Beyond BRCA: Cancer Risk Assessment in the Era of Panel Genetic Testing

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Objectives

- To create awareness of tools available for hereditary breast and ovarian cancer (HBOC) risk assessment
- To provide an understanding of the resources available for genetic counseling
- To familiarize providers with the most common genes involved in hereditary breast and ovarian cancer
- To provide an overview of the most common other hereditary cancer susceptibility syndromes

Conflicts of Interest: None
Cancer Risk Assessment
Case Presentations
Case 1: MK

- MK is a 38 yo G2P2002 who presents to your office as a new patient for an annual exam. No current complaints.
  - PMH: anxiety
  - PSH: laparoscopic appendectomy
  - FH:
    - Mother with breast cancer at 41
    - MGM breast cancer at 48
    - Maternal aunt with breast cancer at 47
    - Maternal uncle prostate cancer 55
    - Maternal first cousin ovarian cancer 45
  - SH: teacher, occasional alcohol, no drugs or tobacco
Case 1: MK

What hereditary cancer syndrome do you suspect runs in her family?

**HBOC** – hereditary breast and ovarian cancer syndrome

Specifically, pathogenic variants in **BRCA1** and **BRCA2**
Case 2: LS

- LS is a 48 yo G1P1001 female who presents with abnormal uterine bleeding (AUB) with spotting between menstrual cycles.
  - PMH: hypertension, BMI 51
  - PSH: laparoscopic cholecystectomy
  - FH:
    - Father with colon cancer at 45
    - Paternal grandfather with colon cancer at 42
    - Paternal aunt with ovarian cancer 48
    - Paternal 1st cousin with endometrial cancer 51
  - SH: Accountant. 1/2 ppd smoker. Social alcohol, no drug use.
Case 2: LS

What disease process do you suspect may be occurring in the patient?

Endometrial cancer

What hereditary cancer syndrome may this represent?

Lynch Syndrome
Genes MSH2, MSH6, MLH1, PMS2
Case 3: JT

- Ms. JT is a 41 yo G3P3003 with a history of Stage 1 RIGHT breast invasive lobular cancer who presents her yearly exam.
  - PMH: breast cancer, diabetes
  - PSH: RIGHT lumpectomy and sentinel lymph node biopsy, cesarean section
  - FH:
    - Paternal grandfather appendiceal cancer unknown age
    - Paternal uncle with gastric cancer 35
    - Paternal first cousin gastric cancer 25.
  - SH: occasional alcohol. No drug or tobacco use.
Case 3: JT

What gene could explain the development of all the cancers in her family including the patient’s own cancer?

**CHD1**
Hereditary Cancer Susceptibility Syndromes
Why do we care...? ¹

- Lifetime risk (LTR) of cancer ≈ 40% in USA
- LTR of dying of cancer ≈ 20% in USA

https://www.nationalbreastcancer.org/breast-cancer-facts
Most cancers are not inherited

15-20% familial

5-10% inherited

70-80% sporadic

https://www.memorangapp.com/flashcards/68088/10-13%2C+Genetic+Counseling+for+Hereditary+Cancer/
Genetic mutations or pathogenic variants

Mitotic Cell Division

Parent cell

S-phase DNA replication

Two daughter cells
Cancer susceptibility: Tumor suppressors
Cancer susceptibility: Mismatch repair²

Hereditary Breast and Ovarian Cancer (HBOC)

- Families with breast and ovarian cancer
- Traditionally thought to be due to BRCA1 and BRCA2 pathogenic variants

BRCA 1 and BRCA2

- Tumor suppressors genes
- Pathogenic variants found in 1/40 of those with Ashkenazi Jewish heritage

**BRCA1 Lifetime Risk (LTR)**
- Breast cancer ~70-80%
- Ovarian cancer ~ 40%
- Prostate cancer up to 16%
- Male breast cancer 1.2%
- Increased risk of pancreatic cancer

**BRCA2 Lifetime Risk (LTR)**
- Breast Cancer ~70-80%
- Ovarian Cancer ~ 20%
- Pancreatic cancer 7%
- Male breast cancer 6.8%
- Prostate Cancer 20%
- Increased risk of melanoma
Other causes of hereditary breast cancer

• **Hereditary Cancer Syndromes**
  - Diffuse hereditary gastric syndrome (CDH1)
  - Li-Fraumeni syndrome (TP53)
  - Cowden’s syndrome (PTEN)
  - Lynch or HNPCC syndrome (MMR genes)
  - Peutz-Jegher’s syndrome (STK11)

• **Specific Genes**
  - ATM
  - BRIP1
  - CHEK2
  - NF1
  - NBN
  - PALB2
  - RAD50
  - RAD51C
  - RAD51D
Risk Assessment:
Identification of Patient’s Hereditary Cancer Risk
HBOC risk assessment

• Family History
  – Close blood relatives include:
    • 1\textsuperscript{st}: children, siblings, parents
    • 2\textsuperscript{nd}: grandparents, aunts, uncles, half-siblings
    • 3\textsuperscript{rd}: great aunt and uncles, nieces and nephews, 1\textsuperscript{st} cousins
  – Create a pedigree
  – Ask specifically about broad range of different cancer types
  – Get specifics
    • Age of diagnosis/death
    • Specific type of cancer/treatments
    • Adopted
  – Ethnic heritage
  – Update annually
Pedigree tool in MiChart/EPIC

- **Father**: Breast cancer 30y, Hypertension
- **Mother**: Ovarian cancer 40y
- **Mat Aunt**: Breast cancer 48y, Ovarian cancer

- **Patient**: 34y
Breast and HBOC risk assessment tools

- GAIL model
- Tyrer-Cuzick (IBIS)
- Claus model
- BCSC Risk Calculator
- Ontario Family History Assessment Tool
- Manchester Scoring System
- Referral Screening Tool (B-RST)
- Pedigree Assessment Tool
- FHS-7
HBOC risk calculators

- GAIL calculator
IBIS (Tyrer-Cuzick) HBOC risk calculator

- Woman's age: [ ]
- Menarche: [ ]
- Height (m): [ ]
- Weight (kg): [ ]

- Nulliparous: [ ]
- Parous: [ ]
- Unknown: [ ]

- Age of First Child: [ ]

- No prior biopsy / no proliferative disease: [ ]
  - Prior biopsy: result unknown: [ ]
  - Hyperplasia (not atypia): [ ]
  - Atypical hyperplasia: [ ]
  - Lobular Carcinoma in Situ (LCIS): [ ]

- Premenopausal: [ ]
- Perimenopausal: [ ]
- Postmenopausal: [ ]
- Age at Menopause: [ ]

- Mammographic density (age 40+): [ ]
  - % Volpara® Volumetric Density*: [ ]
  - % VAS Percentage Density*: [ ]
  - BI-RADS® ATLAS Density*: [ ]

- Ashkenazi inheritance: [ ]

- Mother: [ ]
  - Ovarian: [ ]
  - Bilateral: [ ]
  - Breast cancer: [ ]
  - Age: [ ]

- Sisters: [ ]
  - Number: [ ]
  - Ovarian: [ ]
  - Bilateral: [ ]
  - Breast cancer: [ ]
  - Age: [ ]

- Paternal Gran.: [ ]
  - Ovarian: [ ]
  - Breast cancer: [ ]
  - Age: [ ]

- Maternal Grand.: [ ]
  - Ovarian: [ ]
  - Breast cancer: [ ]
  - Age: [ ]

- Paternal aunts: [ ]
  - Number: [ ]
  - Ovarian: [ ]
  - Breast cancer: [ ]

- Maternal aunts: [ ]
  - Number: [ ]
  - Ovarian: [ ]
  - Breast cancer: [ ]

- Daughters: [ ]
  - Ovarian: [ ]
  - Breast cancer: [ ]
NCCN 2019 BRCA1/2 Testing Guidelines

- **Breast Cancer**
  - ≤ age 45
  - Triple negative ≤ age 60
  - Ages 45-60
    - 2nd primary breast cancer, ≥ 1 close relative with high grade prostate or breast cancer at any age
  - Any age
    - ≥ 1 close relative breast cancer ≤ 50, ovarian cancer, male breast cancer, metastatic prostate, or pancreatic cancer
    - ≥2 close relatives with breast cancer any age h/o pancreatic cancer
  - Male
  - Ashkenazi Jewish ancestry

- **Ovarian Cancer**
- **Pancreatic Cancer**
- **Metastatic prostate cancer**
- **Known pathogenic variant in family or tumor sample**
- **Individual with 1st or 2nd degree relative that meets the above criteria**
Genetic Counseling and Testing
Consideration for genetic testing: Which patients?

- Patients that meet NCCN guidelines for BRCA testing or other genetic testing
- Patients that have a $\geq 20\%$ lifetime risk of breast cancer
- Patients with multiple cancers in family
  - Refer to genetic counselor for a risk assessment if unsure
Genetic counseling and testing

- **Options**
  - Order test as physician or advanced practitioner
  - Refer to genetic counselor
  - Direct to consumer testing
  - Tumor genetic testing

https://www.bizjournals.com/boston/news/2018/05/15/viewpoint-ancestry-dna-testing-may-reveal-more.html#i/10260896
Provider ordered testing

- Provider must choose what genes or panels should be performed
- Be aware of different state laws for who can order genetic testing
- Companies vary with support for testing results
  - Myriad
  - Ambry Genetics
  - Invitae Labs
  - Counsyl
  - Quest Diagnostics
  - GeneDx
  - Ethigen
  - Fulgents
  - Lab Corps
- Provider responsible for accurately counseling patients
Genetic counseling

- Benefits of genetic counseling
  - Will determine if genetic testing is recommended
  - Will determine the exact genetic panel to be tested
  - Will determine risk of particular cancers based on family history and/or genetic testing
  - Will give management recommendations for positive genetic tests and/or family history
  - Will discuss negative or variants of uncertain significance (VUS) results
  - Will discuss emotional, financial, legal, ethical ramifications of genetic testing
Legal Considerations

• ACA requires private insurers to cover BRCA1/2 counseling and testing for patients who meet USPSTF guidelines with no out of pocket cost
  – Some require pretest genetic counseling by credentialed genetics provider prior to authorizing tests

• Medicare does not cover if no cancer diagnosis is associated with pathogenic variants ordered
  – Unaffected individuals are not covered
  – Genetic counseling not separately billable service

• GINA – Genetic Information Nondiscrimination Act 2008
  – Health insurance and employment discrimination
  – Does not cover life, disability, or long-term-care insurance
Ethical considerations

- Psychosocial implications
- Coercion of family member
- Age of consent
- Discussions of PGD by IVF
- Confidentiality in EHR
- Informed consent
- Use of DNA in future “research”

Vincent Freeman in GATTACA: “I belonged to a new underclass, no longer determined by social status or the color of your skin. We now have discrimination down to a science.”
Personalized medicine

- Tumor genetic or molecular testing
  - Specific genes
    - HER2/neu in breast cancer
    - BRAF in melanoma
  - Panel testing
    - MMR genes in colon and endometrial cancer
    - OncotypeDx in breast and prostate cancer
  - DNA sequencing for all gene alterations
    - FoundationOne™
    - Mi-OncoSeq
Direct To Consumer Testing (DTC)

- Major options
  - 23andMe
  - Color Hereditary Cancer Test
  - Third party apps
    - AncestryDNA
    - Geno 2.0

- Pitfalls
  - High error rates
  - False sense of security
  - Personal information not secure
How a Genealogy Site Led to the Front Door of the Golden State Killer Suspect

What the Golden State Killer case means for your genetic privacy

By Susan Scutti, CNN
Updated 1:20 AM ET, Tue May 1, 2018

How DNA from family members helped solve the 'Golden State Killer' case: DA

By EMILY SHAPIRO and WHIT JOHNSON  Apr 28, 2018, 10:51 AM ET

Rewriting Life

“Hundreds” of crimes will soon be solved using DNA databases, genealogist predicts

CeCe Moore's company has been helping police departments solve cold cases by uploading crime-scene DNA to public genealogy databases.

by Antonio Regalado  September 13, 2018

DNA in NorCal Rapist case links suspect to sexual assaults in 6 counties

By Elliott C. McLaughlin, CNN
Updated 11:18 PM ET, Sun September 23, 2018

Can police legally obtain your DNA from 23andMe, Ancestry?

How a Tiny Website Became the Police's Go-To Genealogy Database

“I never expected anything like this.”

SARAH ZHANG  JUN 1, 2018

It started as a hobby. Now they're using DNA to help cops crack cold cases

By Eric Lawerson, CNN
Management of Hereditary Cancer Syndromes and Pathogenic Genetic Variants
BRCA 1 and BRCA2

• **Intensive surveillance**
  – Annual breast MRI starting at 25
  – Annual mammography starting at age 30
  – Clinical breast exam q6 months
  – Can consider annual pelvic ultrasound and CA-125 (poor evidence)

• **Risk-reduction**
  – Bilateral mastectomy reduces risk of breast cancer by 93%
  – Chemoprevention with tamoxifen or raloxifene decreased by ~50%
  – Risk-reducing bilateral salpingo-oophorectomy (RRSO or RR-BSO) decreasing risk of serous pelvic cancer 90%
    • BRCA1: ages 35-40
    • BRCA2: ages 40-45
• **LTR Cancer**
  – Breast cancer in women 28-37%
  – Prostate cancer in men 24-44%
  – Colorectal cancer (CRC) 10%
  – Four-fold increase in thyroid cancer

• **Management**
  – Annual mammogram and breast MRI starting at 40
  – Colonoscopy q3-5 years starting at 40
  – Thyroid ultrasound q3-5 years starting at diagnosis
Palb2

- **LTR Cancer**
  - Breast cancer 35%
    - If 2 first degree relatives, LTR increases to 58%
  - Insufficient evidence for ovarian cancer risk

- **Management**
  - Annual mammogram and breast MRI starting at 30
  - Clinical breast exam q6-12 months
  - Can consider RR-BSO based on family history of ovarian cancer
## HBOC additional genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Lifetime Risk (LTR) of Cancer</th>
<th>Management Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Breast Cancer 38-69%</td>
<td>Annual MRI + Mammogram at 40</td>
</tr>
<tr>
<td>BRIP1</td>
<td>Late-onset Ovarian Cancer 5.8-12%</td>
<td>RRSO by 45-50</td>
</tr>
<tr>
<td>NF1</td>
<td>Breast cancer ≤ 60%</td>
<td>Annual Mammogram at 30 + MRI at 30-50</td>
</tr>
<tr>
<td>NBN</td>
<td>Breast Cancer ≤ 30%</td>
<td>Annual MRI + Mammogram at 40</td>
</tr>
<tr>
<td>RAD50</td>
<td>Increased breast cancer risk</td>
<td>Manage according to family history</td>
</tr>
<tr>
<td>RAD51C</td>
<td>Late-onset Ovarian Cancer 6.7%</td>
<td>RRSO by 45-50</td>
</tr>
<tr>
<td>RAD51D</td>
<td>Late-onset Ovarian Cancer ≤ 15%</td>
<td></td>
</tr>
</tbody>
</table>
Hereditary diffuse gastric cancer syndrome: CDH1

- **LTR Cancer**
  - Breast cancer 39-52%
  - Diffuse gastric cancer 60-80%
  - Increased risk of signet cell colon cancer

- **Intensive surveillance**
  - Annual mammogram and breast MRI starting at age 30
  - Clinical breast exam 1-2x yearly
  - Upper endoscopy q6-12 months

- **Risk reduction strategies**
  - Recommend gastrectomy at age 18-40
  - Consider offering prophylactic bilateral mastectomies (insufficient evidence)
Li-Fraumeni syndrome: TP53

- **LTR cancer almost 100%**
  - Breast cancer 54%
  - Soft tissue sarcoma 15%
  - CNS tumor 6%
  - Osteosarcoma 5%
  - Increased rates of leukemia, melanoma, CRC, pancreas, adrenal cancer

- **Management**
  - Annual brain MRI + rapid total body MRI starting in childhood
  - Annual breast MRI at 30
  - TVUS abdomen and pelvis q6 month at 18
  - Colonoscopy/endoscopy q2-5 years at age 25
  - Annual dermatology and GYN exam
  - CBC, ESR, LDH labs q6 months
  - Discuss reproductive options with IVF and PGD
Lynch syndrome – MLH1, MSH2, MSH6, PMS2

• Cancer LTR
  – **MLH1/MSH2** – Colon cancer (CRC) 52-82%, Endometrial cancer 25-60%, Ovarian cancer 15-24%, Prostate cancer 30%
    • Increased risk also of stomach, urinary tract, pancreas, CNS, small bowel, sebaceous neoplasms, hepatobiliary tract
  – **MSH6** – CRC 10-22%, Endometrial cancer 16-26%, Ovarian cancer 1-11%, Prostate ~30%
  – **PMS2** – CRC 15-20%, Endometrial cancer 15%, Ovarian cancer 1-11%, no prostate

• Management
  – Annual colonoscopy starting at 20 or 2-5 years earlier than earliest family member (age 30 for MSH6)
  – Upper endoscopy starting at age 40 q3-5 years
  – Consider annual urinalysis – especially in males with MLH1 or MSH2
  – Annual endometrial sampling at age 30; consider annual TVUS + CA-125
  – Recommend total hysterectomy + BSO by age 40
Cowden syndrome – PTEN³

- **LTR Cancer Risks**
  - Breast cancer 25-50%
  - Colorectal cancer 10-15%
  - Non-medullary thyroid cancer 10%
  - Endometrial cancer 5-10%

- **Management**
  - Annual mammogram and breast MRI at age 30
  - Annual thyroid ultrasound at 20
  - Annual endometrial biopsy at age 30
  - Can consider chemoprevention, bilateral mastectomies
  - Total hysterectomy and bilateral salpingectomies at 35-40

Peutz-Jegher’s syndrome: $\text{STK11}^5$

- **Increased LTR cancer risks**
  - Breast cancer 45-50%
  - Pancreatic cancer 11-36%
  - Gastric cancer 29%
  - Ovarian cancer 18-21%
  - Lung cancer 15-17%
  - Small bowel cancer 13%
  - Cervical cancer 10%
  - Endometrial cancer 9%

- **Management**
  - MR entography starting at 8
  - Males: annual testicular exam starting at 10
  - Females: annual Pap smear, consider TVUS + CA-125 at 18
  - Colonoscopy/EGD q2 years at age 15
  - Breast MRI at 25 + mammography at 30
  - MRCP or endoscopic pancreatic ultrasound q1-2 years at 30

https://emedicine.medscape.com/article/182006-overview
Other hereditary cancer syndromes

- Familial Adenomatous Polyposis (FAP): APC
- Von Hippel Lindau (VHL)
- Multiple endocrine neoplasia 1 and 2 (MEN1/2)
- Beckwith-Wiedemann
- Neurofibromatosis 1 and 2 (NF1/2)
Familial cancers

• How do you manage patients with a family history of cancers but no known pathogenic genetic variants/mutations?
  – Use risk calculators to determine lifetime risk (LTR)

  Ovarian cancer LTR ≥ 5%
  – Refer for RR-BSO

  Breast cancer LTR ≥ 20%
  – Annual breast MRI
  – Annual mammography
  – Clinical breast exam q6 mo
Summary

- Most breast and ovarian cancers are not inherited
- Hereditary breast and ovarian cancer (HBOC) syndromes are caused by more genes than just BRCA 1/2
- Cancers in families other than just breast and ovarian cancer can be associated with breast or ovarian cancer risk
- Risk assessment calculators can guide recommendations for intensive surveillance
- Guidelines exist for the appropriate patients to test
- When in doubt, consider referral to a genetic counselor
Resources: Referrals at Michigan Medicine

• **Internal Referrals**
  – HBOC genetic counseling
    • Cancer Center Breast and Ovarian Cancer
  – Cancer risk assessment, management, and GYN care for breast cancer patients/mutation carriers and those with family history of HBOC:
    • Gynecological Care of Breast Cancer and BRCA at VVWH
  – Breast cancer surgery, mass evaluation, prophylactic mastectomy or medical breast oncology
    • Breast Care Center
  – Discussions of reconstruction options for prophylactic mastectomies or for breast cancer patients
    • Plastic Surgery Adult
  – Concern for non-HBOC cancer syndrome (Lynch, Li-Fraumeni, FAP, etc.)
    • Cancer Center Genetics Clinic
Genetic resources

- **USPSTF: BRCA-Related Cancer: Risk Assessment, Genetic Counseling, and Genetic Testing**

- **Calculators**
  - BSCS: [https://tools.bcsc-scc.org/bc5yearrisk/calculator.htm](https://tools.bcsc-scc.org/bc5yearrisk/calculator.htm)

- **Claus model reference**
Genetic Resources: Genetic counseling

- National Society of Genetic Counselors
  - www.nsgc.org

- Michigan Genetics Resource Center
  - https://migrc.org/Library/MCGA/MCGAMainPage.html
Genetic resources: www.nccn.org

Thank You!
References


