Gynecologic Cancer Genetics

UCSF Obstetrics and Gynecology Update: What Does the Evidence Tell Us?
October 24, 2014

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October 24, 2014

Disclosure

• I have served as a moderator for an advisory board to Genentech
• UCSF has conducted clinical trials using bevacizumab, olaparib, veliparib, rucaparib

Audience response

Have you sent a cancer genetic test for one of your patients?

1. Yes
2. No

A. Positive
B. Negative
C. Variant of unknown significance
D. Don’t know

What was the result?

- Positive: 60%
- Negative: 40%
- Variant of unknown significance: 19%
- Don’t know: 22%
**Objectives**

- To describe Society of Gynecologic Oncology’s initiatives towards identifying women at risk for hereditary gynecologic cancer syndromes
- To describe the complexities of direct to consumer genetic testing, and the significance of genetic counseling
- To outline management options, including screening, risk-reducing surgery, and personalized cancer care

**Audience response**

What genetic counseling did your patient receive before testing?

- A. Genetic counselor
- B. MD Provider
- C. Did not get counseling

<table>
<thead>
<tr>
<th>Genetic counselor</th>
<th>MD Provider</th>
<th>Did not get counseling</th>
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<tbody>
<tr>
<td>60%</td>
<td>33%</td>
<td>8%</td>
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**Image**: The image shows a cover of TIME magazine with the title "The ANGELINA EFFECT". The subtitle reads, "The Purely Theoretical, Gynologically Significant, Family History Disease". A woman is shown holding a sign that says, "FREE OUR GENES!" alongside another sign that reads, "No One Should Own Our DNA!". The image is related to the advocacy for genetic counseling and personalized cancer care.
Next Generation Genetic Testing

BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2

APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D

Universal testing?

Population-Based Screening for BRCA1 and BRCA2

2014 Lasker Award

Based on our 20 years’ experience working with families with cancer-predisposing mutations in BRCA1 and BRCA2, it is time to offer genetic screening of these genes to every woman

Taking a Family History

Features of Hereditary Cancer

• Young ages at cancer diagnosis
• Multiple primary tumors in the same individual
• Bilateral cancers in paired organs (for example, both breasts)
• Multiple family members with cancer in two or more generations
• Types of cancer seen in known hereditary cancer predisposition syndromes
Hereditary Breast-Ovarian Cancer

- Breast cancer diagnosed before age 50
- 2 or more relatives with breast cancer
- Male relative with breast cancer
- Bilateral breast cancer or multiple primaries in the same breast
- Breast cancer and Ashkenazi, or Eastern European Jewish, ancestry
- Ovarian cancer (epithelial; non-mucinous) at any age

Patient 1

49yo G1P1 with BRCA1 mutation

Laparoscopic bilateral risk-reducing salpingo-oophorectomy

Right ovary with < 1cm microscopic focus of high grade papillary serous carcinoma

- Washings
- Remove entire ovaries & tubes
- Frozen section for suspicious lesions only
- Serial sectioning, including entire fimbriae


Patient 1

Staging offered.
Patient elected expectant management.

6 years later
CA125 9→14→40→28→508 over 2 years

CT: Multiple peritoneal implants in the omentum

Exploratory laparotomy, total abdominal hysterectomy, bilateral pelvic & para-aortic lymphadenectomy, omentectomy, tumor debulking, intraperitoneal port placement→ High grade serous carcinoma→ Stage IIIC peritoneal carcinoma
**Patient 1**

IV/IP paclitaxel & cisplatin x 6 cycles, then observation

CA125 = 7, CT c/w complete response

3 years later

CA125 14→ 36→ 39→ 51→ 78 over 1 year

PET/CT → 1.5cm left supraclavicular lymph node, left pleural effusion, nodularity, mediastinal lymphadenopathy, no evidence of disease in abdomen & pelvis

Fine needle aspiration positive for adenocarcinoma

Options:

Veliparib clinical trial

Carboplatin, gemcitabine, +/- bevacizumab

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**PARP Inhibition**

DNA damage (SSBs)

DNA replication (accumulation of DNA DSBs)

Normal cell with functional HR pathway

Impaired HR-mediated DNA repair

HR-deficient tumor cell (e.g. BRCA1/2-/-)

Cell survival

Cell death

Tumor-selective cytotoxicity

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**Olaparib—Phase II**

Phase II trial in BRCA-deficient advanced ovarian cancer, 2 sequential cohorts, 12 sites, 6/07-3/08

n=57, 33 at 400mg BID, 24 at 100mg BID

Confirmed BRCA1 or BRCA2 mutation

Measurable disease

Good performance status (ECOG 0-2)

Response rate 400mg 100mg BID BID

RECIST (radiology) 33% 13%

GCIG (incl CA125) 61% 17%

Median duration of response 9.6 mo. 9.0 mo.

Audeh et al, Lancet, 2010

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**Olaparib & High grade serous ovarian cancer**

Four cohorts: Triple negative breast cancer, BRCA1/2 associated breast cancer, High grade serous ovarian cancer, BRCA1/2 associated ovarian cancer

n=23 breast cancer, 63 ovarian cancer patients, Olaparib 400mg BID

No breast cancer patients responded

41% RECIST response in BRCA1/2-positive ovarian cancer

24% RECIST response in BRCA1/2-negative ovarian cancer

Gelmon et al, Lancet Oncol 2011
Olaparib Maintenance

N=265
Platinum sensitive ovarian cancer patients in 2nd or 3rd remission, randomize to Olaparib 400mg BID versus placebo

Progression-free survival: 8.4 versus 4.8mo.
HR 0.35, 95% CI 0.25-0.49
Overall survival (at 58% maturity): HR 0.88
For BRCA mutation carriers: 11.2 versus 4.3 mo.
HR 0.18, 95% CI 0.11-0.31


Veliparib

GOG #280
N=52, BRCA1 or BRCA2 mutation carriers with recurrent/persistent ovarian/tubal/peritoneal cancer and measurable disease
400mg PO BID

30 platinum-resistant, 20 platinum-sensitive
Median number of cycles: 5.5, 48% with dose reduction
26% response rate (90% CI, 15-38). 1 CR, 12 PR
Median PFS: 8.1 months (90% CI, 5.5-8.8)
Toxicities: fatigue, nausea, vomiting, anemia
Coleman et al, SGO 2014

Rucaparib

ARIEL 2: Phase II study of rucaparib in platinum-sensitive ovarian/tubal/peritoneal cancer
Tissue biopsies pre- and post-treatment will help define subgroups of patients with homologous recombination defects
15 BRCA1/2 mutation carriers
165 BRCA1/2 negative

ARIEL 3: Phase III study of rucaparib as maintenance following platinum-based chemotherapy for patients with platinum sensitive ovarian/tubal/peritoneal cancer

Causes of Ovarian Cancer

Sporadic
BRCA1 (~70%)
Familial (5%-10%)
Hereditary (~8%)
Other single genes (~2%)
LYNCH (~2%)
Genetic Evaluation

N= 360 consecutive women with primary ovarian, tubal, peritoneal cancer
Screened for 21 germline mutations by genomic sequencing

11% BRCA1
6% BRCA2
6% Other: BARD1, BRIP1, CHEK2, MRE11A, MSH6, NBN, PALB2, RAD50, RAD51C, or TP53

31% with no family history of breast/ovarian cancer
63% less than age 60

Walsh et al, Proc Natl Acad Sci USA 2011

SGO Clinical Practice Statement: Genetic Testing for Ovarian Cancer
October 2014

Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of a family history.
Genetic Evaluation

SGO Clinical Practice Statement: Next Generation Cancer Gene Panels Versus Gene by Gene Testing
March 2014

Cancer gene panels use next generation sequencing technology to assess inherited mutations in multiple genes simultaneously and are currently commercially available. Current cancer gene panels vary in size from just two genes (i.e., BRCA1 and BRCA2) to larger panels that include more than 50 genes. However, health care providers need to consider the limitations as well as the advantages of the cancer gene panels.

Patient 2

49yo G0 with Stage IIC high grade serous ovarian carcinoma.

PMHx: Benign breast lump, precancerous skin lesions

FHx: Father with colon cancer in 70s
Sister with breast cancer at age 49. BRCA1/2 neg.
Maternal grandmother with breast cancer in 70s

GeneDx Breast/Ovarian Panel→
PMS2 (400C>T) mutation AND
PALB2 (172_175delTTGT) mutation

Consequences of Panel Testing

UT Southwestern
April 2012-January 2013
N=50 next-generation sequencing panels
10% positive result
30% variant of uncertain significance or variant suspect benign

Kaiser Northern California
N=69 VUS, 30% RRSO, 11% RRM, 56% reclassified

Mauer et al, Genet Med 2014
Garcia et al, Genet Med 2014
Managing BRCA1 & BRCA2 Mutation Carriers

Surveillance recommendations

- Breast examination and annual mammography/MRI, beginning at age 25 (or earlier based on family history)
- Pelvic examination, CA125, pelvic ultrasound every 6 months, beginning at age 30 (or earlier based on family history)
- Recommend risk-reducing salpingo-oophorectomy between ages 35-40, or on completion of childbearing

Also consider oral contraceptives for ovarian cancer risk reduction

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Other mutations besides BRCA1&2

- BRIP1: 1.4% of ovarian cancer cases, 10-15% lifetime risk for ovarian cancer
- RAD51D: 0.6% of ovarian cancer cases, 10-15% lifetime risk for ovarian cancer
- RAD51C: 0.5% of ovarian cancer cases, 10-15% lifetime risk for ovarian cancer
- PALB2?
- BARD1?
- ATM?

PROSper
Prospective Research on Salpingo-oophorectomy

Do you have a BRCA1 or BRCA2 mutation?

PROSper is a research study that aims to evaluate the impact of salpingo-oophorectomy on ovarian cancer risk among BRCA1 and BRCA2 mutation carriers. If you are interested in participating, please contact the research coordinator at 1-877-692-7895.

Rafnar et al, Nat Genet 2011
Loveday et al, Nat Genet 2011
Loveday et al, Nat Genet 2012
Peltari et al, J Med Genet 2012

PROSper provides travelers with information on how to reduce their risk of ovarian cancer, including the potential benefits and side effects of salpingo-oophorectomy.

PROSper does not provide medical advice or treatment. It is important to consult with your healthcare provider before making any decisions about your health.
Genetic Evaluation—clinical benefits

**Decision making for treatment**
- Better short term prognosis (Bolton et al, 2012)
- Favor platinum or Doxil chemotherapy over taxane or topotecan (Safra et al 2014)

**Opportunities for clinical trials**
- PARP inhibitors (Audeh et al 2010, Lederman et al 2014)

**Cancer prevention: personal, family**
- Breast cancer screening by MRI (Sung & Dershaw 2013)
- Risk-reducing surgery (Domchek et al, 2010)

Ovarian Cancer Survival

**Progress is noted over time**
- Surgery
- Chemotherapy
- Targeted therapies
- Genetics

Amsterdam II Criteria

- International Collaborative Group on HNPCC
- Histologically verified Lynch-associated cancer in $\geq 3$ relatives, one of whom is a first degree relative of the other two
- 2 successive generations
- At least 1 diagnosed before age 50
- Lynch-associated cancer = bowel, endometrial, ureter, renal pelvis

SGO Clinical Practice Statement: Screening for Lynch Syndrome in Endometrial Cancer
March 2014

All women diagnosed with endometrial carcinoma should undergo systematic clinical screening (review of personal and family history) and/or molecular screening for Lynch syndrome, a hereditary cancer syndrome.
**Lynch Testing through Pedigree**

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**Identification of Women at Risk**

N=117 women from Lynch families with dual gynecologic and colorectal cancers from 5 Lynch registries

14% patients with synchronous cancers

51% with gynecologic cancer first
- Median age 44, time to second cancer 11 yrs
- 49% with colon cancer first
  - Median age 40, time to second cancer 8 yrs

Lu et al, Obstet Gynecol, 2005

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**Prevalence of Lynch**

543 endometrial cancer patients underwent microsatellite instability testing

118 (21.7%) MSI positive—all underwent mutation testing

10 (1.8%) patients with deleterious germline mutation
- 9 of 118 MSI positive pts—MLH1, 3 MLH2, 5 MSH6
- 1 MSI stable tumor had absence of MSH6 on IHC confirmed on germline mutation

Hampel et al, Cancer Res, 2006

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**Lynch versus HBOC Evaluation**

- **Endometrial cancer**
  - Tumor studies
  - Germline testing (MLH1, MSH2, MSH6, PMS2)
  - Panel testing available

- **Ovarian cancer**
  - Germline testing (BRCA1, BRCA2)
Tumor Studies for Lynch

- **Immunohistochemistry (IHC)**
  - Loss of staining means gene product absent

- **Microsatellite instability (MSI)**
  - Microsatellite instability a hallmark of DNA mismatch repair

- **Hypermethylation of MLH1**
  - Differentiates between somatic vs. germline cause of MLH1 loss

Testing for Lynch

**Patient 3**

67yo G1P1 with Stage II grade 3 endometrial cancer S/P LAVH/BSO/PLND/PALND

12cm FIGO grade 3 adenocarcinoma, 69% invasion, suspicious for lymphovascular space involvement, 33 lymph nodes negative, washings negative

IHC ➔ MLH1 present, MSH2 present, MSH6 present, PMS2 absent. MSI high

Germline genetic testing ➔ PMS2 mutation, 943C>T; arg315stop

Daughter tested negative for mutation

Surveillance recommendations

- Colonoscopy starting at age 20-25, or 2-5 years prior to earliest colon cancer
- Option of office endometrial biopsy annually
  - Dysfunctional uterine bleeding warrants evaluation
- Recommend risk-reducing hysterectomy & bilateral salpingo-oophorectomy on completion of child-bearing
- Consider endoscopy, urine analysis, CNS examination
SGO Genetics Summit

- Assess the current practice of genetic testing
- Identify barriers/challenges to appropriate screening, testing and patient care
- Structure a delivery care model for future practice that is current, forward-thinking and provides optimal access to testing

Summary

Genetics & Personalized care

Individualized cancer risk
- Risk-reducing surgery, salpingectomy
- Colonoscopy

Selection of systemic treatment
- Platinum-based chemotherapy
- Clinical trials: PARP inhibitors
- Tumor testing

Who to test, how to counsel?

Acknowledgements

Beth Crawford, MS CGC
Julie Mak, MS CGC
Amie Blanco, MS CGC
Joseph Rabban, MD MPH
Rebecca A. Brooks, MD
Stephanie M. Ueda, MD
Paul Watkins, Protocol Project Manager
Calvin Cheung, Clinical Research Coordinator
SGO Clinical Practice Committee