tr>
</tbody>
</table>

### HBOC Breast/Ovarian Management

NCCN, 2015

#### WOMEN

- Breast:
  - Breast awareness starting at age 18
  - Clinical breast exam every 6-12 mo and breast MRI annually starting at age 25
  - Breast MRI and mammogram annually between ages 30-75
  - For women s/p treatment, screening of the remaining breast tissue with breast MRI and mammogram annually
  - Discuss risk-reducing mastectomy
  - Discuss chemoprevention options

- Ovarian:
  - Risk-reducing BSO between ages 35-40 or after completion of childbearing
  - Consider screening with transvaginal US and CA-125 after age 30
  - Discuss chemoprevention options

#### MEN

- Breast self-exam training at age 35
- Clinical breast exam every 6-12 mo starting at age 35
- Consider mammogram at age 40, then annually based on findings

### HBOC Other Management

NCCN, 2015

#### MEN

- Prostate screening starting at age 40 with annual digital rectal exams and PSA

#### MEN and WOMEN

- No specific guidelines for pancreatic cancer and melanoma. Personalized recommendations may exist based on family history.
- Education regarding signs and symptoms of cancers
- Patients of reproductive age:
  - Discussion about options for prenatal diagnosis and assisted reproduction (Pre-Implantation Genetic Diagnosis - PGD)
  - Discussion of reproductive risks related to Fanconi anemia for BRCA2 positive individuals
HBOC Genotype-Phenotype Correlations

Association of Type and Location of BRCA1 and BRCA2 Mutations With Risk of Breast and Ovarian Cancer

Hepatic Health South Florida
Combating Medical Illnesses
Genetic testing for BRCA1/2 genes is common practice among general practitioners, breast/GYN specialists, and cancer genetics centers.

When to offer BRCA testing? (NCCN 2015) (1/2)

- Ovarian cancer diagnosis at any age
- Breast cancer diagnosis and any of the following:
  - Age at diagnosis ≤ 45
  - Age at diagnosis ≤ 50 AND any of the following:
    - An additional breast ca primary
    - ≥ 1 close relative with BC at any age, pancreatic or prostate ca (Gleason score ≥7)
    - Limited family history
  - Any age at diagnosis AND any of the following:
    - ≥ 2 individuals with BC, pancreatic or prostate ca in the same side of the family
    - ≥ 1 close relative with BC diagnosed ≤ 50 or ovarian ca at any age
    - Ashkenazi Jewish ancestry
    - Prior history of ovarian/fallopian tube cancer
    - Triple negative histopathology diagnosed at ≤ age 60
    - Male breast ca

When to offer BRCA testing? (NCCN 2015) (2/2)

- Prostate cancer diagnosis (Gleason score ≥7) AND ≥ 1 close blood relative with any of the following:
  - Breast cancer ≤ age 50
  - Invasive ovarian cancer
  - Pancreatic cancer
  - Prostate cancer (Gleason score ≥7)

- Pancreatic cancer diagnosis AND any of the following:
  - Ashkenazi Jewish ancestry
  - ≥ 1 close blood relative with any of the following:
    - Breast cancer ≤ age 50
    - Invasive ovarian cancer
    - Pancreatic cancer
Common Syndromes:
Lynch Syndrome

HEREDITARY CANCER SYNDROMES

Lynch Syndrome

- Generally caused by mutations in DNA-mismatch-repair genes (MLH1, MSH2, MSH6, PMS2) and EPCAM gene deletions
- Accounts for ~1% of all endometrial cancer cases and 1-3% of all colorectal cancer cases
- Associated with increased lifetime risks for endometrial, ovarian, colorectal, stomach cancer (Mono-allelic mutations)
  - Bi-allelic mutations: Constitutional Mismatch Repair Deficiency - CMMRD
- Gene-dependent lifetime cancer risks and surveillance recommendations
- Penetrance: Incomplete
- Prevalence: ~1/400

Cancer General Population Risk MLH1/MSH2 MSH6 PMS2

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>MLH1/MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>~6%</td>
<td>40-80%</td>
<td>44-61 yr</td>
<td>10-22%</td>
</tr>
<tr>
<td>Endometrium</td>
<td>~3%</td>
<td>25-60%</td>
<td>48-62 yr</td>
<td>16-28%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>~2%</td>
<td>4-24%</td>
<td>43 yr</td>
<td>1-11%</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>1-13%</td>
<td>56 yr</td>
<td>&lt;4%</td>
</tr>
</tbody>
</table>

Other cancers with increased lifetime risks <10% primarily associated with MLH1/MSH2 mutations:
- Hepatobiliary and urinary tract, small bowel, brain/CNS, sebaceous neoplasms, pancreatic.
Prophylactic hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) should be considered by women who have completed child-bearing.

Patient awareness about dysfunctional bleeding (evaluation needed)

Annual office endometrial sampling and/or ultrasound is optional.

Annual or semi-annual routine ovarian screening with transvaginal US and CA-125 is optional.

Increased breast cancer risk? Currently, average-risk breast cancer screening recommendations are supported.

GI/GU/CNS:
- Colonoscopies every 1-2 yr starting at age ~20 (MLH1/MSH2/EPCAM) or ~25 (MSH6/PMS2)
- Consider annual urinalysis starting at ages 25-30
- Consider annual endoscopy with extended duodenoscopy every 3-5 yr starting at ages 25-30
- Annual physical/neurological exam starting at ages 25-30

Patients of reproductive age:
- Discussion about options for prenatal diagnosis and assisted reproduction (Pre-Implantation Genetic Diagnosis - PGD)
- Discussion of reproductive risks for CMMRD

Germline diagnostic molecular testing
- Sequencing and deletion/duplication analysis of MMR genes associated with LS

Screening tests (colon and endometrial tissue):
- IHC: staining tumor tissue for protein expression of the 4 MMR genes associated with Lynch Syndrome.
  - Normal IHC result: All 4 MMR proteins are normally expressed (LS unlikely)
- MSI: PCR analysis of microsatellite markers to assess for MMR function
  - MSI-H (microsatellite instability-high) tumors: Changes in 2 or more of the 5 microsatellite markers are detected (LS likely)

Many centers perform IHC and sometimes MSI in all newly diagnosed CRC and endometrial cancer cases regardless of family history. (Universal Tumor Screening)
Rare Syndromes:
Cowden Syndrome
HEREDITARY CANCER SYNDROMES

Cowden Syndrome
- Caused by germline mutations in the PTEN tumor suppressor gene (New gene: KILLIN)

- Nomenclature: Cowden Syndrome is part of a clinical spectrum associated with PTEN mutations (PTEN Hemartomatous Tumor Syndrome - PHTS)

- Highly variable presentation associated with benign findings and increased risk for malignancy (Relevant clinical scenarios: GYN, pediatrics, neurology, GI, oncology, breast surgery, dermatology...)

- Penetrance: Incomplete

- Prevalence: ~1/200,000 (underestimate)

Clinical Dx: Major Criteria
- Breast cancer
- Endometrial cancer
- Thyroid cancer
- Multiple GI hemartomas or ganglioneuromas
- Macrocephaly
- Skin lesions (macular pigmentation of glans penis, trichilemmomas, etc.)

Clinical Dx: Minor Criteria
- Autism spectrum disorder
- Colon cancer
- Intellectual disability
- Lipomas
- Renal cell carcinoma
- Vascular anomalies
### Lifetime Cancer Risks Through Age 70 for Cowden Syndrome vs. General Population

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>PTEN Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>~12%</td>
<td>25-50%*</td>
</tr>
<tr>
<td>Endometrial</td>
<td>~3%</td>
<td>5-10%*</td>
</tr>
<tr>
<td>Thyroid</td>
<td>~1%</td>
<td>3-10%*</td>
</tr>
<tr>
<td>Colorectal</td>
<td>~6%</td>
<td>9-16%</td>
</tr>
</tbody>
</table>

*Risks from other studies are higher
- Breast cancer: 75-85%
- Thyroid: 35-38%
- Endometrial: up to 28%
- Renal: up to 34%

Tan et al 2012; Riegert-Johnson DL et al 2010; Buvien V1 et al 2013 (Ascertainment bias)

### Cowden Syndrome Breast/Endometrial Management NCCN, 2015

**WOMEN**
- Breast awareness starting at age 18
- Clinical breast exam every 6-12 mo starting at age 25
- Breast MRI and mammogram annually between ages 30 or 35-75
- For women s/p treatment, screening of the remaining breast tissue with breast MRI and mammogram annually
- Discuss risk-reducing mastectomy

**Endometrial**
- Consider annual endometrial sampling and/or ultrasound starting at age 30-35
- Patient awareness about dysfunctional bleeding
- Discuss risk-reducing hysterectomy

### Cowden Syndrome Other Management NCCN, 2015

**MEN and WOMEN**
- Annual comprehensive physical exam starting at age 18 with particular attention to thyroid exam
- Annual thyroid ultrasound starting at the time of diagnosis
- Colonoscopies every 5 yr starting at age 35 unless symptoms or a personal history of polyps are present
- Consider renal ultrasound every 1-2 yr starting at age 40
- Consider dermatology management
- Consider psychomotor assessment in children at diagnosis and brain MRI if there are symptoms
- Education regarding the signs and symptoms of cancers
- Patients of reproductive age:
  - Discussion about options for prenatal diagnosis and assisted reproduction (Pre-Implantation Genetic Diagnosis –PGD)
Peutz-Jeghers Syndrome

Caused by germline mutations in STK11.

Variable clinical presentation associated with benign features and increased risk for malignancy (Possible clinical scenarios: GYN, GI, oncology, breast surgery...). Clinical diagnostic criteria are available.

Penetrance: Complete

Prevalence: 1/25,000-1/280,000

Lifetime Cancer Risks Through Age 70 for Peutz-Jeghers Syndrome vs. General Population

(Adapted from NCCN 2015)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>STK11 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>~12%</td>
<td>45-50%*</td>
</tr>
<tr>
<td>Colorectal</td>
<td>~6%</td>
<td>39%</td>
</tr>
<tr>
<td>Stomach</td>
<td>~1%</td>
<td>29%</td>
</tr>
<tr>
<td>Small intestine</td>
<td>&lt;1%</td>
<td>13%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>~1%</td>
<td>11-36%</td>
</tr>
<tr>
<td>Ovarian (non-ovarian)</td>
<td>~2%</td>
<td>18-21%</td>
</tr>
<tr>
<td>Cervical</td>
<td>~1%</td>
<td>10%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>~3%</td>
<td>9%</td>
</tr>
<tr>
<td>Lung</td>
<td>~7%</td>
<td>17-17%</td>
</tr>
<tr>
<td>Peutz-Jeghers Breast/GYN Management NCCN, 2015</td>
<td></td>
<td></td>
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<tr>
<td>------------------------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>• Mammogram and breast MRI annually starting at age 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clinical breast exams every 6-12 mo starting at age 25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pelvic exam and PAP-smear annually starting at age 18-20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Consider annual transvaginal US starting at age 18-20</td>
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<table>
<thead>
<tr>
<th>Peutz-Jeghers Other Management NCCN, 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Colonoscopy and upper endoscopy every 2-3 yr starting in the late teens</td>
</tr>
<tr>
<td>• Magnetic resonance cholangiopancreatography or endoscopic US every 1-2 yr starting at age 30-35</td>
</tr>
<tr>
<td>• Small bowel visualization starting at age 8-10 (CT/MRI enterography baseline at age 8-10 with follow up interval based on findings but at least by age 18, then every 2-3 yr)</td>
</tr>
<tr>
<td>• Smoking cessation</td>
</tr>
<tr>
<td>• Education regarding signs and symptoms of cancers</td>
</tr>
<tr>
<td>• Patients of reproductive age:</td>
</tr>
<tr>
<td>• Discussion about options for prenatal diagnosis and assisted reproduction (Pre-Implantation Genetic Diagnosis –PGD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New genes HEREDITARY CANCER SYNDROMES</th>
</tr>
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<tbody>
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</tbody>
</table>
New Genes

- **BRIP1, RAD51C, RAD51D**: 10-15% lifetime risk for ovarian cancer
- **SMARCA4**: Small cell ovarian carcinoma, hypercalcemic type- no lifetime risk estimates yet available
- **DICER1**: Sex-cord and stromal ovarian tumors- No lifetime risk estimates yet available
- **POLD1**: Endometrial cancer and clinical presentation similar to Lynch Syndrome- No lifetime risk estimates are yet available
- **PALB2? CHEK2?**

**ASSESSMENT FOR A HEREDITARY CANCER SYNDROME**

- Ideally performed by professionals with expertise in cancer genetics (genetic counselors, physicians, advanced practice nurses)

**Pre- and Post-Test Counseling**

- Targeted medical history intake
- Detailed family history intake
- Education
- Informed consent and decision-making/Counseling
- Test facilitation
- Results disclosure and follow-up
- Identification of available support resources
**Assessment for a Hereditary Cancer Syndrome**

**Targeted medical history intake**
- Cancer history (Pathology, age at diagnosis, laterality, treatment)
- Screening and relevant findings (Breast/GYN/GI)
- Carcinogen exposure (i.e. mantle radiation)
- Reproductive history
- Hormone and oral contraceptive use
- Dermatological features commonly associated with hereditary cancer syndromes
- Ethnicity
- Genetic testing history (Year performed, name of the test, name of the laboratory, copy of the report!)

**Assessment for a Hereditary Cancer Syndrome**

**Detailed family history intake**
- Three generation pedigree to include first-, second-, and third-degree relatives (FDR, SDR, TDR, respectively)
  - FDR: parents, siblings, children
  - SDR: grandparents, uncles, aunts, nieces, nephews, grandchildren, half-siblings
  - TDR: first cousins, great-grandparents, great-aunts, great-uncles, great-grandchildren
- Types of cancer, laterality, age at diagnosis
- **Pay attention to risk assessment confounders! (Adoption, early death, TAH/BSO for reasons unrelated to cancer)**

**Assessment for a Hereditary Cancer Syndrome**

**Education**
- Basic genetics (Genes, inheritance, penetrance, variable expressivity)
- Risk factors for a hereditary cancer susceptibility
- Hereditary cancer syndromes of interest
- Testing strategies
- Genetics Information and Non-Discrimination Act (GINA)

**Informed consent and decision-making/Counseling**
- Possible results and plan to manage them
- Timing
- Coping strategies and support system
- Impact of results on personal health and relationships
Assessment for a Hereditary Cancer Syndrome

Test facilitation
- Choosing a laboratory
- Clinical appropriateness of the test
- Cost effectiveness
- Turn-around time
- Completing appropriate documentation
- Communicating regularly with testing laboratory and insurance company about documentation and authorizations

Assessment for a Hereditary Cancer Syndrome

Results disclosure and follow-up
- In-person/telephone disclosure
- Referral to genetic specialists for complex results should be considered if a genetic specialist is unavailable during pre-test counseling
- Referral to research/national registries available for patients with positive results or variants of unknown significance

Assessment for a Hereditary Cancer Syndrome

Identifying support resources
- FORCE
- SHARSHERET
- ClinicalTrials.gov
CHANGING LANDSCAPE OF GENETIC TESTING

Changing Landscape of Genetic Testing

- Multi-gene panel testing was introduced in 2012 in clinical practice (Technological advancements parallel to ethical/legal changes)
- Syndrome-driven and multi-gene panel testing options are currently widely used
- General indications to consider panel testing:
  - Personal and family history strongly suggestive of a hereditary component
  - The personal/family history could be explained by 2 or more hereditary cancer syndromes
- Multi-gene panels, though popular, are not currently the standard of care

Multi-gene Panel Testing

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased diagnostic yield</td>
<td>Increased likelihood of variants of unknown significance</td>
</tr>
<tr>
<td>Minimized testing fatigue</td>
<td>Limited clinical utility for moderate-risk genes</td>
</tr>
<tr>
<td>May open unforeseen opportunities for prevention</td>
<td>Incident results</td>
</tr>
<tr>
<td>Cost effectiveness (*)</td>
<td>Wide variation among testing laboratories</td>
</tr>
</tbody>
</table>
Professional Statements on Multi-gene Panel Testing

- **National Comprehensive Cancer Consortium Network (NCCN) (2015)**
  "Multi-gene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling"

- **Society of Gynecologic Oncology (SGO) (2014)**
  "Advantages of cancer gene panels include decreased cost and improved efficiency of cancer genetic testing by reducing the time involved, number of patient visits, and number of tests sent... Involvement of a cancer genetics professional is important to help order the most appropriate genetic test and to interpret the results."

---

**CLINICAL VIGNETTES**

### Case #1

- 26 yo G1P1 premenopausal Hispanic female
- Referred by GYO for consideration of multi-gene panel testing due to a personal and family history of cancer
- Personal history of an endometroid adenocarcinoma of the right ovary diagnosed at 23
- The patient is s/p unilateral salpingo-oophorectomy and omentectomy.
- Followed with CT scan, transvaginal US, and CA-125 every 3 mo
- **BRCA1/2** sequencing and deletion analysis done in early 2015 with negative results
Case #1
- Topics of discussion during pre-test counseling session:
  - Flags for a hereditary cancer susceptibility syndrome (targeted assessment)
  - Availability of multi-gene panel testing
  - Differences between high- and moderate-risk gene mutations
  - Potential impact of positive, negative results, or variants of unknown significance
  - Increased lifetime risk for breast cancer (23-30%) (Tyrer-Cuzick v6, v7)
- Test of choice:
  - 22-gene breast and GYN cancers panel
- Results:
  - "Negative result. No Pathogenic sequence variants or deletions/duplications identified."

CONSIDERATIONS FOR POST-TEST COUNSELING
- What does a negative result mean in this context?
- Should genetic testing be considered in other family members?
- What does risk-management entail for unaffected family members?
Case #2

- 54 yo G2P2 postmenopausal Middle Eastern female
- Referred by her breast surgeon due to a family history of ovarian cancer
- Followed by GYN with yearly mammograms, transvaginal US and CA-125 screening every 6 mo
- Menarche at 12; menopause at 52
- No history of OCP use
- No history of hormonal therapy

Topics of discussion during pre-test counseling session:
- Limitations of genetic testing in unaffected individuals
- Availability of syndrome-driven and multi-gene panel testing
- Differences between high- and moderate-risk gene mutations
- Potential impact of positive, negative results, or variants of unknown significance
- GINA

Test of choice:
- 25-gene cross-cancer panel

Results?
“Positive- Clinically significant mutation identified. 
**BRIP1**, dup exon 17 (Heterozygous) 
This patient has BRIP1-associated Cancer Risk.”

**CONSIDERATIONS FOR POST-TEST COUNSELING**
- What does a positive result mean in this context?
- Should genetic testing be considered in other family members?
- What does risk-management entail for unaffected family members?
- Discuss importance of testing affected sister

Case #2
- Affected sister presents for genetics evaluation
- 25-gene cross cancer panel ordered
- Result?

“Negative- No clinical significant mutation identified”

**CONSIDERATIONS FOR POST-TEST COUNSELING**
- Is there room for confirmatory testing?
  - New samples sent to original laboratory
  - Blind samples sent to second laboratory
- Should genetic testing for the **BRIP1** mutation be considered in other family members?
- What does risk-management entail for unaffected family members who test negative for the **BRIP1** mutation?

**Clinical Pearls**
- GYN/GYO MDs and allied health professionals have a major role in identifying patients at increased risk of inherited cancer syndromes
- New genetic testing strategies may bring about complex test results
- Genetic testing availability is continuously changing
- Genetics follow-up is important in some cases
- The hereditary bases of GYN cancers is an unfinished story
Thank you!
References


